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Industria y Comercio

SUPERINTENDENCIA

PCT

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DIVISION DE NUEVAS CREACIONES

08 - 13175

SOLICITUD DE PATENTE DE INVENCION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

TITULO DERIVADOS DE XANTINA COMO AGONISTAS SELECTIVOS DE HM74A

SOLICITANTE SMITHKLINE BEECHAM CORPORATION

DIRECCION One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101 E U A

A61K 31/495

APODERADO CARLOS R OLARTE

BOGOTA 8 de Febrero de 2008

P2008/000032

55

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-013175- -00000-0000
Fecha: 2008-02-11 12:33:22 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 489

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000032**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SMITHKLINE BEECHAM CORPORATION
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Número _____

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(5) **PCT (86)**

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

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

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SI [X] **NO** [ ]

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(9) **Comprobante de pago No.** **08-10,529** **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. 06-045.057
- [ ] 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

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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NIT : 800176089-2

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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 - Inglés
Resolución No. 2117 del 7 Oct 1987

DE PINNA
NOTARIES

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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

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
   a été signé par

3. Acting in the capacity of **Notary Public**
   agissant en qualité de

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

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
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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

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(72) Inventors; and

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report*

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

(54) Title: XANTHINE DERIVATIVES AS SELECTIVE HM74A AGONISTS

(57) Abstract: The present invention relates to compounds1 of formula (I) 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.

WO 2007/017261 A1

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.

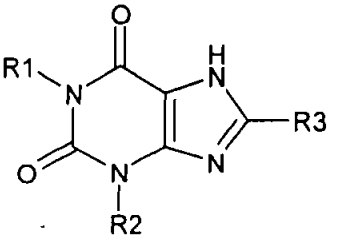
Summary of the Invention

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 m and n represent the number of carbon atoms in the alkylene chain;

Wherein X represents a group selected from heteroaryl and heterocyclyl;

Wherein Y represents a group selected from aryl, heteroaryl and O-aryl;
which may be optionally substituted by one or more groups independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, $-(CH_2)_qNR^5R^7$, $-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$, $-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)NR^5R^6$, $-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2NR^5R^6$, $-C_{1-6}$ haloalkyl, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, CN, $-SO_2R^9$, $-(CH_2)_n$heteroaryl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$cycloalkyl, $-(CH_2)_n$cycloalkenyl, and $-(CH_2)_n$aryl;

R^2 represents C_{1-6} alkyl which may be optionally substituted by one or more groups independently selected from cycloalkyl, C_{1-6} haloalkyl, halogen, -CN and $-OR^4$;

R^3 represents halogen;

R^4 represents a group 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 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_t$ cycloalkyl, $-(CH_2)_t$ cycloalkenyl, $-(CH_2)_t$ heterocyclyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl;

R^8 represents 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 3 and 4;

n represents an integer selected from 0 and 1;

p represents an integer selected from 0 and 1;

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

t represents an integer selected from 1 and 2.

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The compound(s) are believed to be 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 and 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. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

In one embodiment of the present invention, X represents a heteroaryl. In another embodiment X represents a heteroaryl comprising a nitrogen heteroatom, for example, triazolyl, furazanyl, oxadiazolyl, tetrazolyl, imidazolyl or pyrazolyl. In a further embodiment X represents a group selected from oxadiazolyl and tetrazolyl.

In another 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 represents an optionally substituted group selected from aryl and heteroaryl. In one embodiment Y is selected from aryl.

In one embodiment of the present invention, Y 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, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, CN $-SO_2R^9$, $-(CH_2)_n$heteroaryl, $-(CH_2)_n$heterocycyl, $-(CH_2)_n$cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$aryl;

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^8CN, 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 another embodiment, Y is not further substituted.

In one embodiment of the present invention, X and Y each independently represent a heteroaryl comprising a nitrogen heteroatom. In a further embodiment X represents oxadiazolyl and Y represents pyridinyl. In another embodiment X represents tetrazolyl and Y represents phenyl. In yet another embodiment of the present invention X represents oxadiazolyl and Y represents phenyl

In one embodiment of the invention, m is 4 and n is 0. In a further embodiment, m is 3 and n is 1.

In one embodiment of the present invention, R^2 is selected from C_{3-6} alkyl, for example butyl or pentyl, for example n-butyl or n-pentyl.

In a further embodiment of the present invention, R^3 is selected from chlorine and bromine. In another embodiment, R^3 represents chlorine.

In one embodiment of the present invention R^7 represents a group selected from 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;

In one embodiment of the present invention X represents oxadiazolyl, Y represents phenyl, R^2 is butyl, R^3 represents chlorine and m is 4 and n is 0.

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_6alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 6 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" as used herein means both straight and branched saturated or unsaturated 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, -(alkylene)$_m$-, where m 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. For example, as used herein -(alkylene)$_n$ where n = 1 means -CH_2-. As used herein -(alkylene)$_n$ where n = 0 means there is no alkylene linker at this position.

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.

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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 and cyclooctyl.

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, cyclooctenyl 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, each independently 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 each independently 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.

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The terms "halogen" or "halo" as used herein refer to for example, 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, 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.

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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.

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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-Ham's F-12 media (available from Invitrogen) 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

Compounds of the invention 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 (10,000g 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 compounds of the invention 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.

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Some 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:
8-chloro-3-(3,3-dimethylbutyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione;
have utility as intermediates in the production of other compounds according to formula (I).

The exemplified compounds (Examples 1 - 512) 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.

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.

^{1}H 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.

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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.

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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.

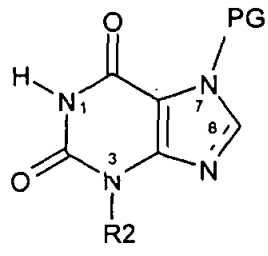
When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

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;

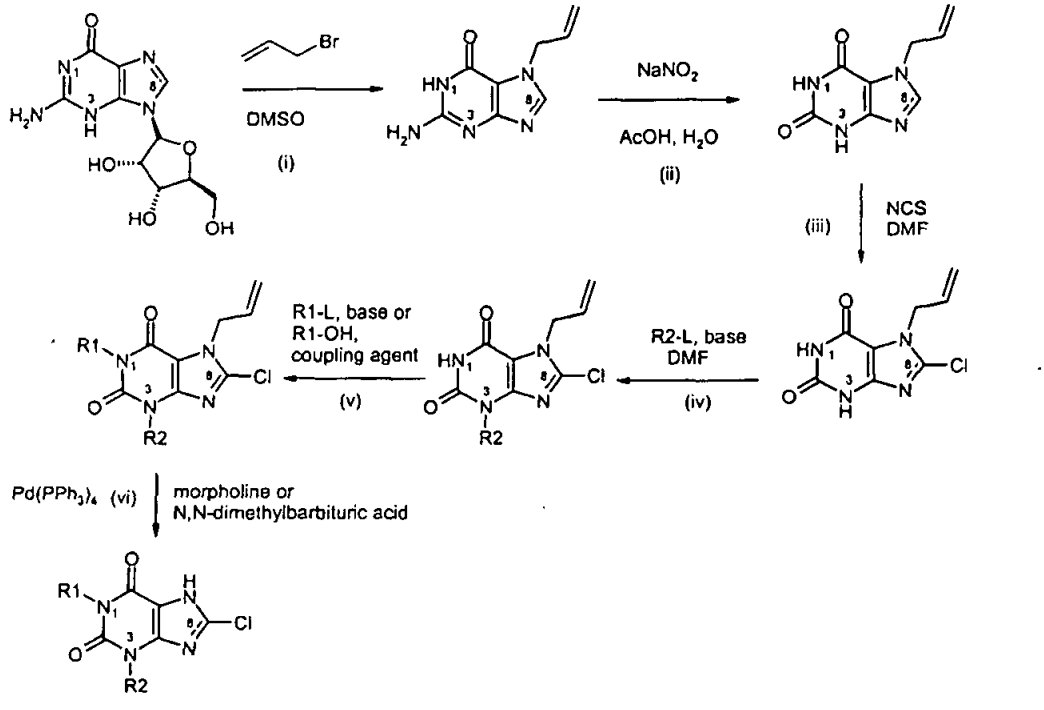
(iii) halogenation at C8; and

(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 heterocyclyl, heteroaryl or aryl and R1 represents Cl.



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 (Examples of suitable bases include Na_2CO_3, Cs_2CO_3, K_2CO_3)

v) Alkylation at N1 (Examples of suitable bases include Na_2CO_3, Cs_2CO_3, K_2CO_3)

vi) Palladium catalysed removal of the allyl group

wherein L represents a leaving group, for example halogen.

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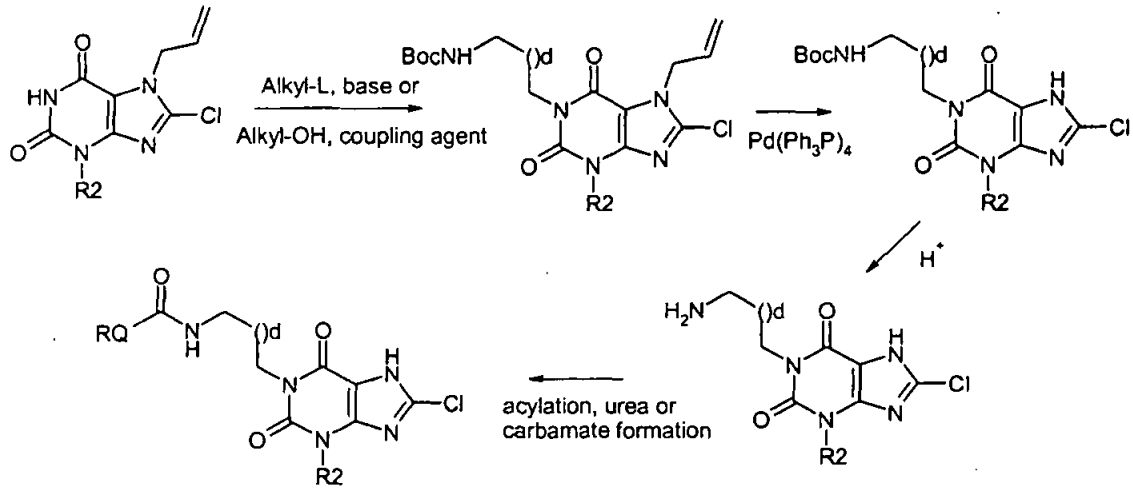
Process 2:

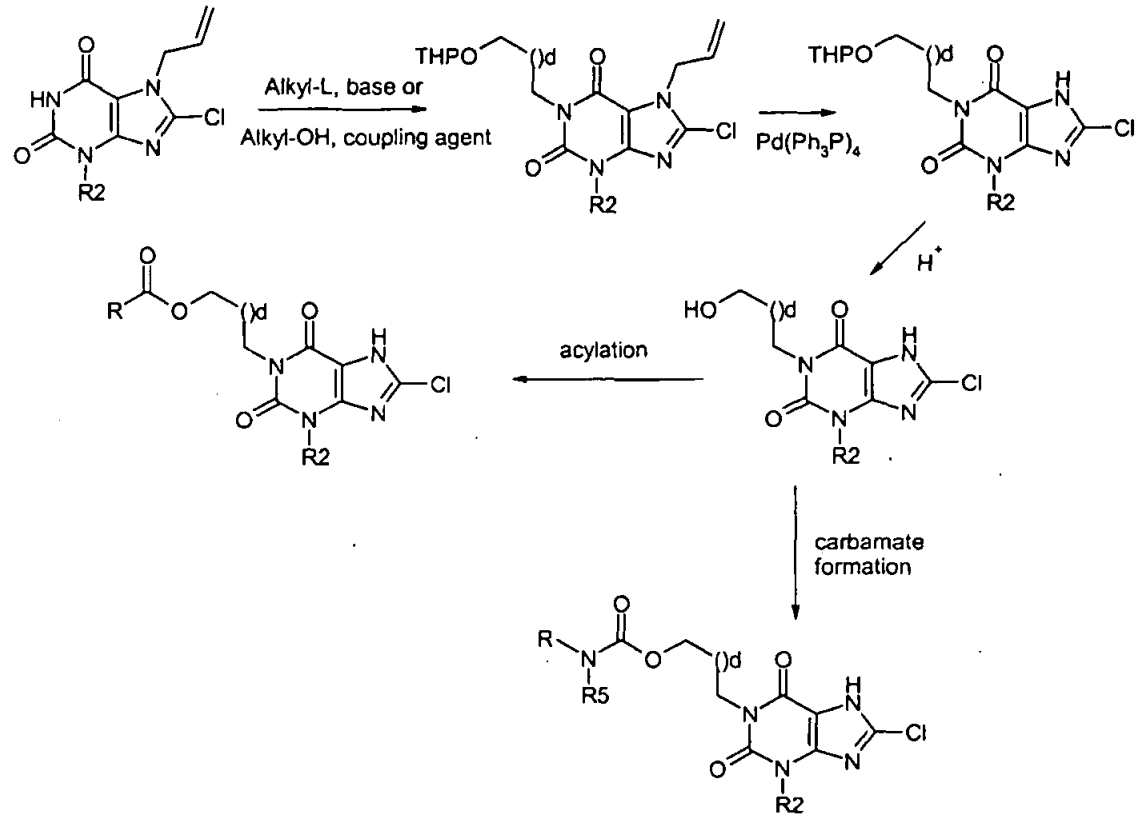
A process according to the invention for preparing intermediates in which R1 incorporates an amide, carbamate or urea, which may be useful for production of compound(s) of formula (I).



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:

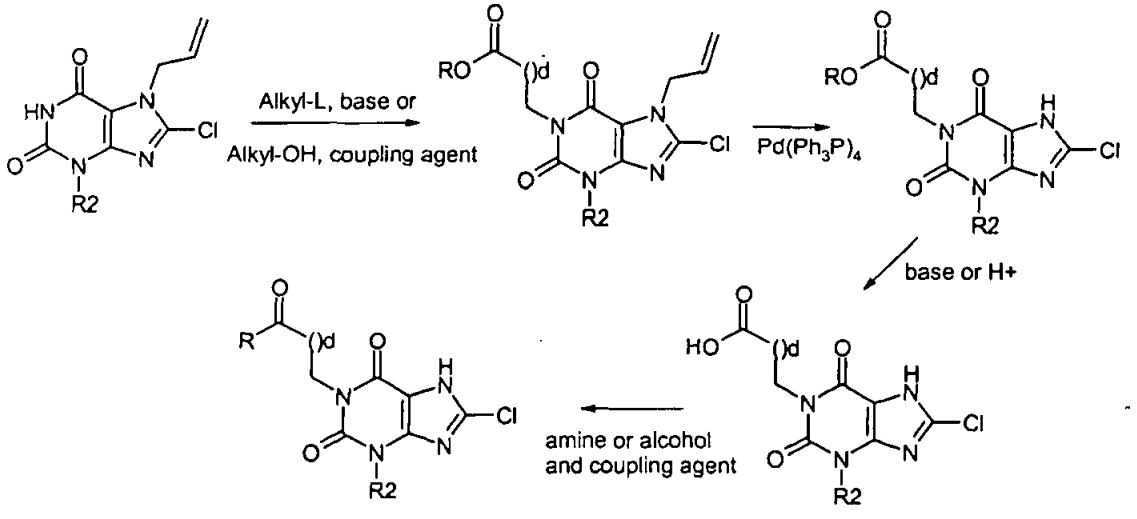
A process for preparing intermediates in which R1 incorporates a 'reverse' carbamate or ester, which may be useful for production of compound(s) of formula (I).



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

Process 4:

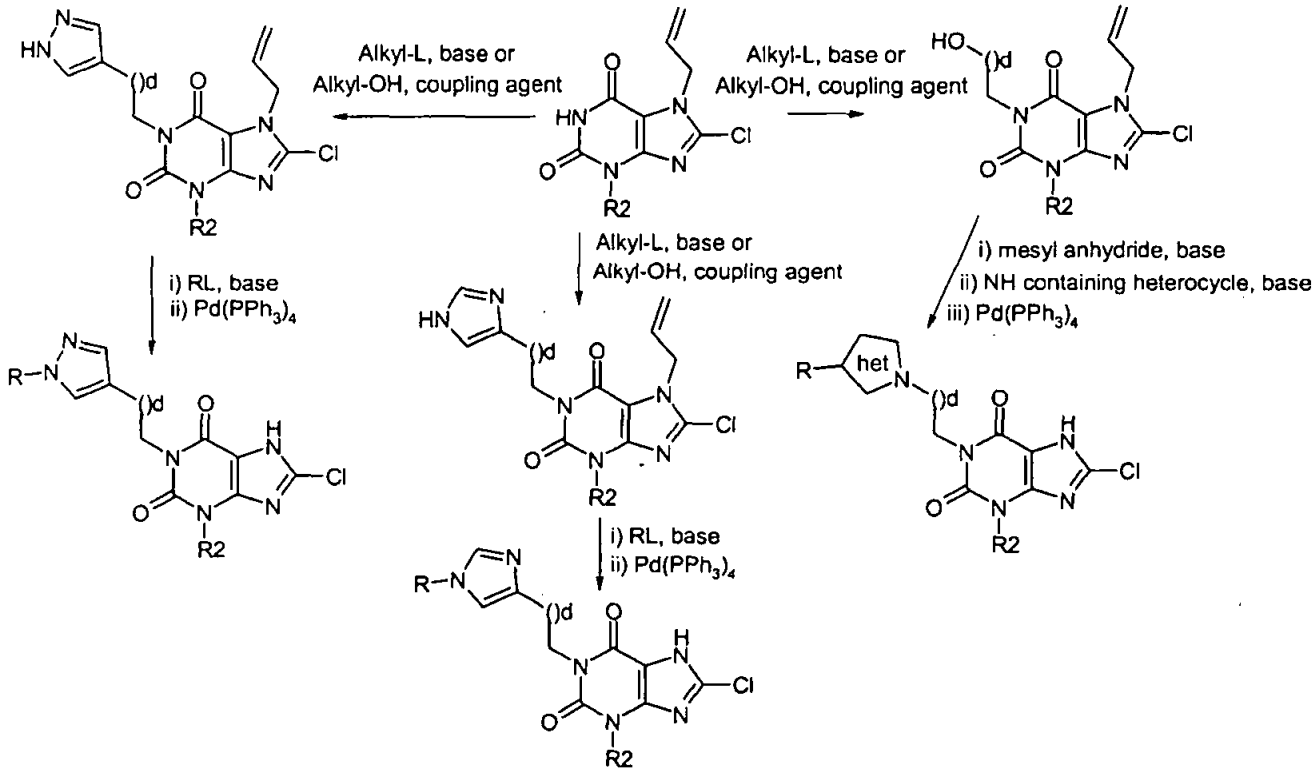
A process according to the invention for preparing intermediates in which R1 incorporates an ester or amide, which may be useful for production of compound(s) of formula (I).



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 X incorporates a pyrazole, imidazole or tetrazole.



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

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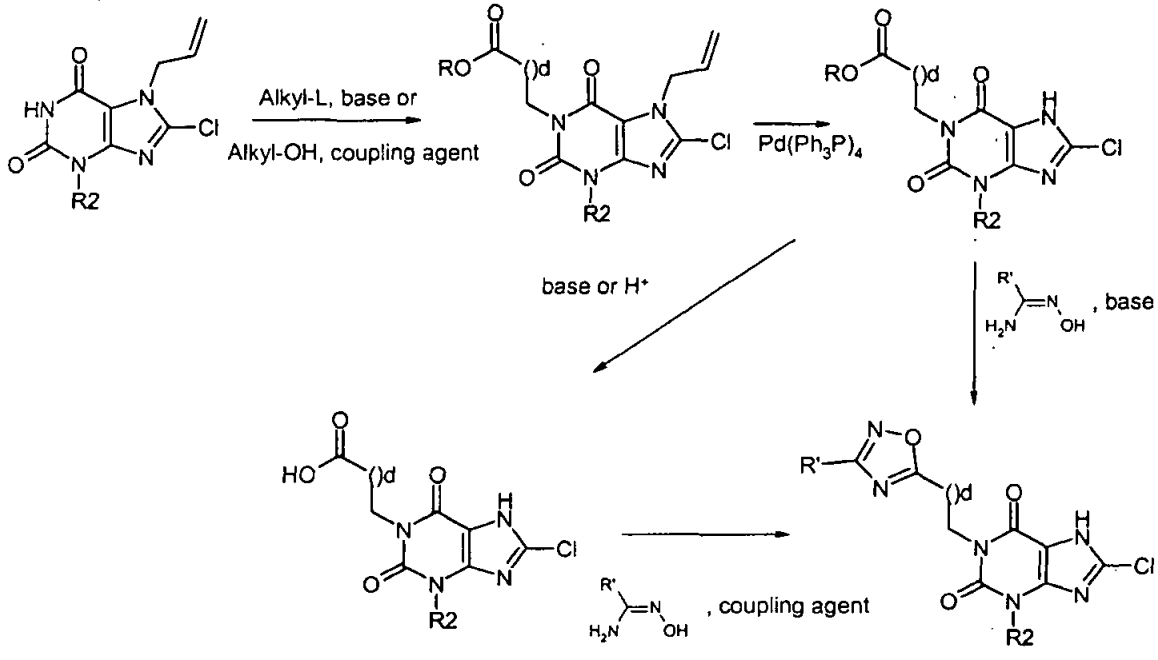
Process 6:

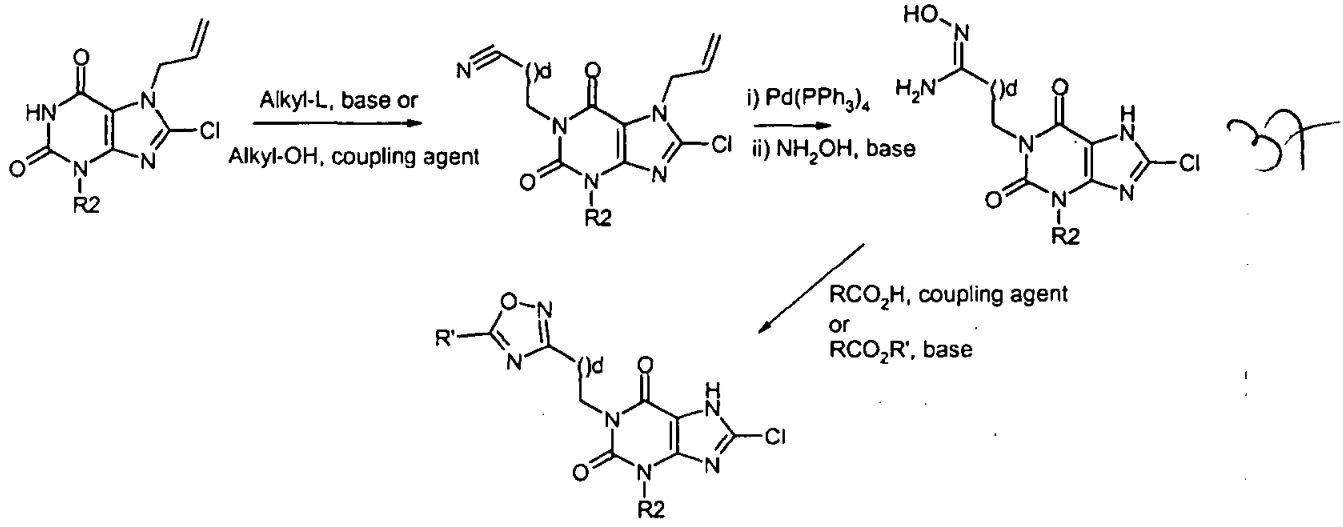
A process according to the invention for preparing compound(s) of formula (I) in which X incorporates an oxadiazole.



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 X incorporates an oxadiazole

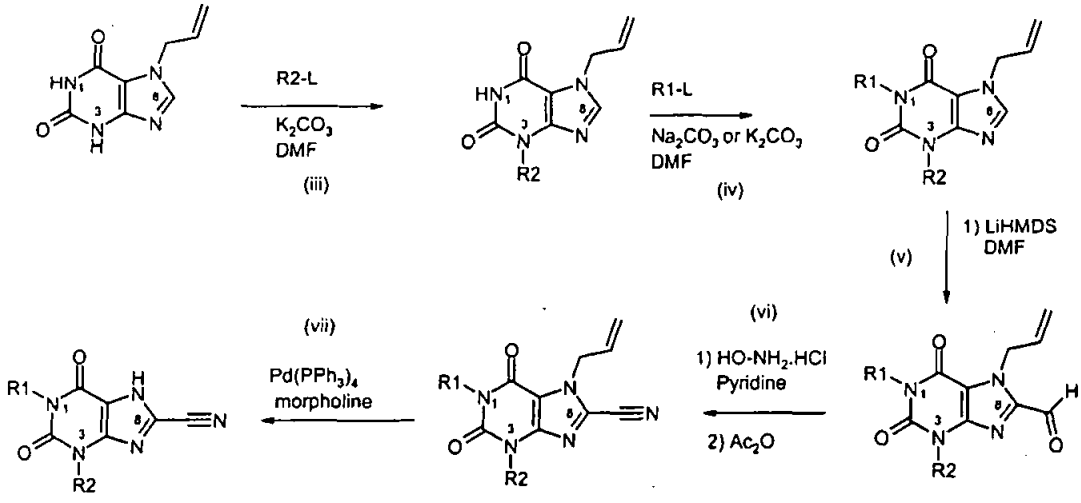


wherein L represents a leaving group, for example halogen, d represents (m-1), R represents an alkyl group and R' represents -(alk)$_n$-Y.

Process 8:

A process according to the invention for preparing intermediates in which R^3 is CN, which may be useful for preparation of compound(s) of formula (I).

This 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.

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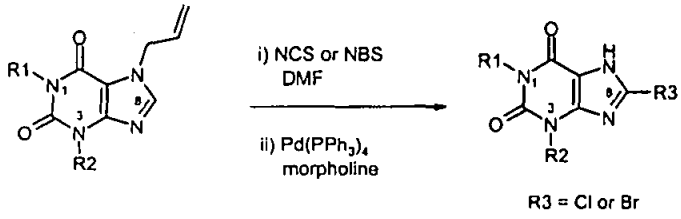
Process 9:

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:

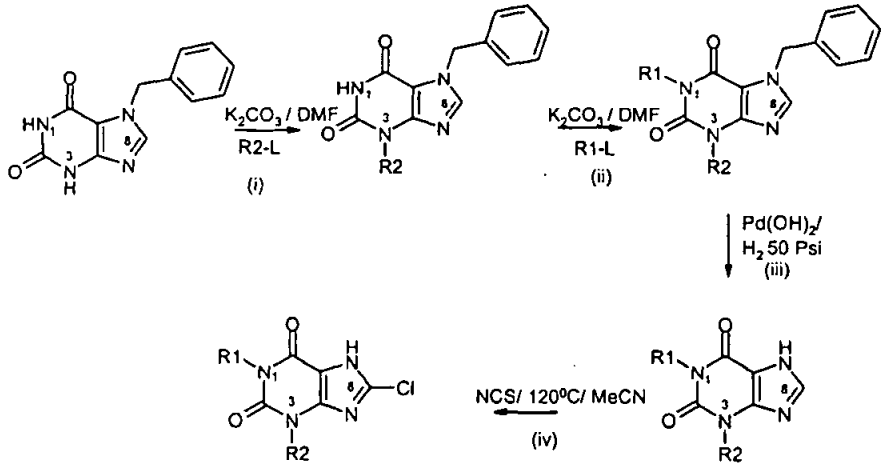


i) Halogenation at C8 using NCS or NBS

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 Cl comprises:



i) Alkylation at N3

ii) Alkylation at N1

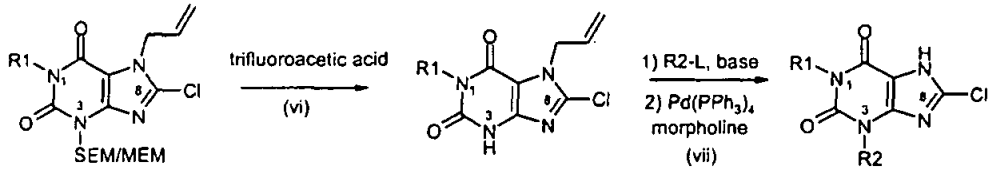
iii) Debenzylation

iii) Chlorination at C8

wherein L represents a leaving group

Process 11:

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:



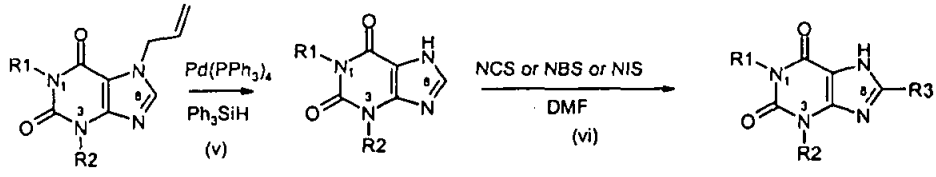
vi) Cleavage of MEM or SEM protecting group group

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

wherein L represents a leaving group

Process 12:

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:

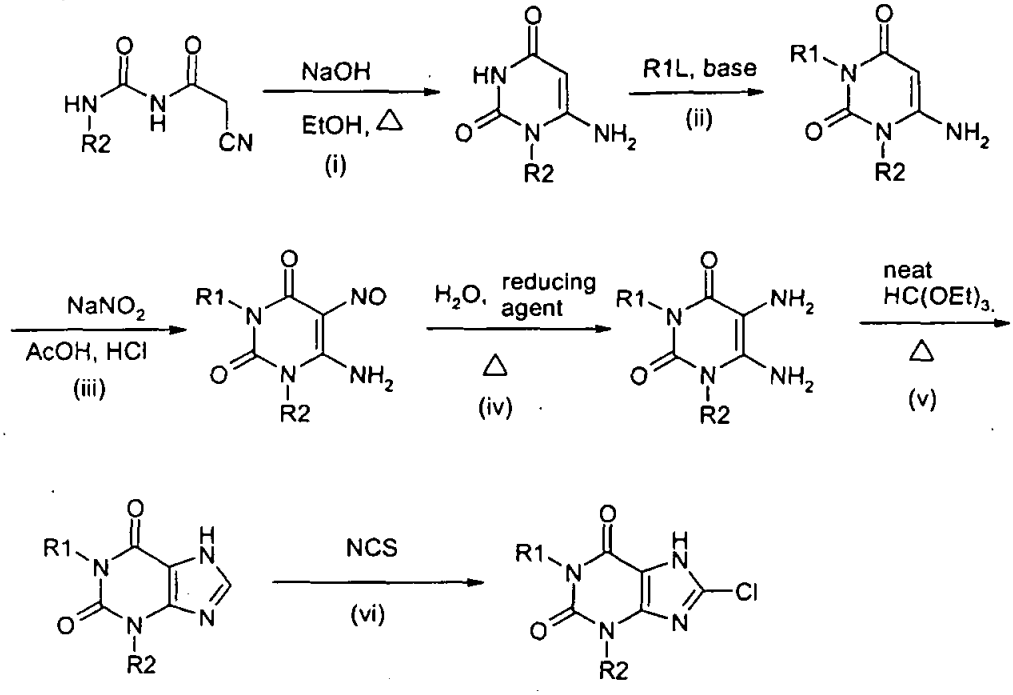


v) Palladium catalysed removal of allyl group

vi) Halogenation at C8 using NCS, NBS or NIS

Process 13:

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

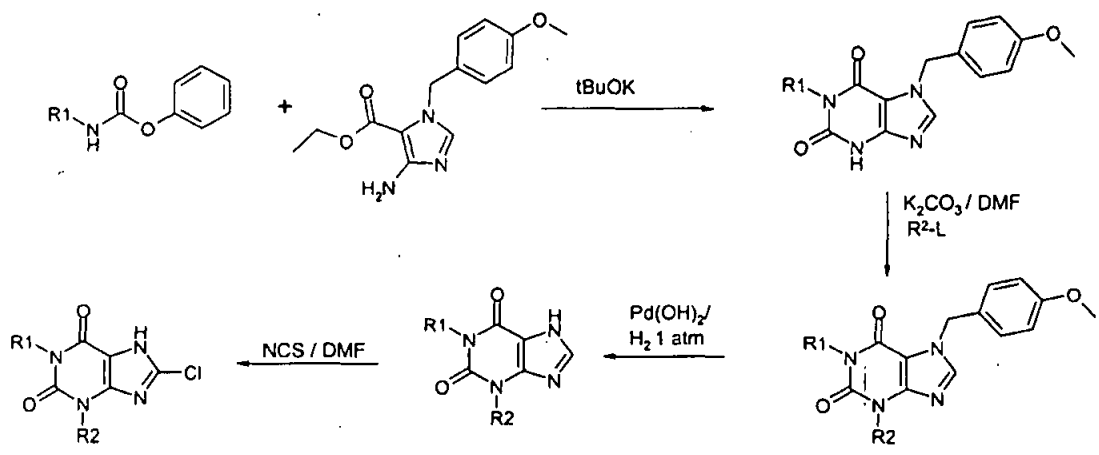


i) Pyrimidinedione formation
ii) Alkylation at N1
iii) Nitrosation
iv) Reduction using $Na_2S_2O_4$ or a similar reducing agent
v) Xanthine formation
vi) Halogenation at C8 using NCS

wherein L represents a leaving group

Process 14:

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



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 derivative, for example a resultant compound of formula (I) can be converted into a salt form or vice versa or converting one salt form into another pharmaceutically acceptable salt form. These processes will be known to a person skilled in the art.

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

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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.

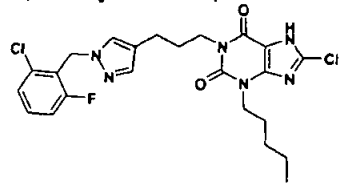
The following non-limiting examples illustrate the present invention:

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)

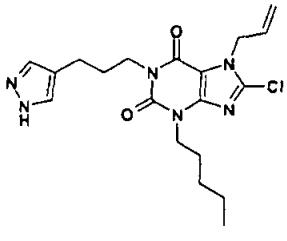
Example 1 : 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

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

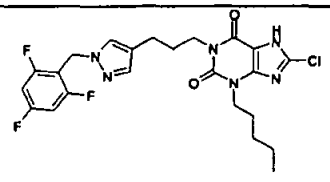
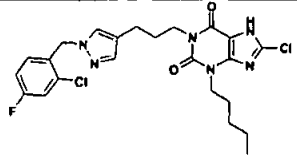
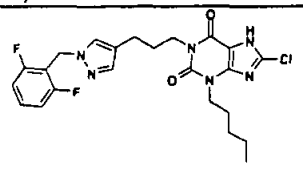


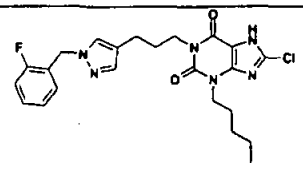
3-Pentyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5g, 16.86mmol) and 3-(1*H*-pyrazol-4-yl)propan-1-ol (2.12g, 16.8mmol) were stirred in dry THF (150ml) at 3°C. Dibenzyl azodicarboxylate (10.05g, 33.7mmol) was added followed by the dropwise addition of triphenylphosphine (8.83g, 33.7mmol) 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 1, from the corresponding benzyl halides.

Table 1

Example	structure	Yield (mg)	LC/MS:
2	 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
3	 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
4	 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

5	 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 [a]	m/z 473 $[MH]^+$ RT 3.55 min

[a] after additional purification by MDAP.

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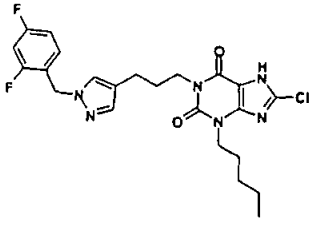
NMR details for selected examples from Table 1

Example 2: 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 6: 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



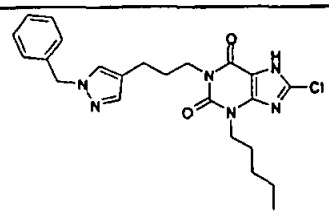
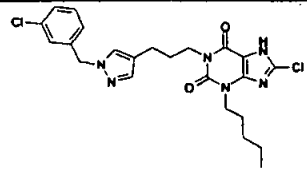
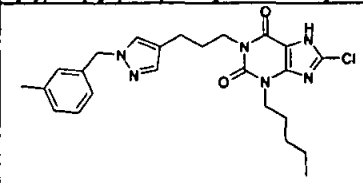
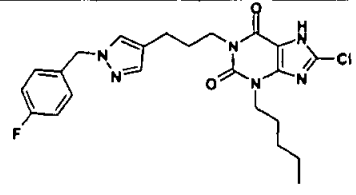
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (81mg, 0.2mmol) and sodium carbonate (85mg, 0.8mmol) were stirred in dry DMF (2ml) with 2,4-difluorobenzyl bromide (166mg, 0.8mmol) at 45°C for 18h. The mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (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.

The following compounds (Table 1) were prepared using a method analogous to that for Example 6, from the corresponding benzyl halides.

Table 2

Example	Structure	Yield	LC/MS:

		(mg)	
7	 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	17[a]	m/z 455 $[MH]^+$ RT 3.52 min
8	 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[a]	m/z 489 $[MH]^+$ RT 3.52 min
9	 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
10	 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

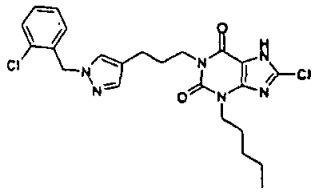
[a] after additional purification by MDAP.

NMR details for selected examples from Table 2

Example 6: ^{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).

Example 7: 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 11: 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



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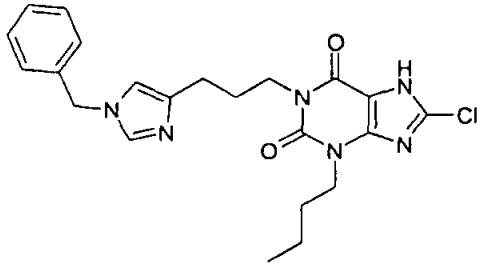
Prepared by the method for 8-chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione, Example 6 but from 2-chlorobenzyl bromide (164mg, 0.8mmol). However, in order to complete the deprotection step further tetrakis(triphenylphosphine)palladium(0) (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 12: 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.

^{1}H 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).

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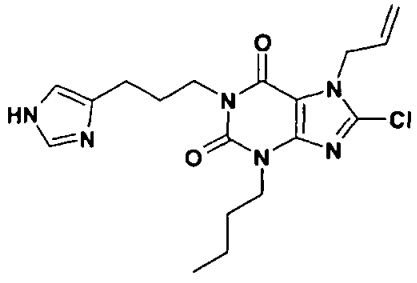
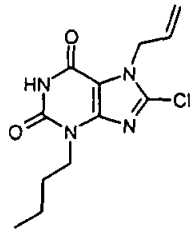
b) 3-Butyl-8-chloro-1-[3-(1*H*-imidazol-4-yl)propyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



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

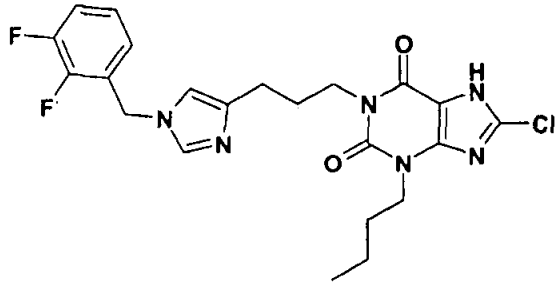


To a solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.34g, 13.4mmol) in anhydrous DMF (19ml) was added NCS (1.97g, 14.8mmol) and left to stir at rt under nitrogen for 22h. The mixture was concentrated *in vacuo* to give a yellow solid which was filtered and washed with MeOH 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 $[MH]^+$.

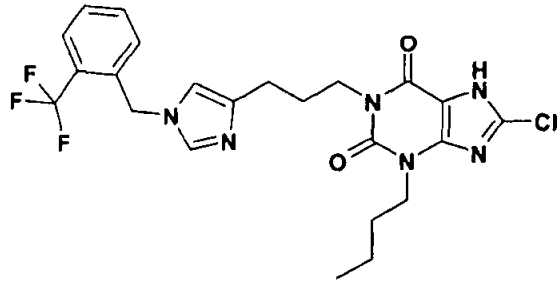
Example 13: 3-Butyl-8-chloro-1-(3-{1-[(2,3-difluorophenyl)methyl]-1*H*-imidazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

50



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 14: 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.

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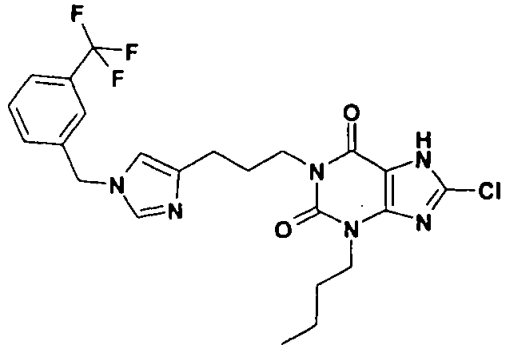
Example 15: 3-Butyl-8-chloro-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-imidazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



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 16 : 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

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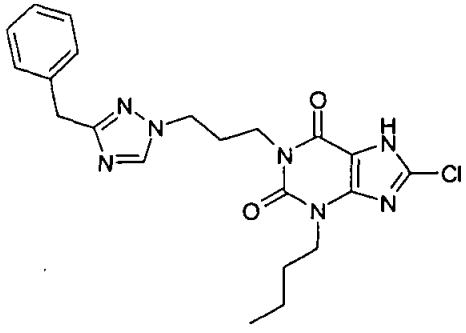
a) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

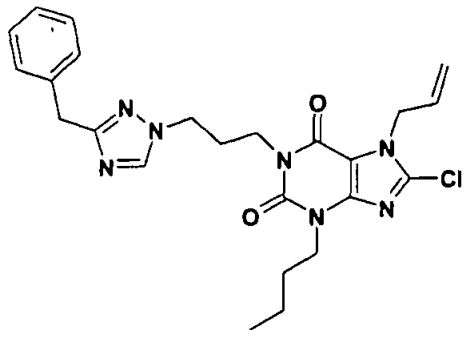


A solution of 3-butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (669mg, 1.39mmol) in THF (7ml) was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (160mg, 0.14mmol) was added and the mixture degassed 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.

^1H 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



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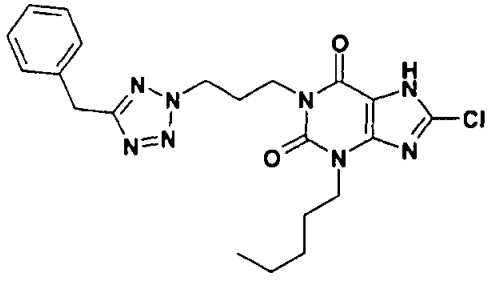
A solution of 3-(phenylmethyl)-1*H*-1,2,4-triazole (2.1g, 13.2mmol) in MeOH (40ml) was treated with 0.5M NaOMe in MeOH (29ml) followed by 1,3-dibromopropane (1.7ml). After stirring for 5h at 50°C the mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, 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 17 : 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.

^{1}H 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).

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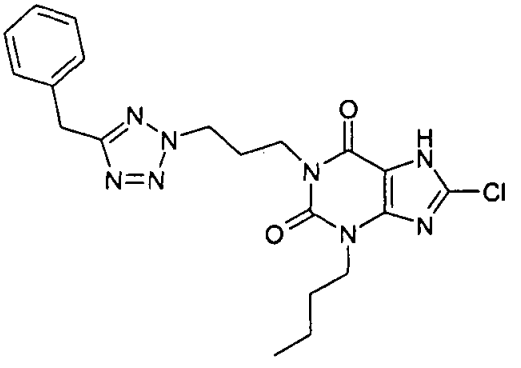
Example 18: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-2*H*-tetrazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



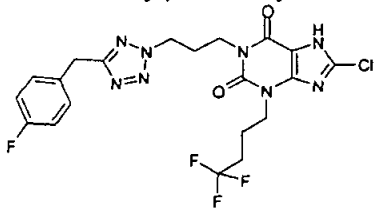
A solution of 5-benzyl-1H-tetrazole (1.8g, 11.2mmol) in MeOH (30ml) was treated with 1,3-dibromopropane (5.7ml, 56.2mmol) and 0.5M NaOMe in MeOH (31.5ml) then stirred at 40°C under nitrogen for 60h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with 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 19: 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

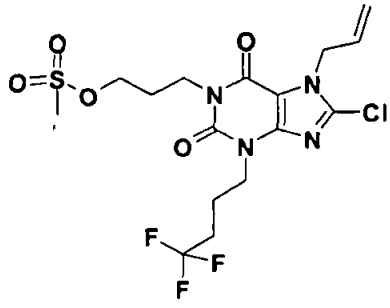
a) 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



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%).

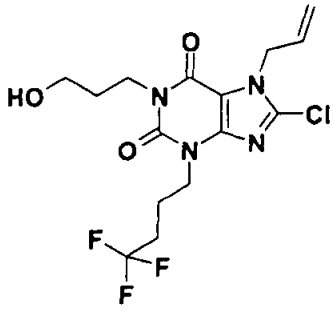
LC/MS: m/z 515 $[MH]^+$, RT 3.31min.
^1H NMR ($CDCl_3$) δ: 2.06 (m, 2H), 2.21 (m, 2H), 2.45 (m, 2H), 4.17 (m, 4H), 4.24 (t, 2H, J = 7.0Hz), 4.70 (t, 2H, J = 7.2Hz), 6.96 (m, 2H), 7.25 (m, 2H).

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.

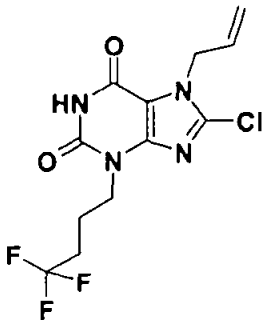
c) 8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



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%).

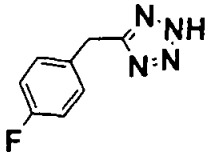
LC/MS: m/z 395 $[MH]^+$, RT 2.90min.

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 19: 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:

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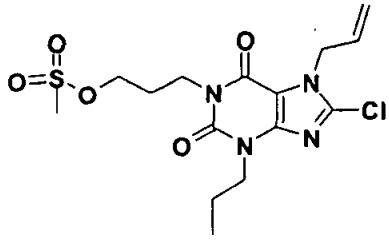
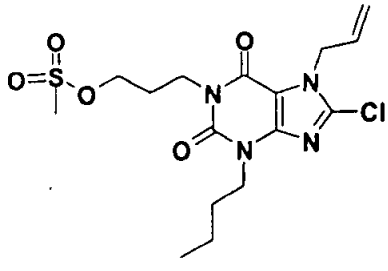
3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



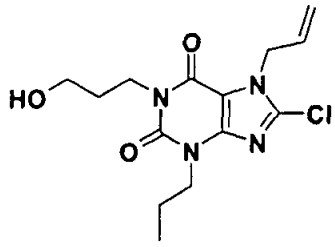
A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (1.99g, 6.1mmol) in DCM (50ml) was treated with triethylamine (1.2ml, 8.6mmol) and methanesulfonic anhydride (1.2g, 6.9mmol). After 1.5h the mixture was treated with water (50ml). The mixture was separated 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



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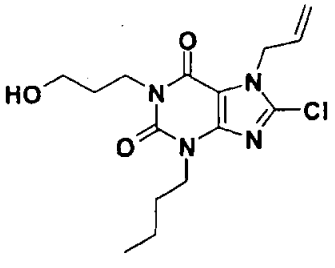
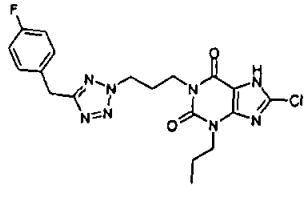
A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 11.1mmol) in DMF (20ml) was treated with caesium carbonate (3.7g, 11.4mmol) and 3-bromo-1-propanol (1.6g, 11.5mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned 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.

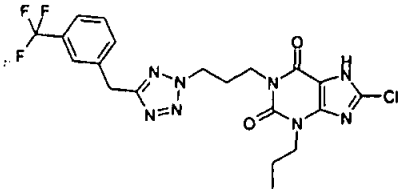
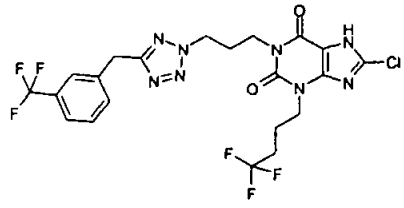
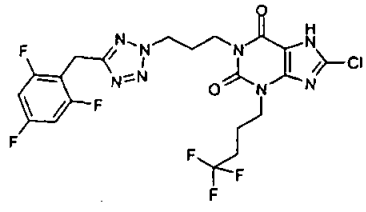
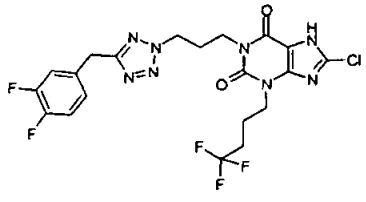
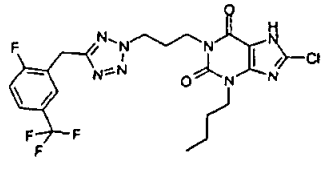
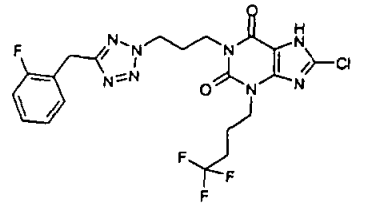
3-Butyl-8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

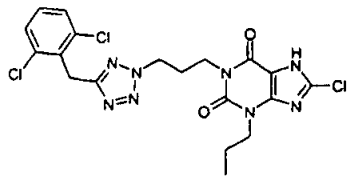
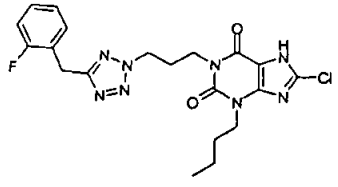
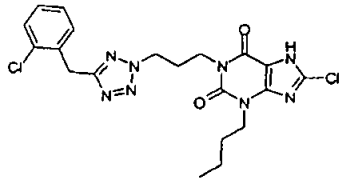
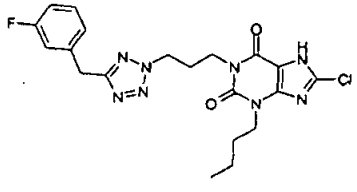
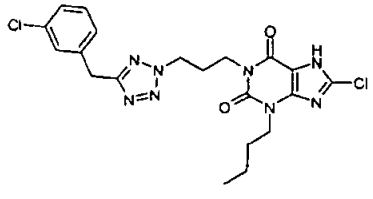
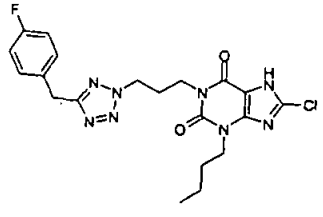


Prepared according to the method used for 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione to give the title compound as a colourless oil (2.3g).
LC/MS: m/z 341 $[MH]^+$, RT 2.85min.

Table 3

#	Structure	Name	Yield	LC/MS:
20		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

21		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
22		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
23		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
24		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
25		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
26		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

27		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
28		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
29		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
30		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
31		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
32		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

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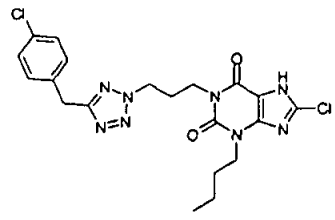
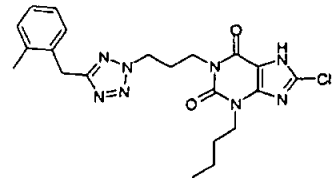
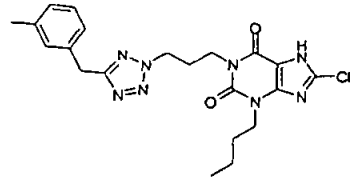
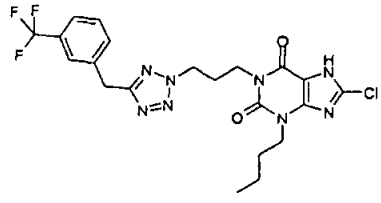
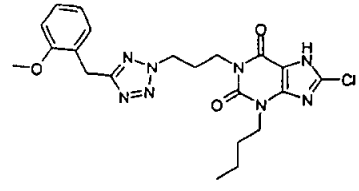
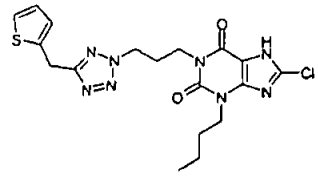
33		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.1mg (35%)	m/z 477 $[MH]^+$ RT 3.46 min
34		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	39.5mg (43%)	m/z 457 $[MH]^+$ RT 3.37 min
35		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
36		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
37		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
38		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

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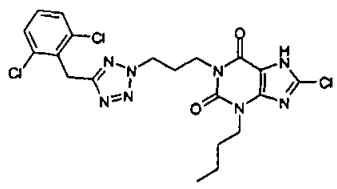
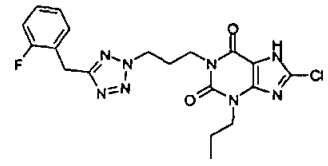
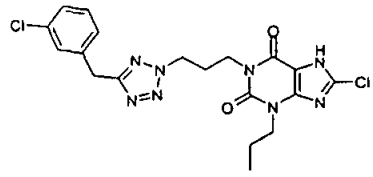
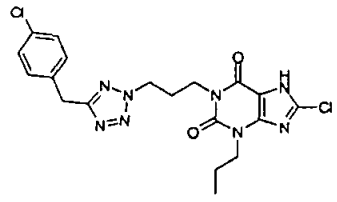
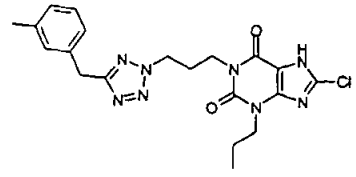
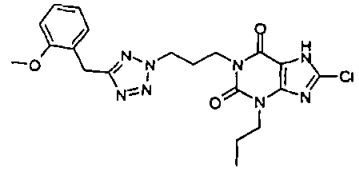
39		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.4mg (36%)	m/z 511 $[MH]^+$ RT 3.49 min
40		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.6mg (6%)	m/z 447 $[MH]^+$ RT 3.10 min
41		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
42		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
43		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
44		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

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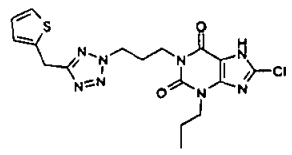
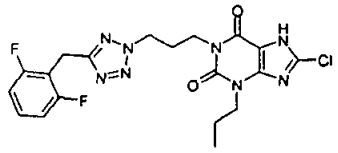
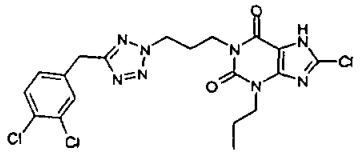
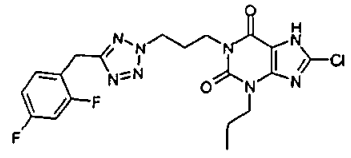
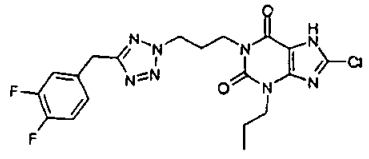
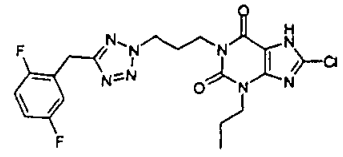
45		8-chloro-3-propyl-1-{3-[5-(2-thienylmethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	17.0mg (20%)	m/z 435 $[MH]^+$ RT 3.02 min
46		8-chloro-1-(3-{5-[(2,6-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	18.4mg (20%)	m/z 465 $[MH]^+$ RT 3.11 min
47		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
48		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
49		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
50		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

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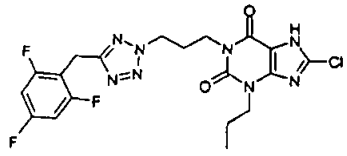
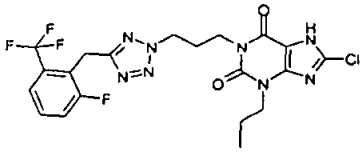
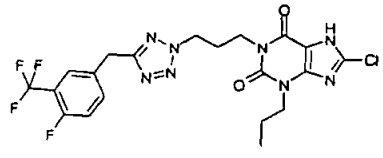
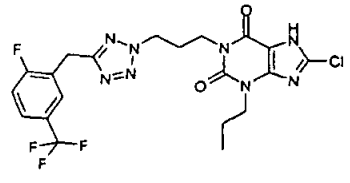
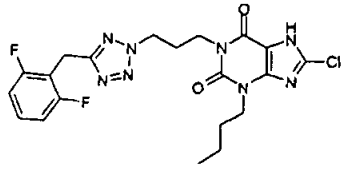
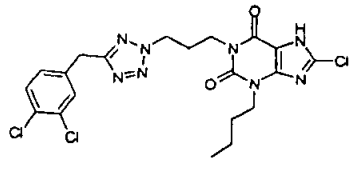
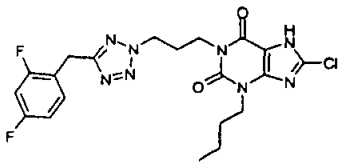
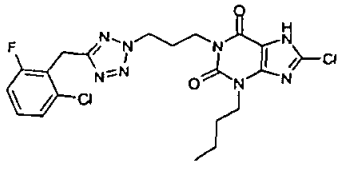
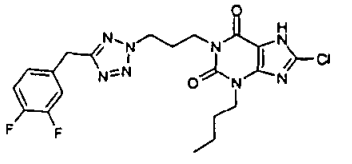
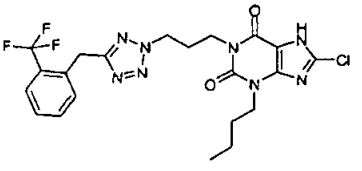
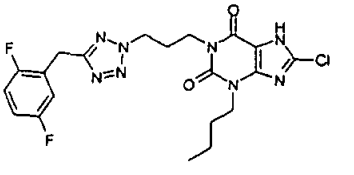
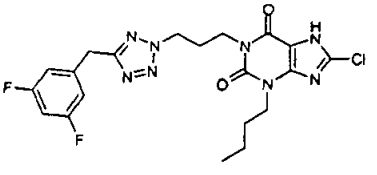
51		8-chloro-3-propyl-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.4mg (18%)	m/z 483 $[MH]^+$ RT 3.09 min
52		8-chloro-1-[3-(5-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.3mg (22%)	m/z 515 $[MH]^+$ RT 3.28 min
53		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
54		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
55		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
56		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

57		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
58		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
59		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
60		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
61		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
62		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

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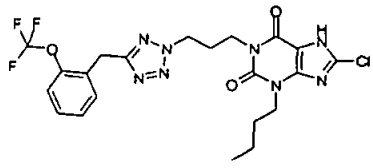
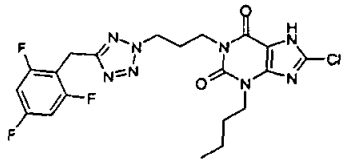
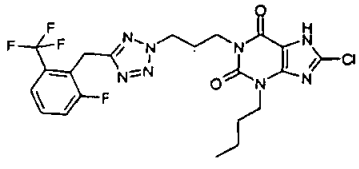
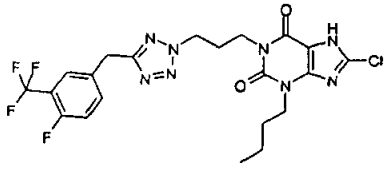
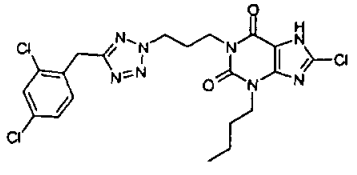
63		3-butyl-8-chloro-1-{3-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	32.8mg (31%)	m/z 527 $[MH]^+$ RT 3.51 min
64		3-butyl-8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20.7mg (21%)	m/z 497 $[MH]^+$ RT 3.35 min
65		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
66		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
67		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 20: 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

^1H 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 23 : 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 24: ^{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). 68

Example 27: ^{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 28: ^{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 29: ^{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 30: 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 31: ^{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 32: 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 33: 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 48: 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 51: 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 52: ^{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).

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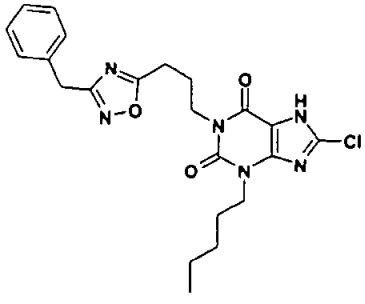
Example 59: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.6Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.17 (s, 2H), 4.24 (t, 2H, J=7.5Hz), 4.71 (t, 2H, J=7.3Hz), 7.00-7.14 (m, 3H), 13.07 (bs, 1H).

Example: 61: ^{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 64: 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 68 : 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

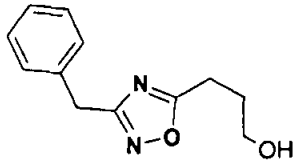


A solution of 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (88mg, 0.4mmol) in THF (4ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.34mmol) and PPh_3 (115mg, 0.44mmol) under nitrogen. DBAD (101mg, 0.44mmol) was added in one portion and the 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).

70

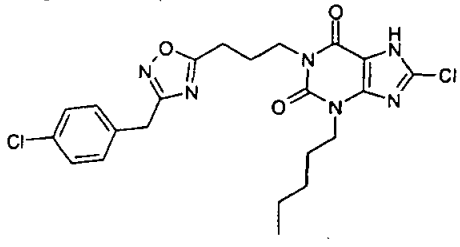
b) 3-[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol



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.

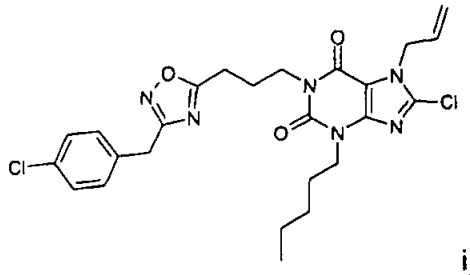
Example 69 : 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

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



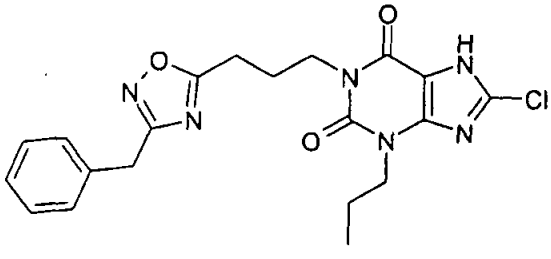
i)

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 70 : 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

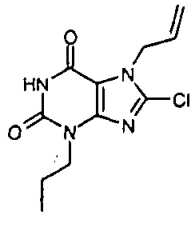


A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.74mmol) in THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (195mg, 0.89mmol) and PPh_3 (254mg, 0.96mmol). DBAD (223mg, 0.96mmol) was added in one portion and the mixture was left 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.

^1H 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

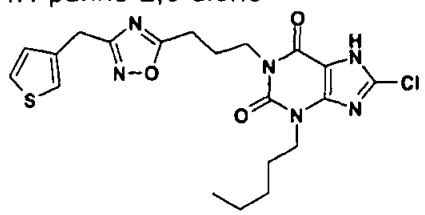


A mixture of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.6mmol), 1-iodopropane (1.2g, 6.9mmol) and sodium carbonate (0.9g, 8.5mmol) in DMF (40ml) was heated at 50°C for 18h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (60ml) and extracted 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 $[MH]^+$.

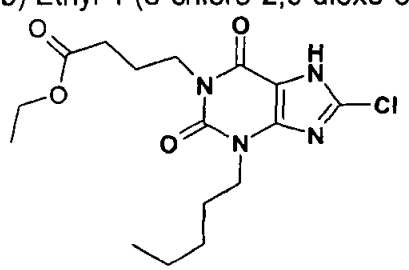
Example 71: 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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.

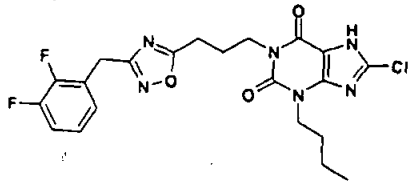
b) Ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



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 72 : 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

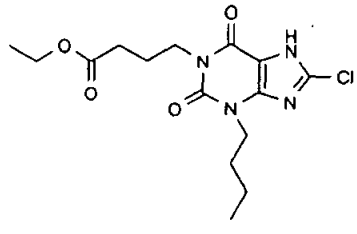


2,3-Difluorophenylacetonitrile (23mg, 0.15mmol) was dissolved in EtOH (1ml). Hydroxylamine hydrochloride (14mg, 0.20mmol) was added, followed by water (0.5ml) and potassium carbonate (41mg, 0.3mmol). The mixture was heated at reflux overnight and then cooled and partitioned between EtOAc and brine. The 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).

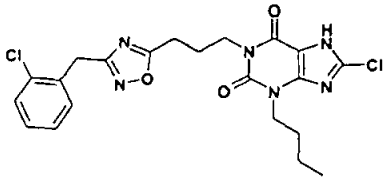
b) Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



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).

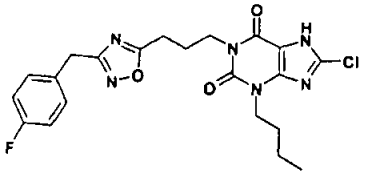
LC/MS: m/z 357 $[MH]^+$, RT 3.06min.
^{1}H NMR (d^4 MeOH) 0.96 (3H, t, J = 7Hz), 1.33-1.42 (2H, m), 1.64-1.74 (2H, m), 2.12-2.21 (2H, m), 2.95 (2H, t, J = 8Hz), 3.99 (2H, t, J = 7Hz), 4.03 (2H, s), 4.11 (2H, t, J = 7Hz), 7.03-7.21 (3H, m).

Example 73 : 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



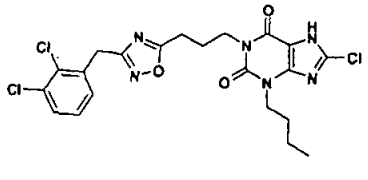
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1Z)-2-(2-chlorophenyl)-*N*-hydroxyethanimidamide (30mg, 0.18mmol; Entry **1**, table 7) were heated in EtOH (0.75ml) with 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) at 140°C for 10min. The mixture 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.
^{1}H 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 74 : 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 (1Z)-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.

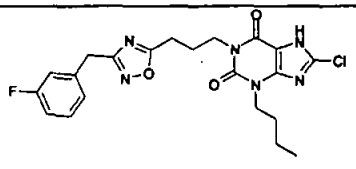
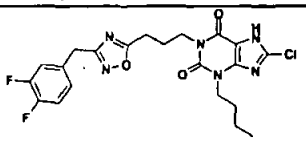
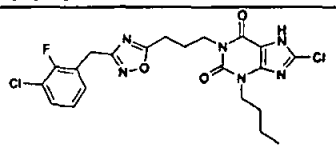
Example 75 : 3-Butyl-8-chloro-1-{3-[3-(2,3-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

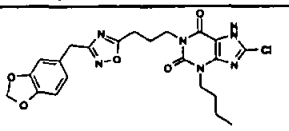
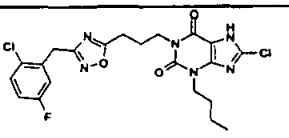
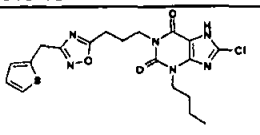
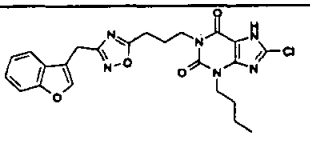
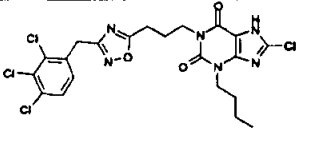
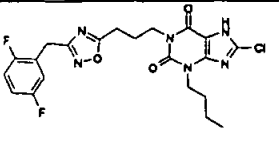


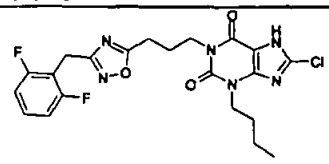
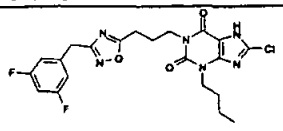
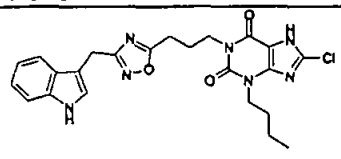
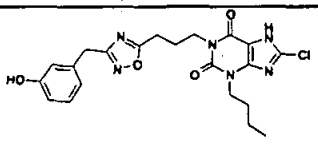
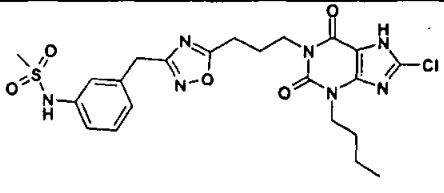
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1Z)-2-(2,3-dichlorophenyl)-*N*-hydroxyethanimidamide (36mg, 0.165mmol; Entry **3**, Table 7) and 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) were heated together in EtOH (0.75ml) in the microwave 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 75, using the appropriate amidoxime, (with the exceptions that for Example **87** (Table 4) during workup the pH was adjusted to 5 prior to extraction with EtOAc; and in the case of Example **88** (Table 4) the crude product was stirred for 18h with EtOH (1ml) and 2M NaOH (0.5ml) and Example **89** (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 :
76	 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
77	 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
78	 3-butyl-8-chloro-1-{3-[3-(3-chloro-2-fluorobenzyl)-1,2,4-oxadiazol-5-	**6**	33	32.3	m/z 495 $[MH]^+$ RT 3.55 min

	yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione				
79	 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
80	 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
81	 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
82	 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
83	 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
84	 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-	**16**	31	34.8	m/z 479 $[MH]^+$ RT 3.35 min

	dione				
85	 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
86	 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
87	 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
88	 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
89	 *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

NMR details for selected examples from Table 4:

Example 76: 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 77: 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).

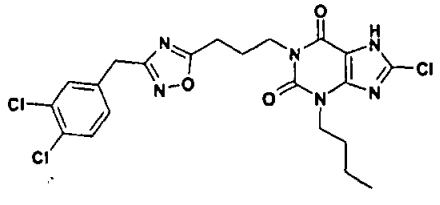
Example 79: 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.58-1.68 (m, 2H), 1.98-2.09 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.88-3.95 (m, 4H), 3.99 (t, 2H, J = 7Hz), 5.98 (s, 2H), 6.70-6.86 (m, 3H).

Example 87: 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 88: 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 89: *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).

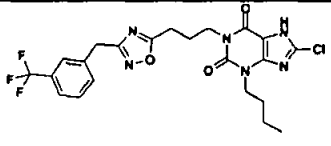
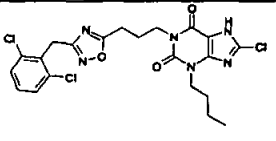
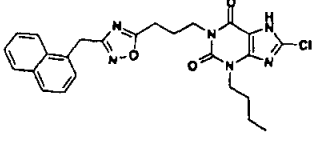
Example 90: 3-Butyl-8-chloro-1-(3-{3-[(3,4-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

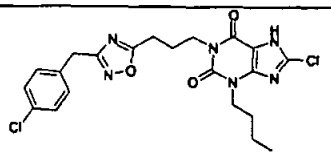
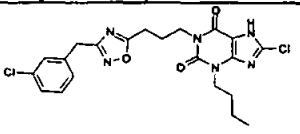
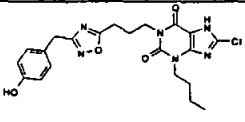
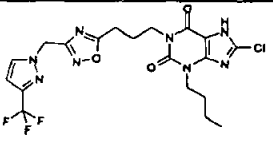
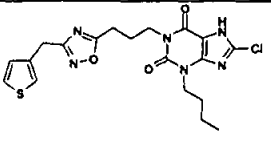


Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (71mg, 0.2mmol), (1*Z*)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (48mg, 0.22mmol) and 21% by wt. ethanolic sodium ethoxide (0.111ml, 0.3mmol) were heated together in EtOH (1ml) in the microwave reactor at 140°C for 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 90, using the appropriate amidoxime (with the exception that for Example **91** , 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:
91	 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
92	 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
93	 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

94	 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*Z*)-2-(4-chlorophenyl)-*N*-hydroxyethanimidamide	41	35.6	m/z 477 $[MH]^+$ RT 3.60 min
95	 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	(1*Z*)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide	41	39.4	m/z 477 $[MH]^+$ RT 3.64 min
96	 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*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide	36	53.5	m/z 459 $[MH]^+$ RT 3.08 min
97	 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*Z*)-*N*-hydroxy-2-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanimidamide	46	58.1	m/z 501 $[MH]^+$ RT 3.33 min
98	 3-butyl-8-chloro-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-(3-thienyl)ethanimidamide	34	32.6	m/z 449 $[MH]^+$ RT 3.31 min

NMR details for selected examples from Table 5

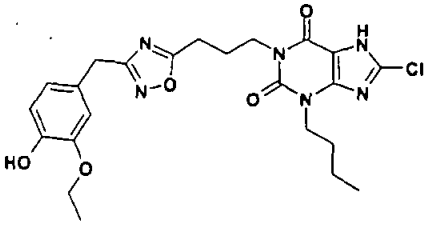
Example 91: ^{1}H NMR (d^6 DMSO) 0.88 (3H, t, J = 7Hz), 1.24-1.33 (2H, m), 1.56-1.65 (2H, m), 1.98-2.06 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.97 (2H, t, J = 7Hz), 4.14 (2H, s), 7.52-7.70 (4H, m).

Example 94: 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 96: 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 97: 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).

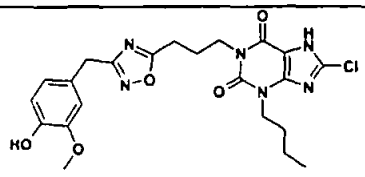
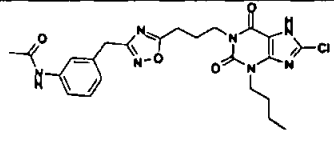
Example 99 : 3-Butyl-8-chloro-1-[3-(3-{[3-(ethyloxy)-4-hydroxyphenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



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 99, using the appropriate amidoxime (with the exception that for Example **100** (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

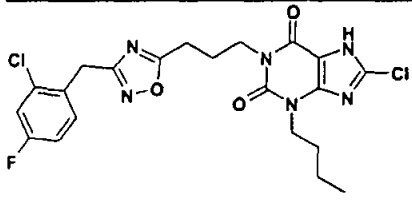
Example	Structure	Amidoxime (see table 7)	Wt of aldoxime mg	Yield mg	LC/MS:
100	 3-butyl-8-chloro-1-[3-(3-{[4-hydroxy-3-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	**12**	32	19.3	m/z 489 $[MH]^+$ RT 2.98 min
101	 *N*-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]acetamide	**14**	34	23.6	m/z 500 $[MH]^+$ RT 2.94 min

NMR details for selected examples from Table 6

Example 101: *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 102: 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 103 : 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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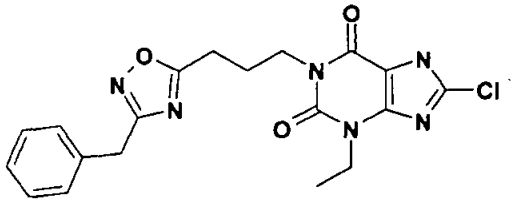
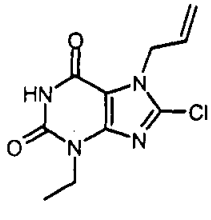
a) 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



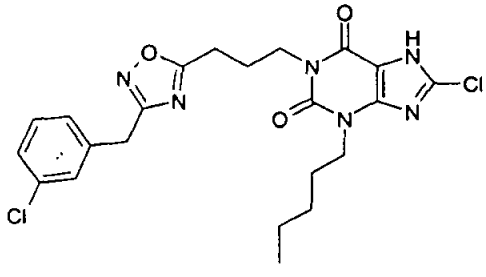
A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.59mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (154mg, 0.71mmol) and triphenylphosphine (200mg, 0.76mmol). DBAD (162mg, 0.71mmol) was added in one portion 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
^{1}H 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



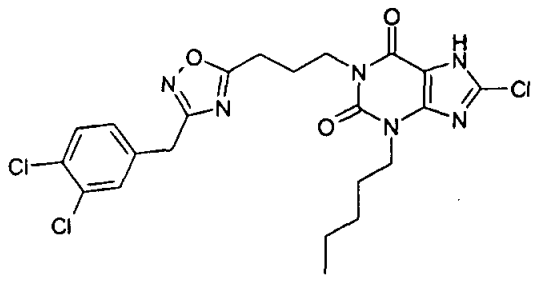
A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 0.044mol) in anhydrous DMF (100ml) was treated with iodoethane (5.4ml, 0.068mol) and Na_2CO_3 (4.9g, 0.046mol). The reaction mixture was left to stir at rt under nitrogen for 2 days. Iodoethane (0.35ml, 0.0044mol) was added 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 104 : 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



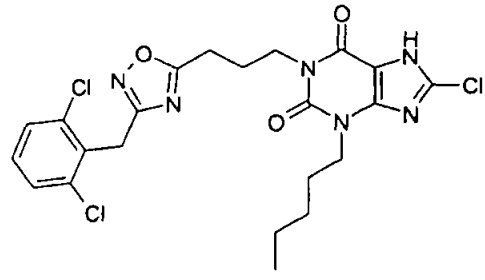
Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1*Z*)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide (38mg, 0.21mmol). The reaction was heated in 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.
^1H 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 105: 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



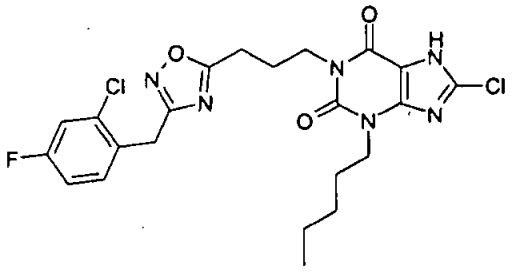
Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1Z)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (46mg, 0.21mmol). The reaction was heated 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 106 : 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 107 : 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



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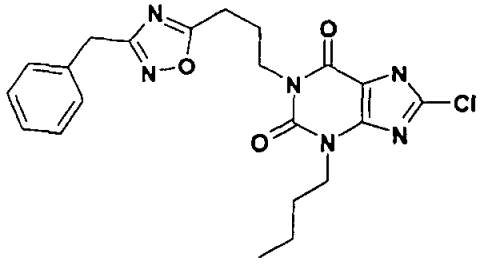
Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1Z)-2-(2-chloro-4-fluorophenyl)-*N*-hydroxyethanimidamide (42mg, 0.21mmol). The reaction was heated 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 108 : 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).

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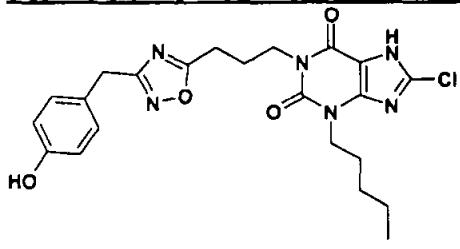
Example 109: 8-Chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

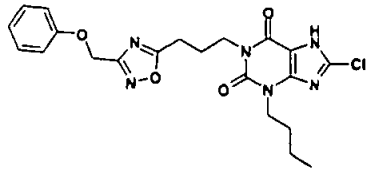


Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (29mg, 0.078mmol) and (1*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide (14mg, 0.084mmol) were heated in EtOH (1ml) with 21% ethanolic sodium ethoxide (0.043ml, 0.117mmol) under microwave irradiation at 140°C for 10min. 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 110: 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

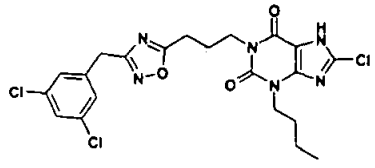


To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (26mg, 0.073mmol) and (1*Z*)-*N*-hydroxy-2-(phenyloxy)ethanimidamide hydrochloride (16mg, 0.079mmol) in EtOH (1ml) was added 21%wt. ethanolic sodium ethoxide solution (0.068 ml, 0.183mmol) and the mixture was heated under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

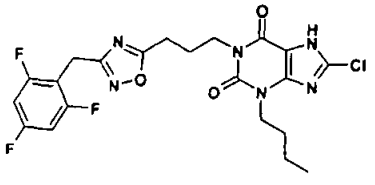
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 8Hz), 1.22-1.36 (m, 2H), 1.57-1.68 (m, 2H), 2.02-2.14 (m, 2H), 3.00 (t, 2H, J = 8Hz), 3.90 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 5.18 (s, 2H), 6.95-7.35 (m, 5H).

Example 111: 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.

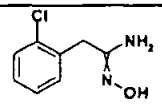
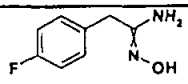
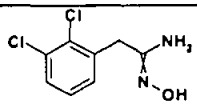
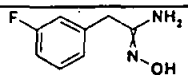
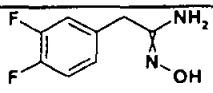
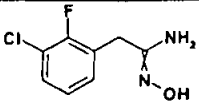
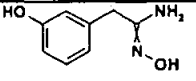
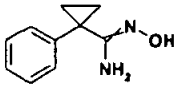
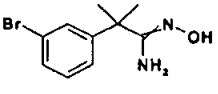
Example 112: 3-Butyl-8-chloro-1-(3-{3-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

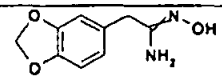
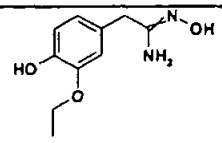
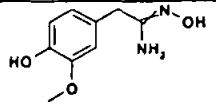
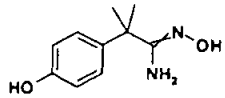
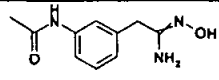
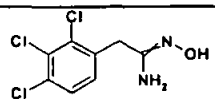
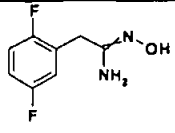
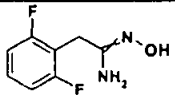
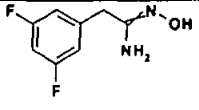
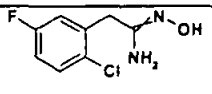


Similarly prepared starting from (1*Z*)-*N*-hydroxy-2-(2,4,6-trifluorophenyl)ethanimidamide (119mg, 0.58mmol; Entry 24, Table 7) in a yield of 135mg.
LC/MS: m/z 497 $[MH]^+$, RT 3.39min.
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, 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

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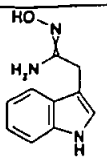
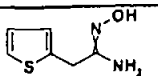
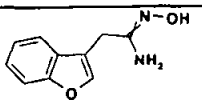
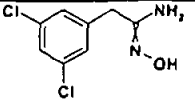
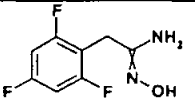
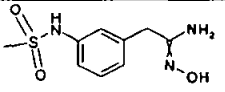
20		**(1Z)-*N*-hydroxy-2-(1*H*-indol-3-yl)ethanimidamide**	C	95	m/z 190 $[MH]^+$ RT 0.90 min
21		**(1Z)-*N*-hydroxy-2-(2-thienyl)ethanimidamide**	C	74	m/z 157 $[MH]^+$ RT 0.38 min
22		**(1Z)-2-(1-benzofuran-3-yl)-*N*-hydroxyethanimidamide**	C	87	m/z 191 $[MH]^+$ RT 1.46 min
23		**(1Z)-2-(3,5-dichlorophenyl)-*N*-hydroxyethanimidamide**	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

It should be noted that as used herein represents a double bond of undefined geometry.

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.

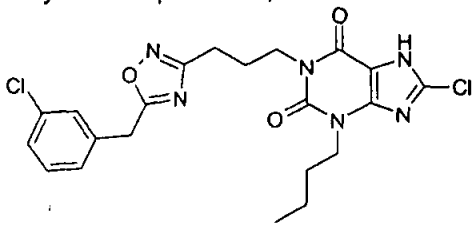
Method E
Similar to Method C except that the scale was 0.753mmol of nitrile.

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.

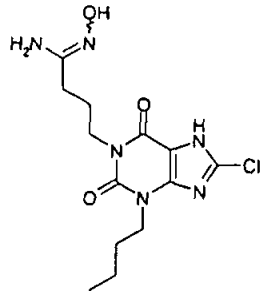
Example 113: 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

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



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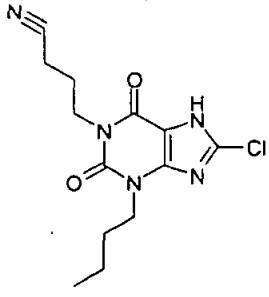
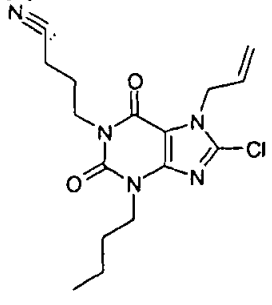
4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanenitrile (1g, 0.0032mol) was stirred in EtOH (3.5ml) and water (1.8ml). Hydroxylamine hydrochloride (344mg, 0.0049mol) and potassium carbonate (652mg, 0.0049mol) were added and the mixture heated at 80°C for 3 days. After cooling the 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.

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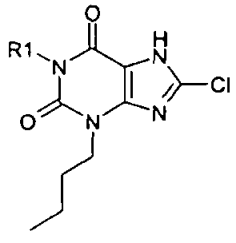
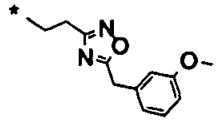
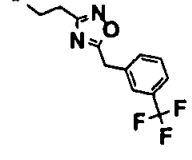
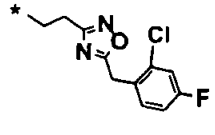
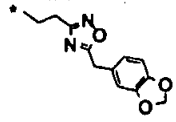
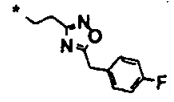
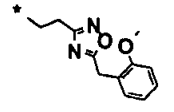
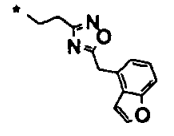
The following compounds (Table 8) were prepared using a method analogous to that for Example 113, from the corresponding acids and (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide.



Where * is used in the examples herein it indicates the attachment point of the R group to the xanthine core.

Table 8

Example		Compound: R1 =	Yield %	LC/MS:
114	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
115	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
116	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

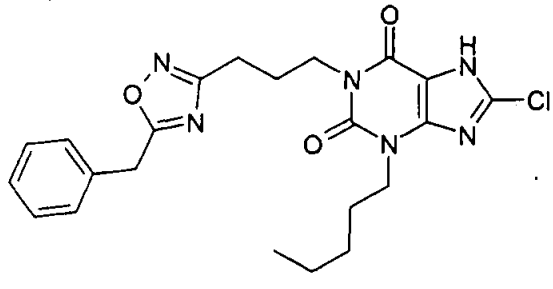
Example		Compound: R1 =	Yield %	LC/MS:
117	1-{3-[5-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione		27	m/z 487 $[MH]^+$ RT 3.3 min
118	3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		28	m/z 461 $[MH]^+$ RT 3.3 min
119	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
120	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 115: ^{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 121: 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-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.

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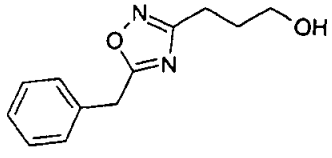
b) 3-[5-(Phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol



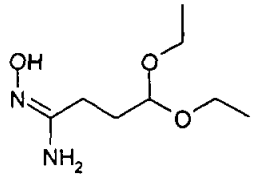
A mixture of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide (3.2g, 16.8mmol), ethyl phenylacetate (2.3ml, 14.4mmol) and sodium ethoxide (21% solution in EtOH, 6.4ml) was heated in a microwave at 140°C for 10min. The material was combined with that from a second reaction (using 1.2g of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide 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



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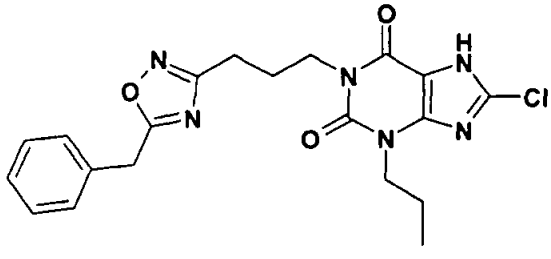
A mixture of 3-cynopropionaldehyde diethylacetal (6.12g, 39mmol), hydroxylamine hydrochloride (4.06g, 58.4mmol), potassium carbonate (10.76g, 77.9mmol) in water (20ml) and EtOH (40ml) was refluxed for 24h. The mixture was allowed to cool and then partitioned between water and EtOAc. The organic layer 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 122 : 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.
^{1}H 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).

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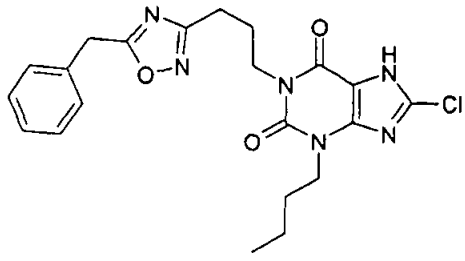
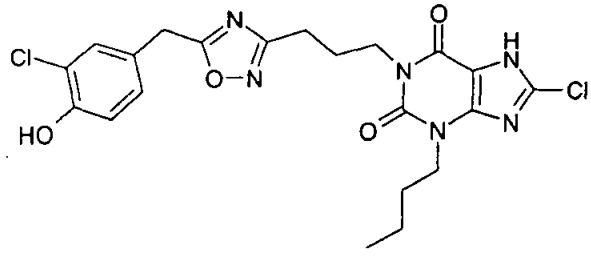
Example 123 : 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



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 124 : 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

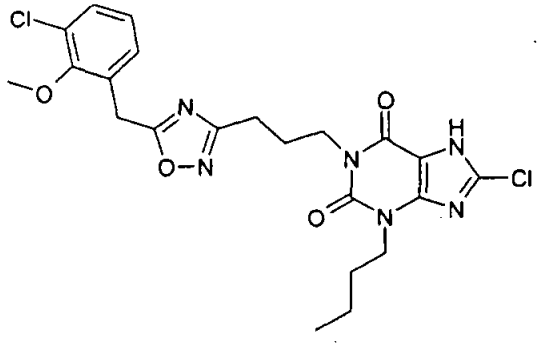


A solution of 3-chloro-4-hydroxyphenylacetic acid (24mg, 0.13mmol) in DMSO (1ml) was treated with CDI (21mg, 0.13mmol) and left to react for 30min. (1Z)-4-(3-Butyl-8-

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.

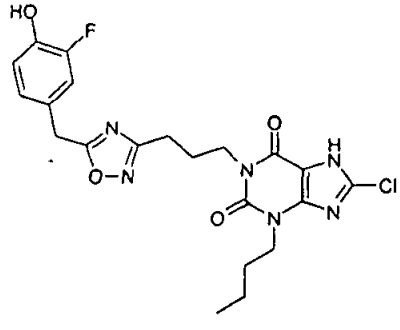
Example 125 : 3-Butyl-8-chloro-1-[3-(5-{[3-chloro-2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



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 126 : 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

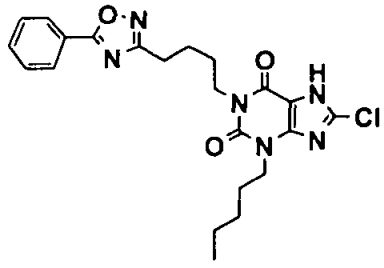


A mixture of (3-fluoro-4-hydroxyphenyl)acetic acid (27mg, 0.16mmol) in DMF (1.5ml) was treated with CDI (26mg, 0.16mmol) and left to react for 45min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (60mg, 0.18mmol) was added and the mixture heated in 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.

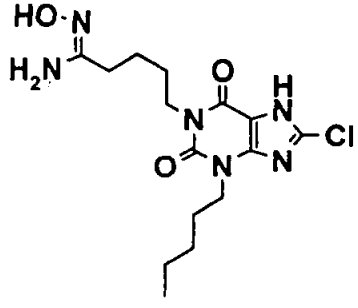
Example 127 : 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

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.
^1H 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).

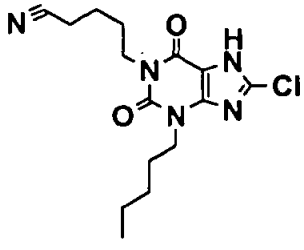
b) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide



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

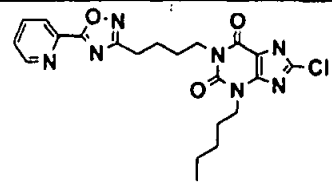
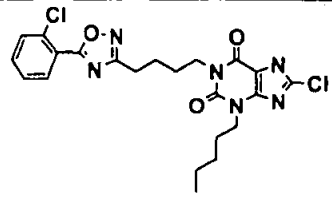
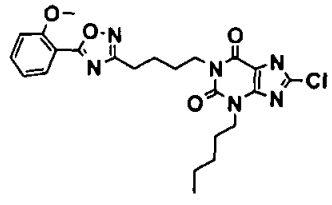
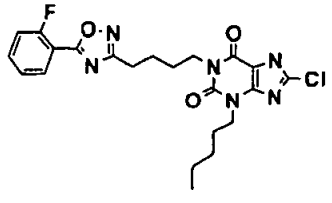


A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (4.0g, 13.5mmol) in DMF (100ml) was treated with caesium carbonate (4.83g, 14.8mmol) and 5-bromopentanenitrile (1.73ml, 14.8mmol). The mixture was heated at 50°C in a nitrogen atmosphere for 19h and then cooled. The mixture 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 127 (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:
128		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
139		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
130		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
131		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

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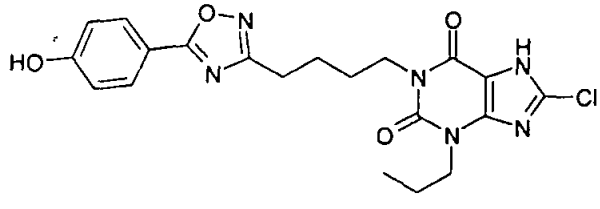
In addition Example **128**, 8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione has the following spectral data: ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3H, J = 6.9Hz), 1.75 (m, 4H), 1.89 (m, 6H), 2.92 (t, 2H, J = 7.1Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H), 13.40 (br s, 1H).

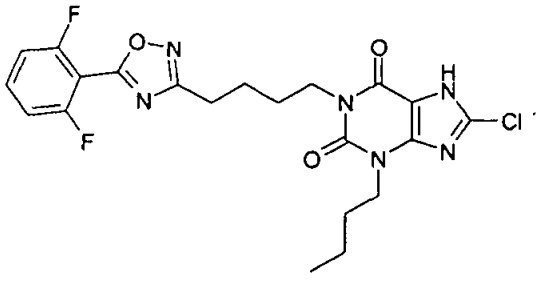
Example 132: 8-Chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



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 128(b)) was added and the

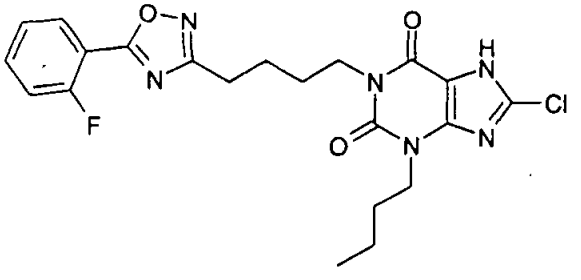
mixture was stirred at 90°C for 2h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated under high vacuum to give the title compound as a white solid (7mg, 11%).
LC/MS: m/z 443 $[MH]^+$, RT 3.28min.

Example 133 : 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



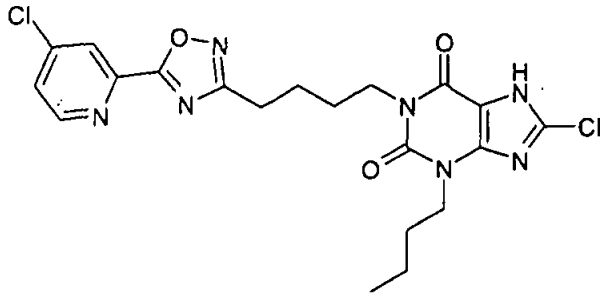
2,6-Difluorobenzoic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction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

Example 134 : 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 135 : 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

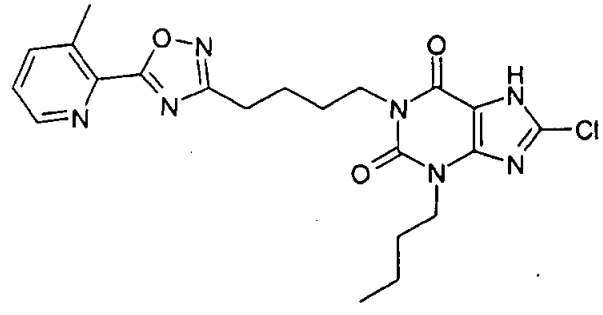


4-Chloro-2-pyridinecarboxylic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h.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

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

^{1}H 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 136 : 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

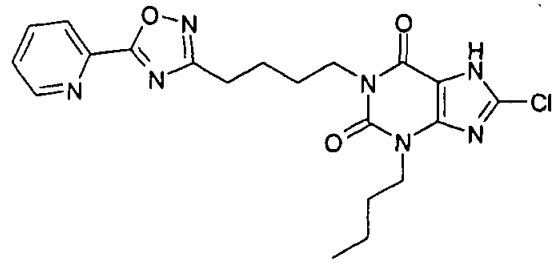


3-Methyl-2-pyridinecarboxylic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h.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

LC/MS: m/z 458 $[MH]^+$, RT 3.13min.

Example 137 : 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

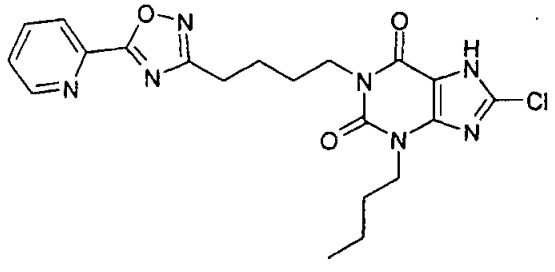


2-Pyridinecarboxylic acid (31mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.5ml) at rt for 1h. A solution of (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the mixture was stirred 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).

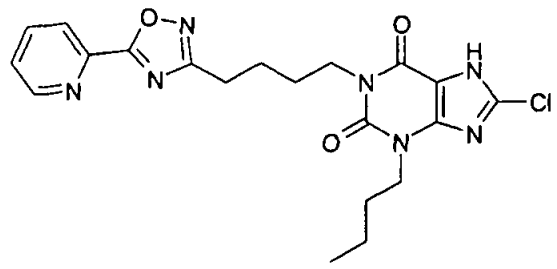
Method B



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.

Methods A, B and C of Example 137 produce 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.

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).

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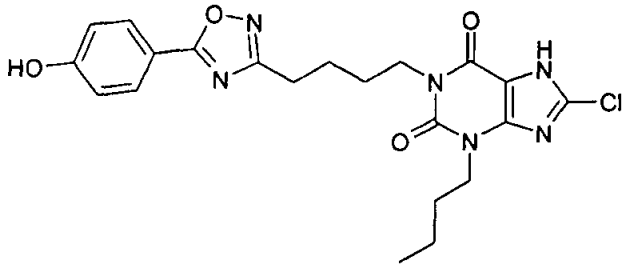
If the form of the sample taken at * is shown to be other than pure Form 1, then **the batch is reheated to 35-45°C and agitated at this temperature for a minimum of 1hour. The thin suspension is then cooled to 20-25°C and held at this temperature for a minimum of 12hours. The suspension thus formed 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.

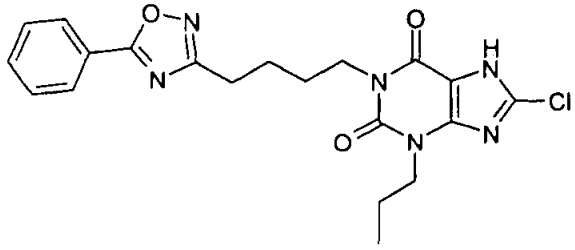
Example 138: 3-Butyl-8-chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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

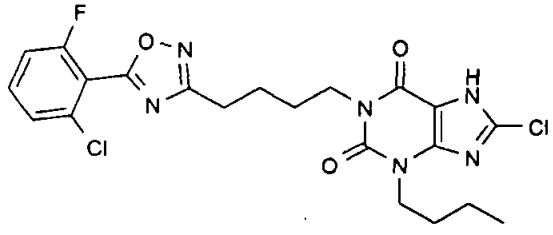
and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP to give the title compound as a white solid (5mg, 4%).
LC/MS: m/z 459 $[MH]^+$, RT 3.24min.

Example 139 : 8-Chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



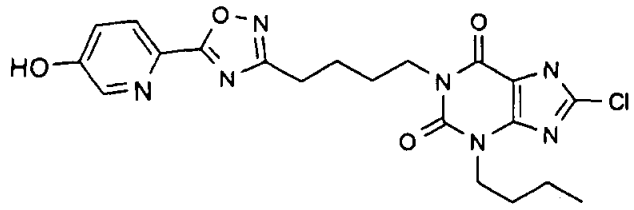
Benzoic acid (9mg, 0.074mmol) and CDI (13mg, 0.081mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (28mg, 0.081mmol) was added and the mixture was stirred at 80°C for 4h. The mixture was purified 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 140: 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. (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 (6.4mg, 5%).
LC/MS: m/z 495 $[MH]^+$, RT 3.58min.

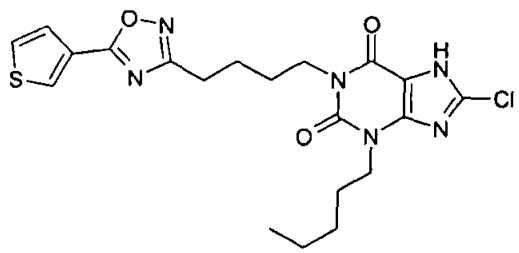
Example 141: 3-Butyl-8-chloro-1-{4-[5-(5-hydroxy-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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.

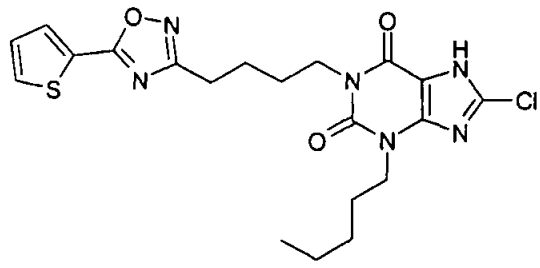
Example 142: 8-Chloro-3-pentyl-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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%).

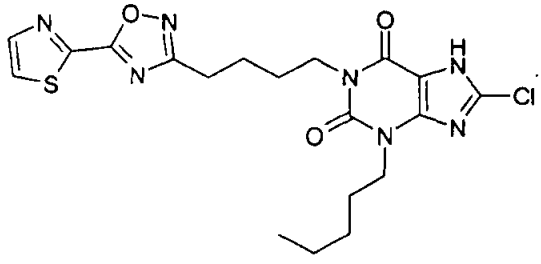
LC/MS: m/z 463 $[MH]^+$, RT 3.6min.

Example 143 : 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.

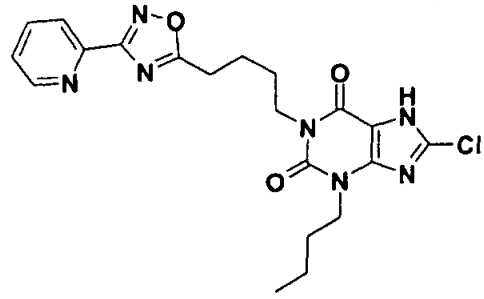
Example 144: 8-Chloro-3-pentyl-1-{4-[5-(1,3-thiazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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 145: 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



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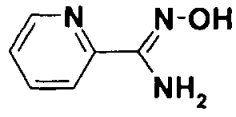
To a mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (120mg, 0.32mmol) and of N-hydroxy-2-pyridinecarboximidamide (50mg, 0.36mmol) in EtOH (2ml) was added a 21% (w/v) solution of sodium ethoxide in EtOH (0.225ml, 0.62mmol) and then heated in a sealed vial in 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.

1H 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



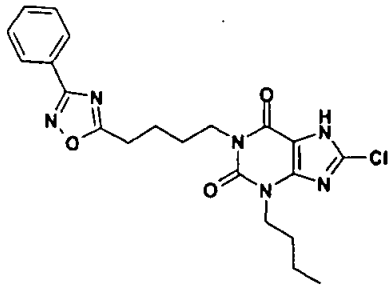
To a mixture of 2-pyridinecarbonitrile (3g, 29mmol) and potassium carbonate (4.1g, 30mmol)in EtOH (30ml) was added water (15ml) and, cautiously, hydroxylamine hydrochloride (2.9g, 42mmol) and then heated at reflux for 6h, cooled and evaporated to dryness. The residue was treated with water (100ml) and 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 146: 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



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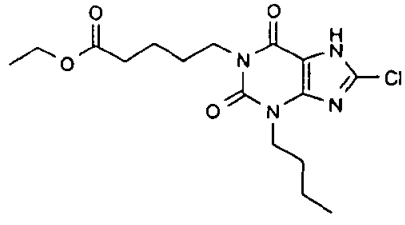
Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (74mg, 0.2mmol) and benzamidoxime (30mg, 0.22mmol) were suspended in dry EtOH (1ml) and ethanolic sodium ethoxide (21% by wt., 0.111ml, 0.3mmol) was added. The mixture was gently warmed until solids were dissolved and then 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).

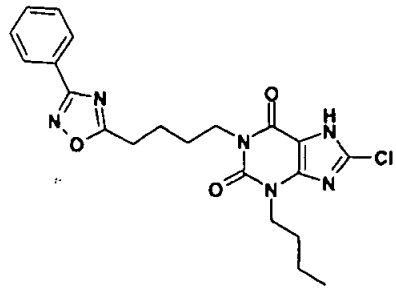
b) Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



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

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



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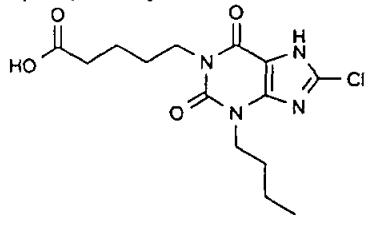
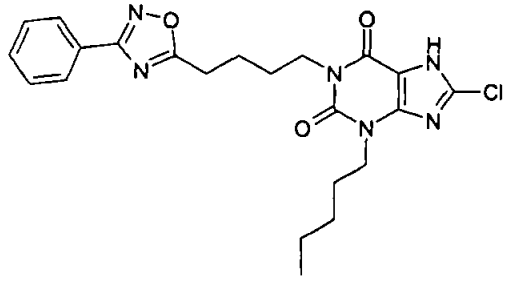
CDI (0.98g, 6.1mmol) was added to a solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (1.89g, 5.5mmol) in DMF (15ml) and stirred under nitrogen for 1.5h. Benzamidoxime (0.91g, 6.1mmol) was added and the mixture stirred at 110°C overnight. The reaction mixture 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.
^1H 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 147 : 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.

^1H 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).

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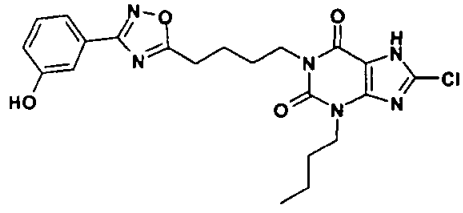
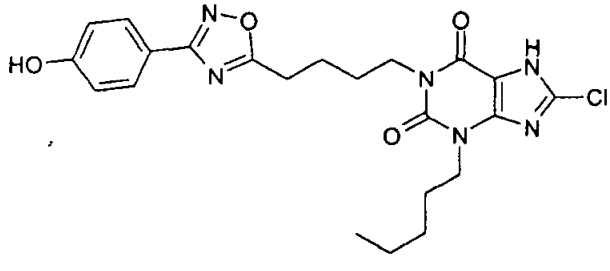
Example 148: 3-Butyl-8-chloro-1-{4-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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 149 : 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.

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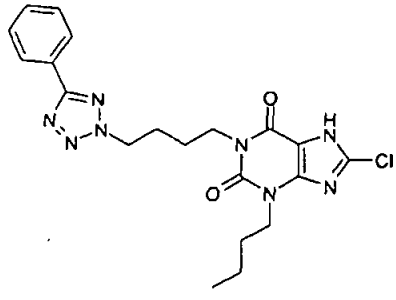
Example 150: 3-Butyl-8-chloro-1-[4-(5-phenyl-2*H*-tetrazol-2-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

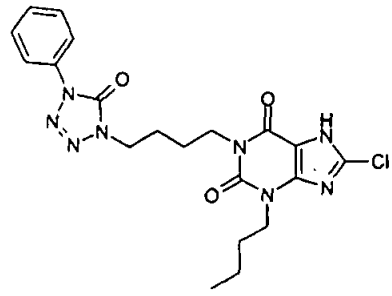


A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 5-phenyl-1*H*-tetrazole (20mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed 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.

^1H 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 151 : 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

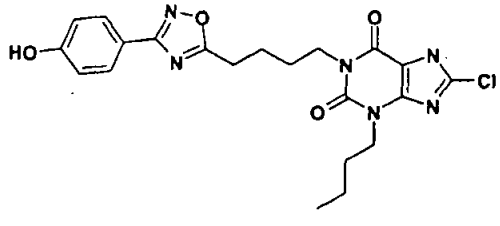


A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 1-phenyl-1,2-dihydro-5*H*-tetrazol-5-one (23mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture 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.

^1H 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 152: 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

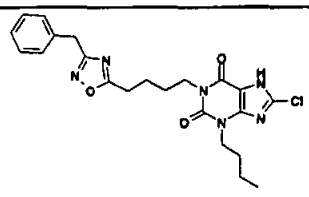
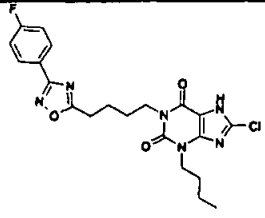
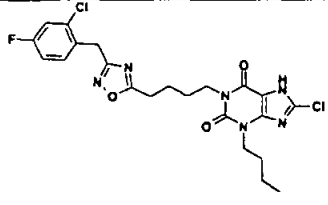


A stirred solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (100mg, 0.29mmol) in DMF (4ml) was treated with CDI (52mg, 0.32mmol). After 1h, *N*,4-dihydroxybenzenecarboximidamide was added and the mixture heated at 100°C for 6h. On cooling, the reaction mixture 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).

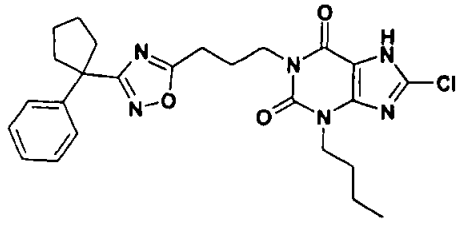
LC/MS: m/z 459 $[MH]^+$, RT 3.27min.

The following compounds (**Table 10**) were prepared using a method analogous to that for **Example 146**, using the appropriate amidoxime.

Table 10

Example	Structure	Yield (mg)	LC/MS
153	 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
154	 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
155	 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

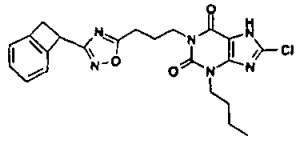
Comparative Example A: 3-Butyl-8-chloro-1-{3-[3-(1-phenylcyclopentyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



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

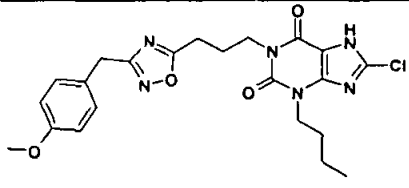
the microwave reactor for 10min. The mixture was then partitioned between ethyl acetate and 2M HCl, the organic phase evaporated and the product purified by MDAP to give the title compound as a solid (29.1mg).
LC/MS: m/z 497 $[MH]^+$, RT 3.76min.

Example 156: 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



This compound was prepared using a method analogous to that for comparative example A, using the appropriate amidoxime.
Yield (mg): 28.8
LC/MS: m/z 455 $[MH]^+$, RT 3.43min.

Example 157: 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

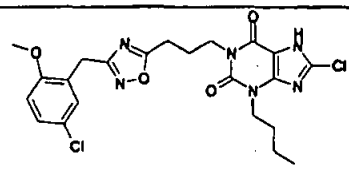
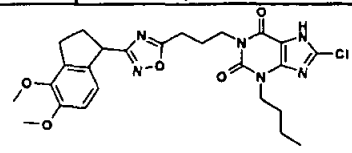
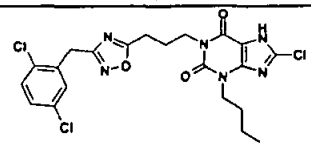
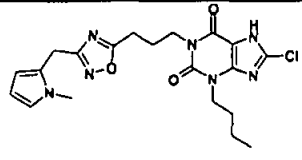
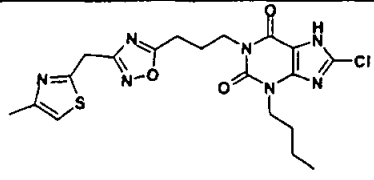


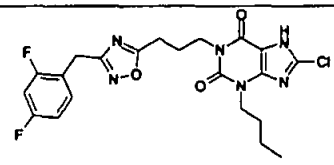
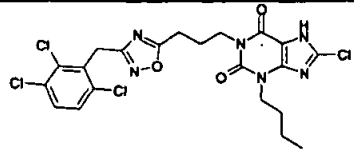
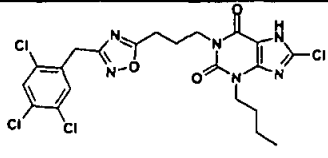
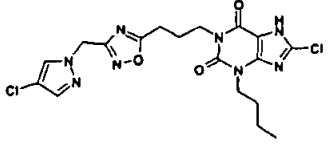
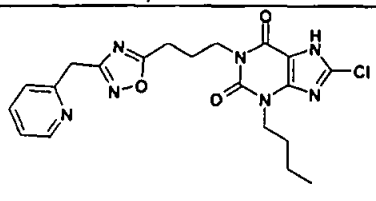
Prepared using a method analogous to that used for **Example 93**, except an additional final purification step using HPLC was employed. Yield 6.0mg.
LC/MS: m/z 473 $[MH]^+$, RT 3.27min.

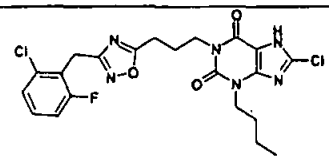
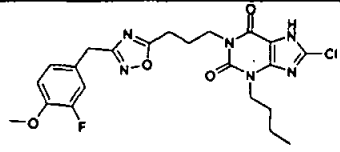
The following compounds (**Table 11**) were prepared using a method analogous to that for **Example 75**, using the appropriate amidoxime [with the exception that for **Example 162** the crude product was stirred in EtOH (0.75ml) with 2M NaOH (0.5ml) overnight prior to the usual EtOAc/HCl workup and MDAP; **Example 164** was isolated as an impurity from the preparation of **Example 165** and was separated from it by HPLC; for **Examples 166**, and **167** the pH during aqueous workup was adjusted to approximately 5 prior to extraction; additionally **Example 167** was further purified by silica SPE (2g, DCM-MeOH 40:1then 20:1) after MDAP].

Table 11

Example	Structure	Yield	LC/MS

		(mg)	
158	 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
169	 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
160	 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
161	 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
162	 3-butyl-8-chloro-1-(3-{3-[(4-methyl-1,3-thiazol-2-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	15.5	m/z 464 $[MH]^+$ RT 2.94min

163	 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
164	 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
165	 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
166	 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
167	 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

168	 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
169	 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

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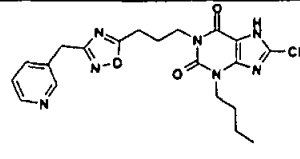
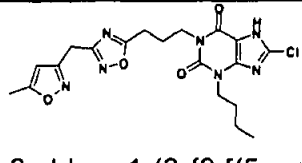
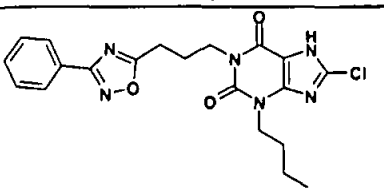
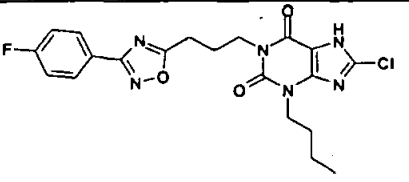
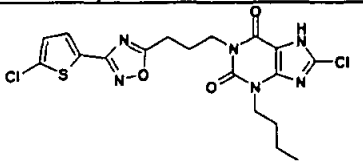
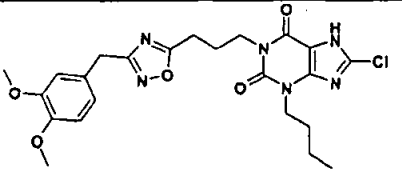
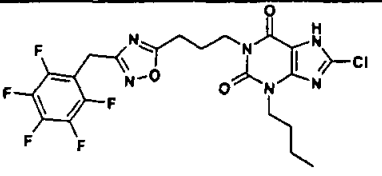
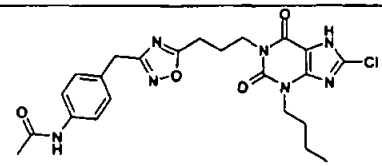
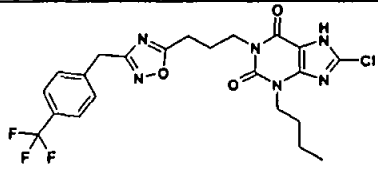
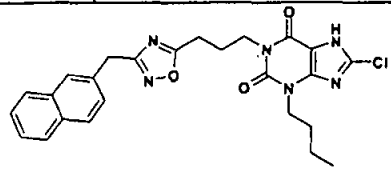
The following compounds (**Table 12**) were prepared using a method analogous to that for **Example 90**, using the appropriate amidoxime [with the exception that **Example 170** was conducted on half the scale of **Example** 90 and during workup the aqueous phase was neutralised prior to extraction; **Example 171** was conducted on half the scale of **Example 90** and the crude product stirred with 2M NaOH (0.5ml) in EtOH (1ml) for 5h prior to workup and MDAP; for **Example 175** 0.185ml (0.5mmol) of 21% NaOEt was used].

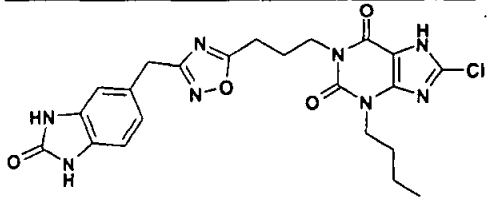
Table 12

Example	Structure	Yield (mg)	LC/MS
170	 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
171	 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-	7.2	m/z 448 [MH]$^+$ RT 3.13min

	dione		
172	 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
173	 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
174	 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
175	 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
176	 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

177	 *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
178	 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
179	 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 180: 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

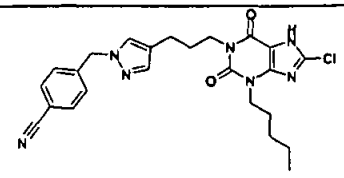
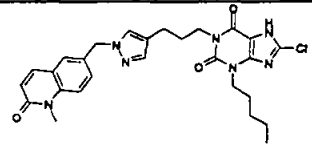
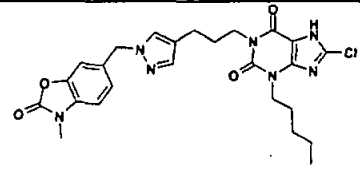
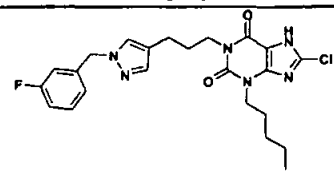


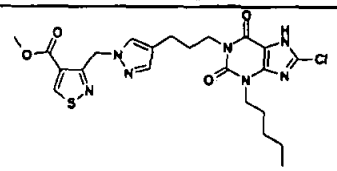
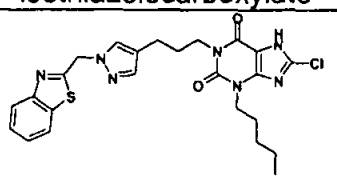
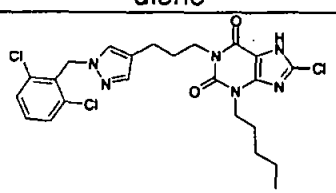
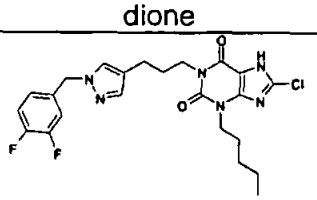
Synthesised by a method analogous to that for **Example 99** with the exception that a further 2 equivalents of 21% sodium ethoxide (0.11ml) was used, the extra heating time was 20min. and the product was isolated by filtration followed by trituration with hot MeOH. Yield 14.5mg.
LC/MS: m/z 499 $[MH]^+$, RT 2.78min.

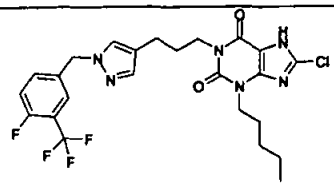
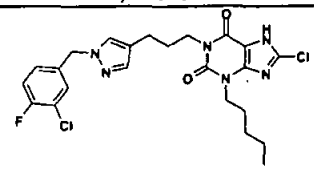
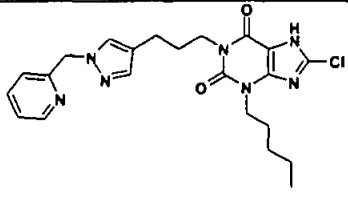
The following compounds (**Table 13**) were prepared by a method analogous to that for **Example 1** [with the exception that **Examples 181-186** were all synthesised on a scale starting from 50mg of 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione; **Examples 184, 186, 188, 189 and 190** were

additionally purified by MDAP following aminopropyl SPE; **Example 185** was additionally purified by recrystallisation from MeOH following aminopropyl SPE; for **Example 191**, 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 184** solids which precipitated during workup were combined with the EtOAc extracts prior to SPE].

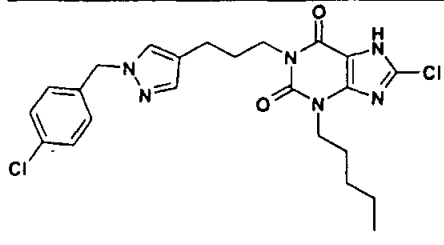
Table 13

Example	Structure	Yield (mg)	LC/MS
181	 4-({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	36.0	m/z 480 $[MH]^+$ RT 3.24min
182	 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
183	 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
184	 8-chloro-1-(3-{1-[(3-	26.2	m/z 473 $[MH]^+$ RT 3.38min

	fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione		
185	 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
186	 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
187	 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
188	 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

189	 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
190	 8-chloro-1-(3-{1-[(3-chloro-4-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	27.0	m/z 507 $[MH]^+$ RT 3.73min
191	 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 192: 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



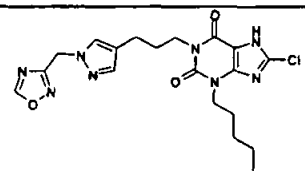
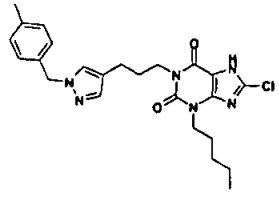
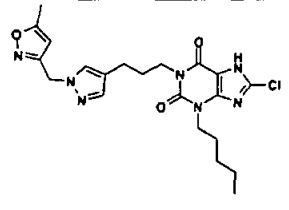
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.123mmol) in dry DMF (1.5ml) was stirred with sodium carbonate (75mg, 0.708mmol) and 4-chlorobenzyl bromide (150mg, 0.73mmol) at 40°C for 18h. The mixture was partitioned between EtOAc and water, 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

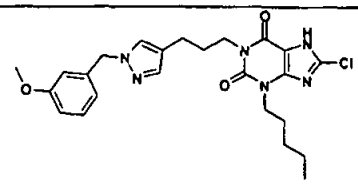
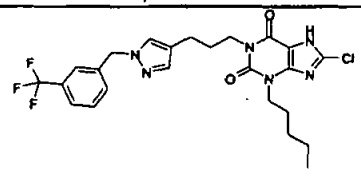
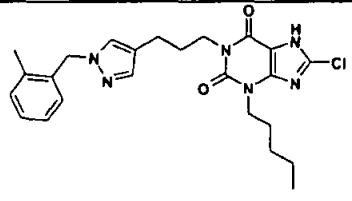
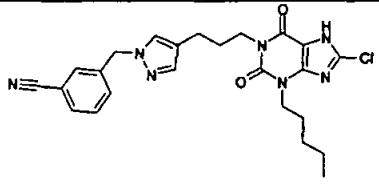
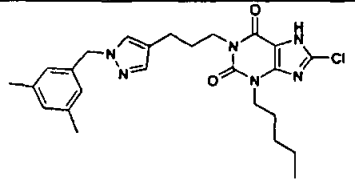
an oil (44mg). This was stirred in degassed, dry DMF (1ml) with tetrakis(triphenylphosphine)palladium(0) (19mg) and morpholine (0.072ml) under nitrogen for 6h. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated and purified by the usual aminopropyl SPE procedure. Yield 21.0mg.

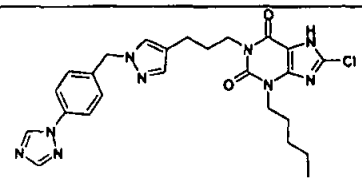
LC/MS: m/z 489 [MH^+], RT 3.59min.

The following compounds (**Table 14**) were prepared by a method analogous to that for **Example 6** [with the exception that for **Example 193** 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 195** required additional purification by MDAP; **Example 200** required additional purification by recrystallisation from MeOH; **Example 201** required additional purification by trituration with MeOH].

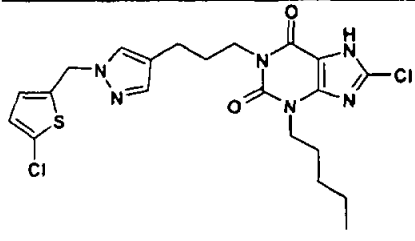
Table 14

Example	Structure	Yield (mg)	LC/MS
193	 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
194	 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
195	 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

196	 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
197	 8-chloro-3-pentyl-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	47.0	m/z 523 $[MH]^+$ RT 3.61min
198	 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
199	 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
200	 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

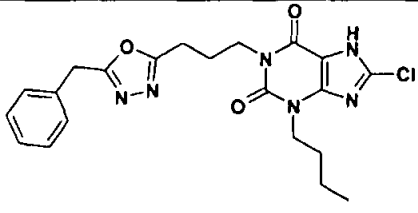
201	 8-chloro-3-pentyl-1-[3-(1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	21.2	m/z 522 $[MH]^+$ RT 3.09min

Example 202 : 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 203: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

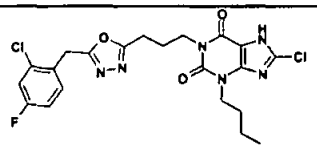
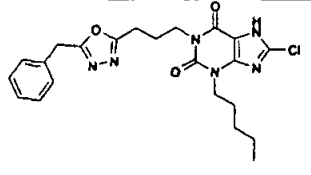
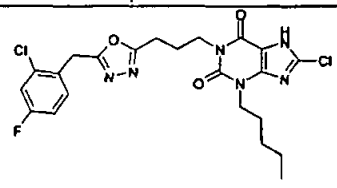


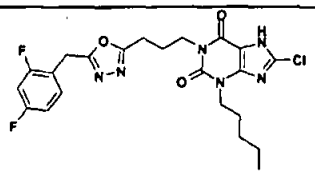
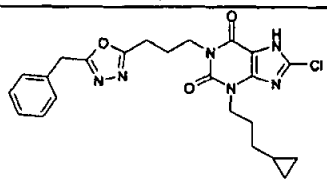
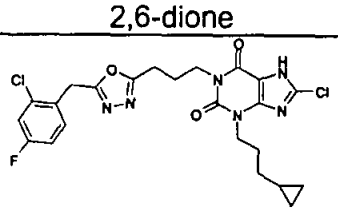
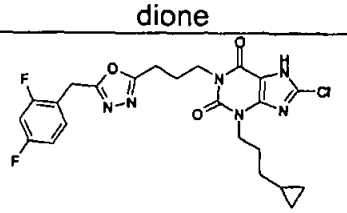
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg, 0.35mmol) in dry DMF (2ml) was added cesium carbonate (137mg, 0.42mmol) followed by a solution in dry DMF (1ml) of 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg, 0.42mmol). The mixture was stirred under nitrogen 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)

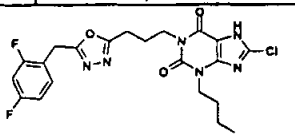
(81mg, 0.07mmol) and morpholine (0.305ml, 3.5mmol) were added and stirring was continued for 5h EtOAc and 2M HCl were added and the mixture stirred for 20min then filtered. The organic phase was separated and evaporated, and the product was purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1) 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 15**) were prepared by a method analogous to that for **Example 203**, with the exception that **Example 211** was further purified by HPLC.

Table 18

Example	Product structure	Xanthine precursor	Alkylating agent	Yield (mg)	LC/MS
204	 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
205	 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
206	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-	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

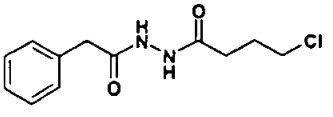
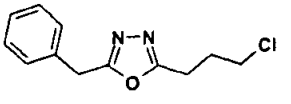
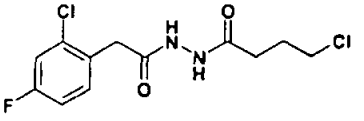
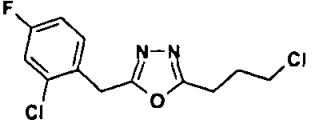
	yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione				
207	 8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (104mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl) methyl]-1,3,4-oxadiazole (111mg)	43	m/z 493 [MH]+ RT 3.40 min
208	 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
209	 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
210	 8-chloro-3-(3-cyclopropylpropyl)-1-(3-	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-	2-(3-chloropropyl)-5-[(2,4-difluorophenyl) methyl]-1,3,4-oxadiazole	49	m/z 505 [MH]+ RT 3.40

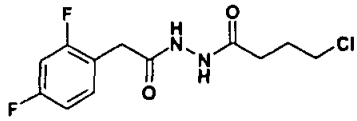
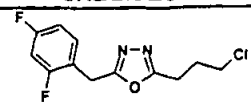
	{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	dione (108mg)	(111mg)		min
211	 3-butyl-8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (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 15:

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-	405	m/z 289 $[MH]^+$ RT 3.17min

	(3-chloropropyl)-1,3,4-oxadiazole		
 4-chloro-*N*'-[(2,4-difluorophenyl)acetyl]butanohydrazide	 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole	333	m/z 273 $[MH]^+$ RT 3.03min

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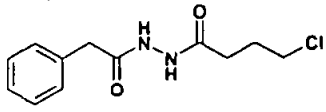
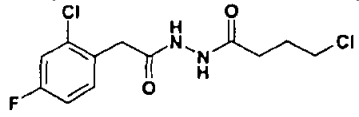
Preparation of 4-chloro-*N*'-(phenylacetyl)butanohydrazide



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



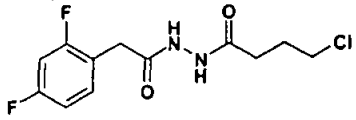
(i) A solution of 2-chloro-4-fluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 20min to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for a further 2h, the mixture was washed with 1M HCl then with aqueous $NaHCO_3$. A 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



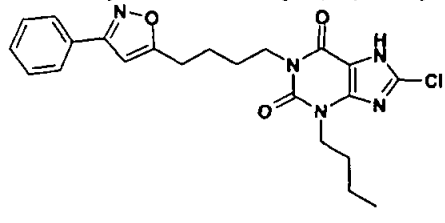
(i) A solution of 2,4-difluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 10min. to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for 1.5h the mixture was washed with 1M HCl then with aqueous $NaHCO_3$. The organic phase 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 212 : 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

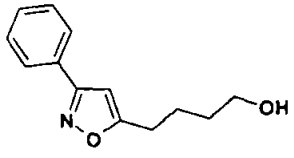
a) 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



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.

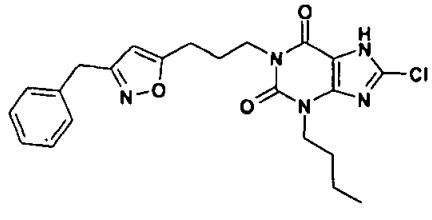
b) 4-(3-Phenyl-5-isoxazolyl)-1-butanol



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.

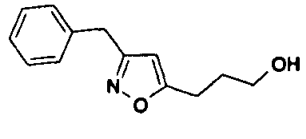
Example 213: 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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 213) 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.

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

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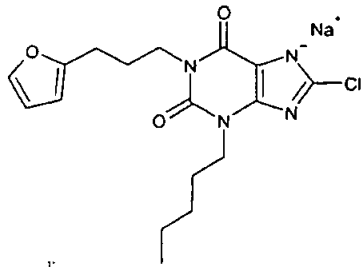
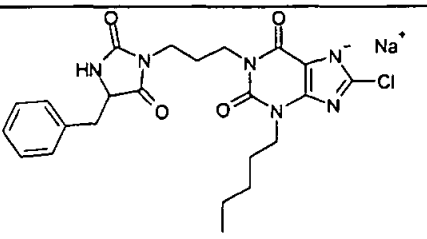
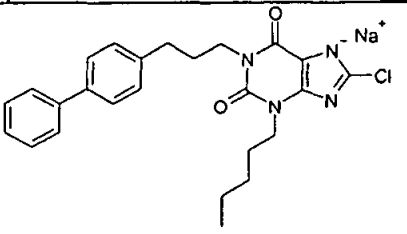


A GreenHouse™ tube equipped with a stirrer was charged with a 0.25ml aliquot of a 0.54M solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.13mmol) in THF. To the mixture was added 3-(2-furanyl)-1-propanol (21mg, 0.16mmol, 1.2eq) in THF (0.25ml), followed by a 0.25ml 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).

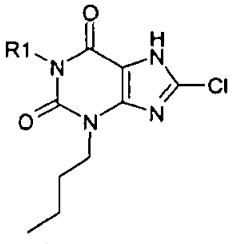
The following compounds (**Table 16**) were prepared by a method analogous to that for **Comparative Example B**.

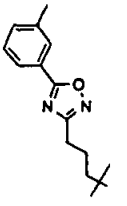
Table 16

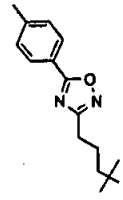
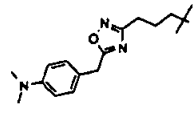
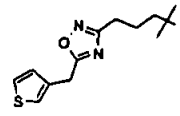
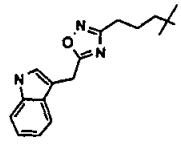
Example	Structure	Yield (mg)	LC/MS
214	 8-chloro-1-{3-[2,5-dioxo-4-(phenylmethyl)-1-imidazolidinyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	9	m/z 487 $[MH]^+$ RT 3.15min
215	 1-[3-(4-biphenylyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	19	m/z 451 $[MH]^+$ RT 4.06min

The following compounds (**Table 17**) were prepared using a method analogous to that for **Example 113**, 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 17

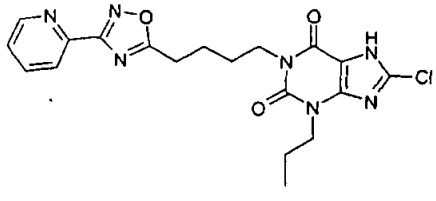


Example	Name	Compound: R1 =	LC/MS
216	3-butyl-8-chloro-1-{3-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 $[MH]^+$ RT 3.47min

Example	Name	Compound: R1 =	LC/MS
217	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
218	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
219	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
220	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 221: 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

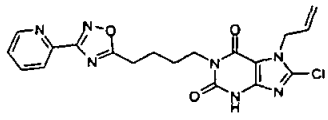
a) 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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.

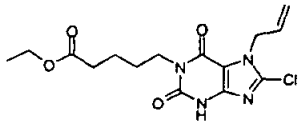
b) 8-Chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



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

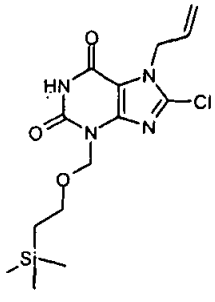


A solution of 8-chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 28mmol) in DMF (10ml) was treated with potassium carbonate (4.8g, 35mmol) and ethyl 5-bromopentanoate (6.5g, 31mmol) and then heated to 70°C for 3h, cooled and evaporated. The residue 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.

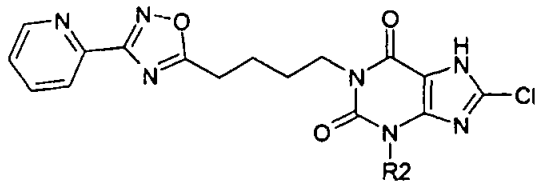
d) 8-Chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1H-purine-2,6-dione

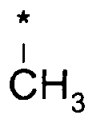
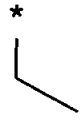
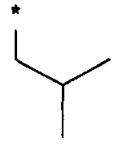
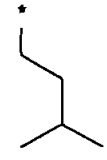
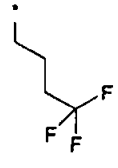
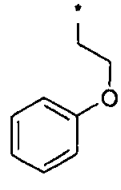


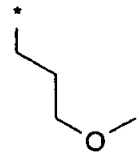
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (5g, 22.1mmol) in DMF (80ml) was added 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (2.6g, 24.2mmol). After stirring at room temperature overnight further 2-2-(trimethylsilyl)ethoxymethyl chloride (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 18**) were prepared by a method analogous to that for **Example 221**, 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 18



Example	R^2 =	Name	Yield (mg)	m/z	RT (min)
222		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
223		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
224		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
225		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
226		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
227		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

Example	R^2 =	Name	Yield (mg)	m/z	RT (min)
228		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

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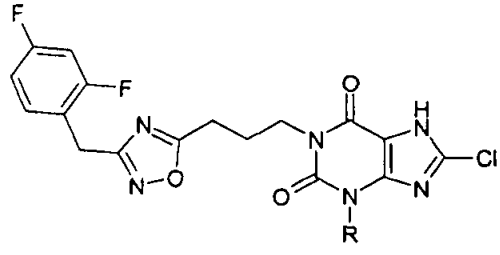
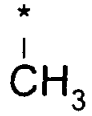
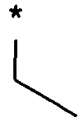
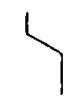
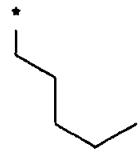
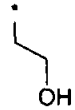
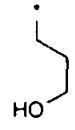
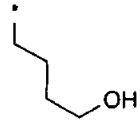
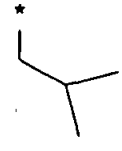
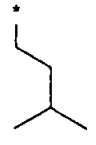
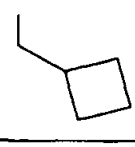
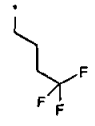
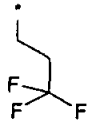
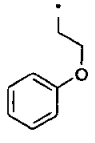
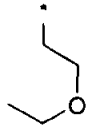
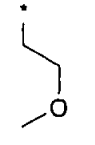
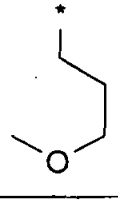
The following compounds **(Table 19)** were prepared by a method analogous to that for **Example 221**, from 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

Table 19



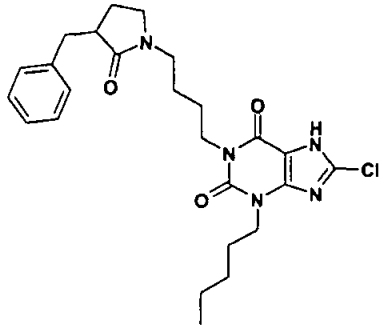
Example	R =	Name	Yield (mg)	m/z	RT (min)
229		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione	1.7	437	2.92
230		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	1.4	451	3.06
231		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

Example	R =	Name	Yield (mg)	m/z	RT (min)
232		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
233		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
234		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
235		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
236		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
237		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
238		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
239		8-chloro-3-(cyclobutylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-	2.2	491	3.45

Example	R =	Name	Yield (mg)	m/z	RT (min)
		dihydro-1*H*-purine-2,6-dione			
240		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
241		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
242		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
243		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
244		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
245		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

Example 246: 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

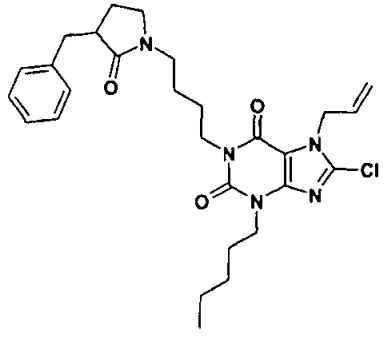
a) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



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 $[MH]^+$

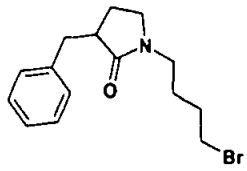
b) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



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 $[MH]^+$

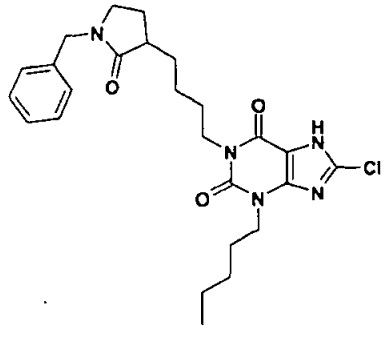
c) 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone



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 $[MH]^+$

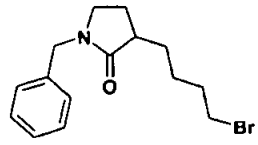
Example 247: 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

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 $[MH]^+$

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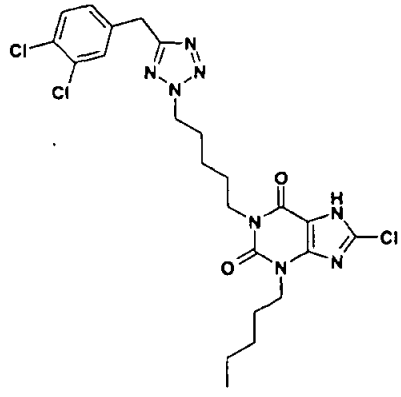
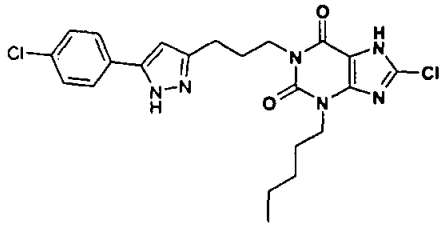
Comparative Example C: 8-Chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



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%).

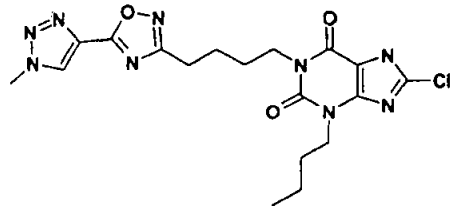
LC/MS: m/z 553 $[MH]^+$

Example 248: 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 (Comparative Example C) 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 $[MH]^+$

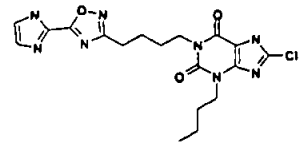
Example 249: 3-Butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

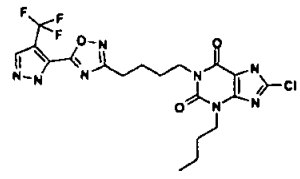
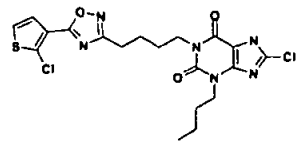
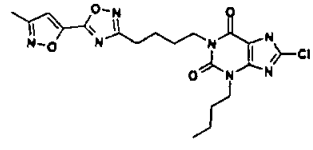
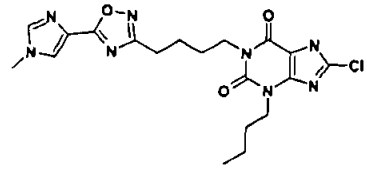
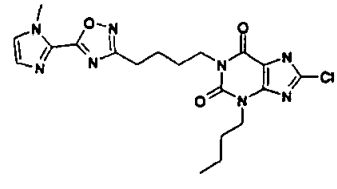
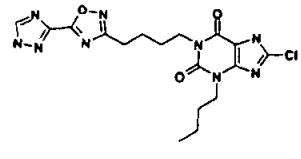
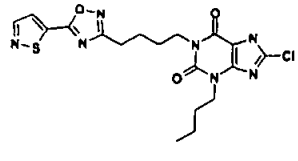


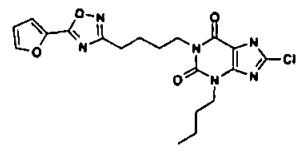
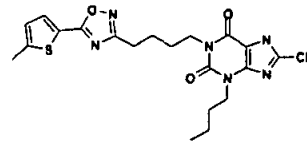
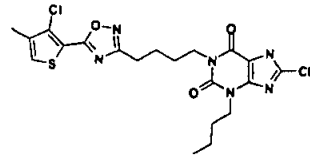
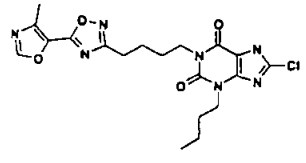
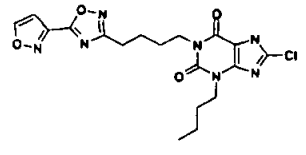
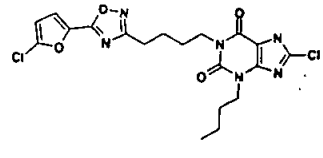
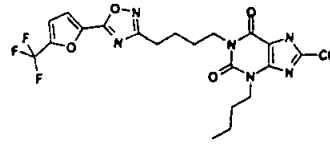
A solution of the 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (18mg, 0.14mmol) in DMF (0.5ml) was treated with CDI (23mg, 0.14mmol) at rt for 1h. A solution of (1Z)-5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.14mmol) in DMSO (0.4ml) was added 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.

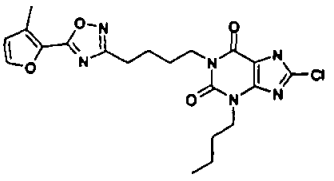
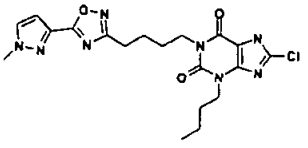
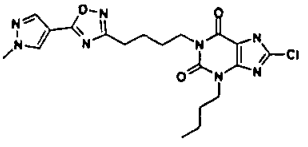
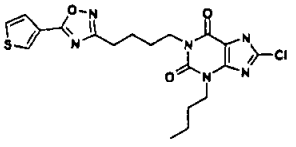
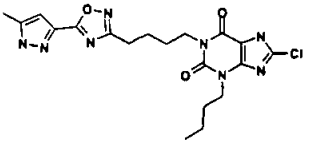
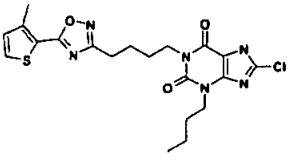
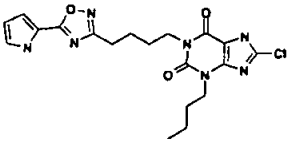
The following compounds (**Table20**) were prepared using a method analogous to that for **Example 249**, using the appropriate carboxylic acid.

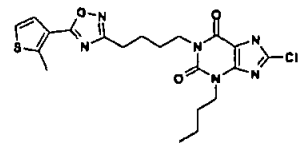
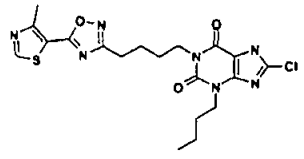
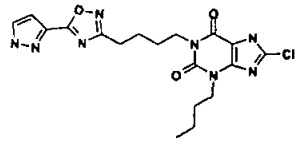
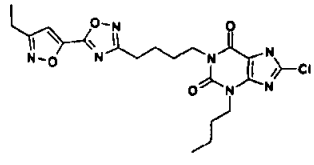
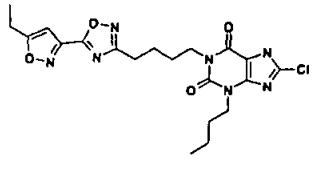
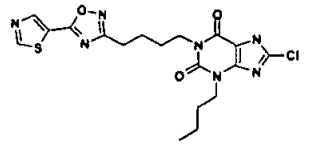
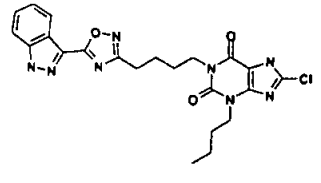
Table 20

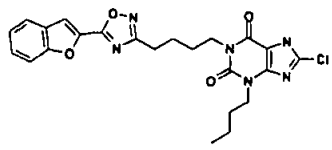
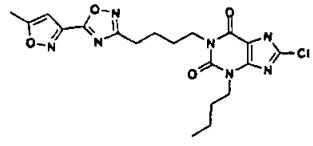
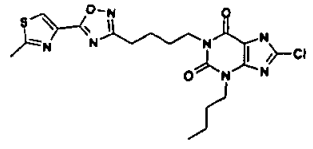
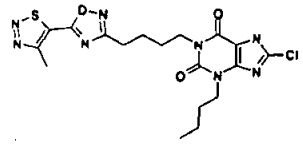
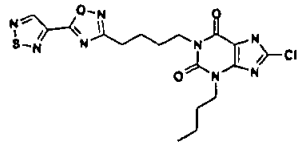
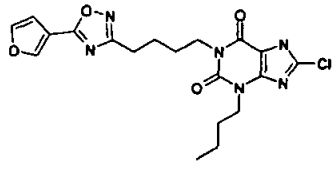
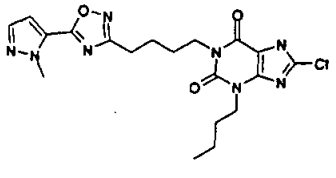
Example	Structure	Name	Yield (mg)	LC/MS
250		3-butyl-8-chloro-1-{4-[5-(1*H*-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 433 $[MH]^+$ RT 2.79min

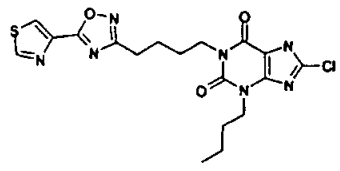
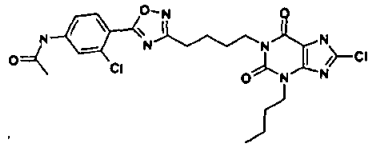
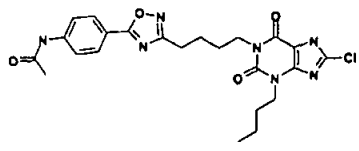
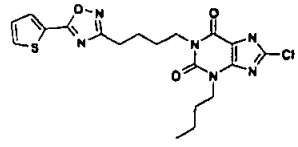
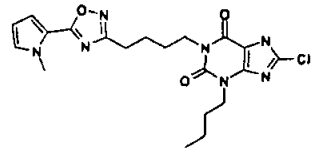
251		3-butyl-8-chloro-1-(4-{5-[4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	19	m/z 501 $[MH]^+$ RT 3.28min
252		3-butyl-8-chloro-1-{4-[5-(2-chloro-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 483 $[MH]^+$ RT 3.59min
253		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
254		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
255		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
256		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
257		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

258		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
259		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
260		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
261		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
262		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
263		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
264		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

265		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
266		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
267		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
268		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
269		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
270		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
271		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

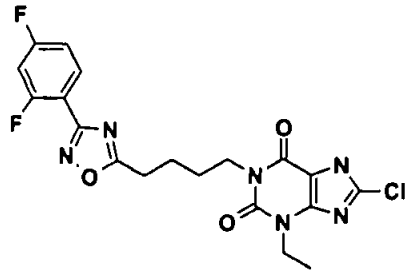
272		3-butyl-8-chloro-1-{4-[5-(2-methyl-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	18	m/z 463 $[MH]^+$ RT 3.64min
273		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 464 $[MH]^+$ RT 3.26min
274		3-butyl-8-chloro-1-{4-[5-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 433 $[MH]^+$ RT 3.00min
275		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
276		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
277		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
278		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

279		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
280		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
2810		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
282		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-2,6-dione	14	m/z 465 $[MH]^+$ RT 3.40min
283		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
284		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
285		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

286		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
287		*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
288		*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
289		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
290		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 291 : 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



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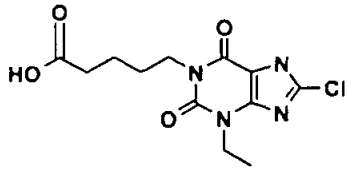
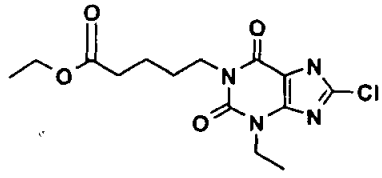
A solution of 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (0.05g, 0.16mmol) in DMSO (1ml) was treated with CDI (0.029g, 0.18mmol) and the mixture stirred at room temperature for 1h. Subsequently, the mixture was treated with 2,4-difluorobenzamidoxime (0.03g, 0.18mmol) 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.

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.

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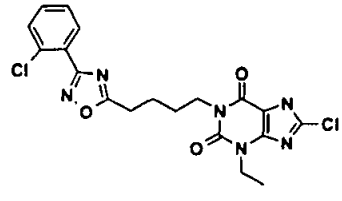
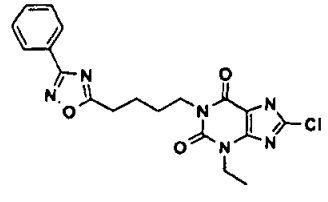
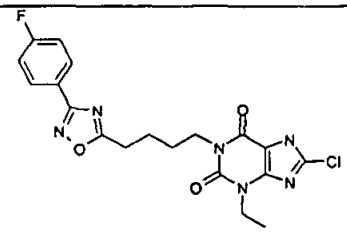
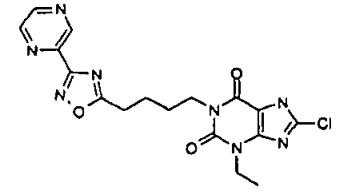
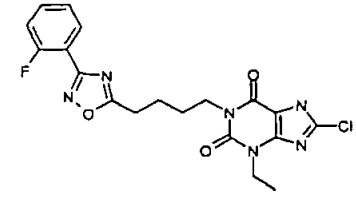
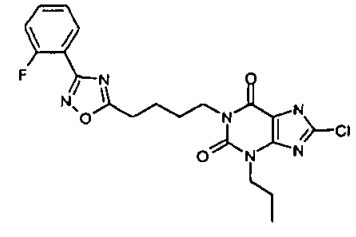
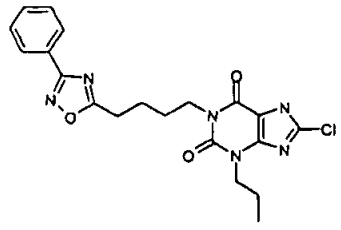
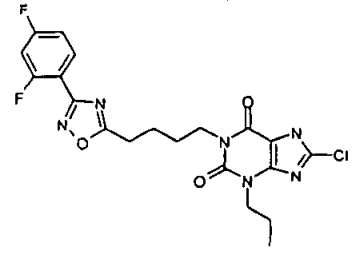
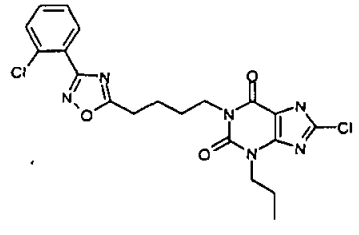
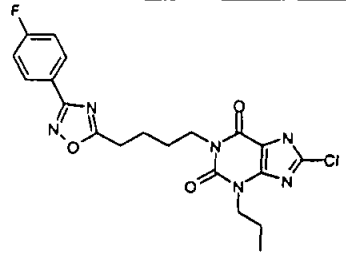
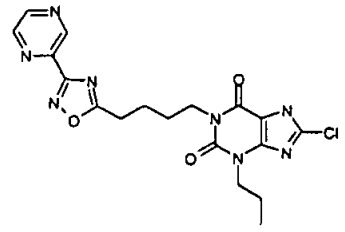
The following compounds (**Table 21**) were prepared by a method analogous to that for **Example 291.**

Table 21

Example	Structure	Precursor	Yield (mg)	LC/MS
292	 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
293	 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

294	 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
295	 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
296	 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
297	 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

298	 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
299	 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
300	 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
301	 8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1H-	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

	purine-2,6-dione			
302	 8-chloro-3-propyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-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	25	m/z 431 $[MH]^+$ RT 3.09min

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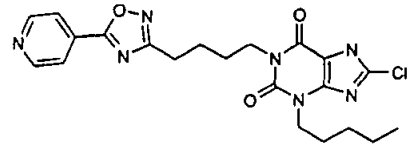
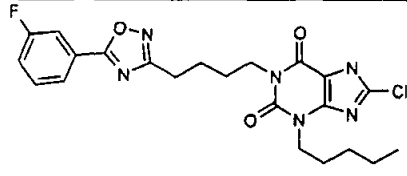
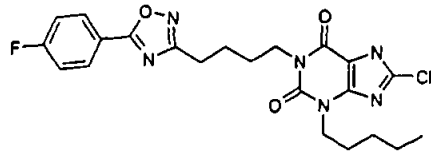
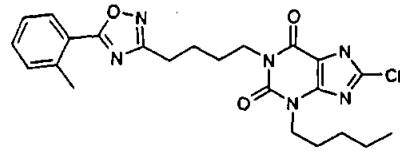
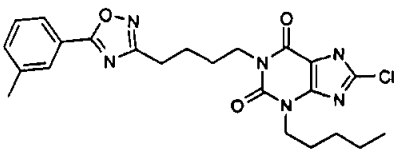
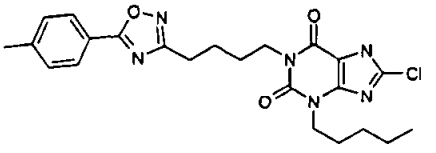
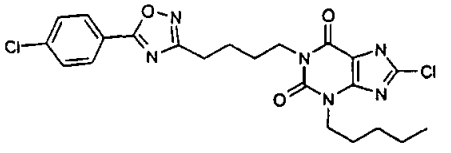
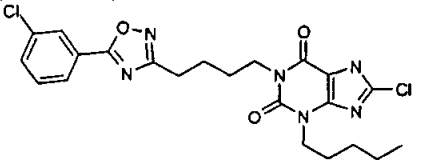
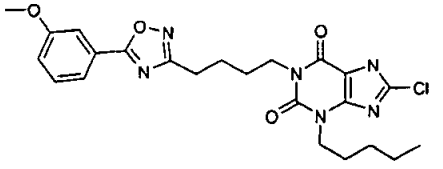
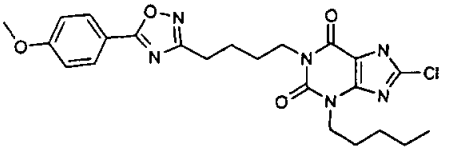
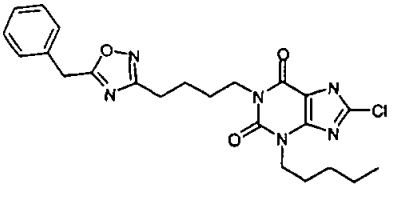
The following compounds (**Table 22**) were prepared using a method analogous to that for **Example 127**, using the appropriate acid.

Table 22

Example	Structure	Name	Yield (mg)	LC/MS
303		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
304		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
305		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
306		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

307		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
308		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
309		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
310		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
311		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
312		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
313		8-chloro-3-pentyl-1-{4-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	21.0	m/z 471 $[MH]^+$ RT 3.55min

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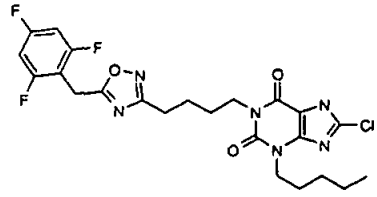
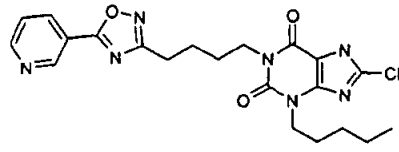
314		8-chloro-3-pentyl-1-(4-{5-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	29.3	m/z 525 $[MH]^+$ RT 3.62min
315		8-chloro-3-pentyl-1-{4-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8.2	m/z 458 $[MH]^+$ RT 3.23min

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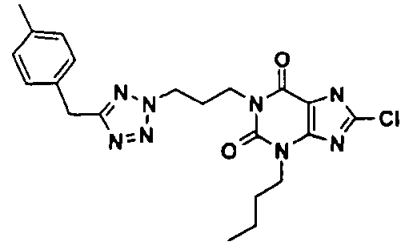
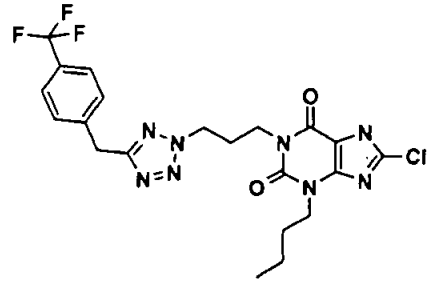
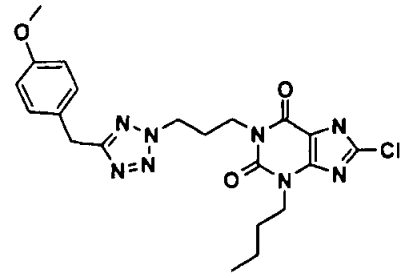
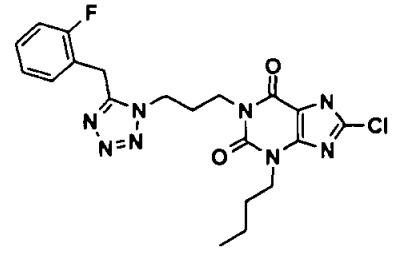
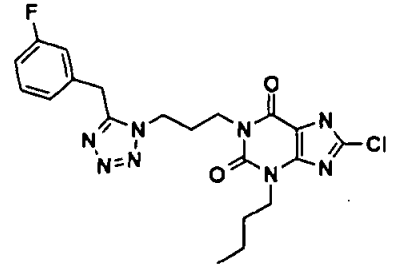
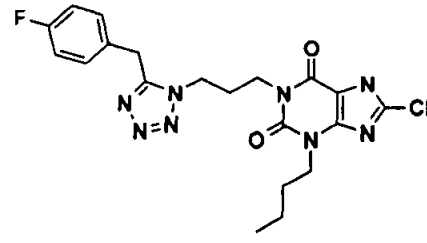
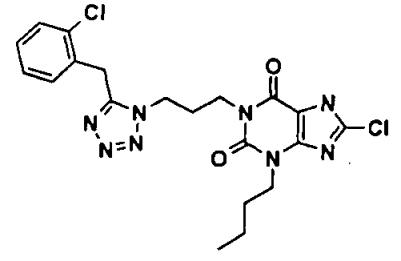
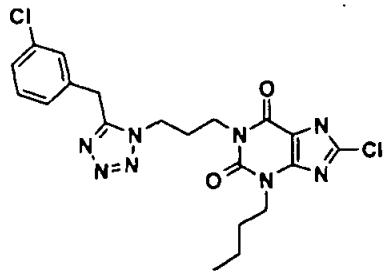
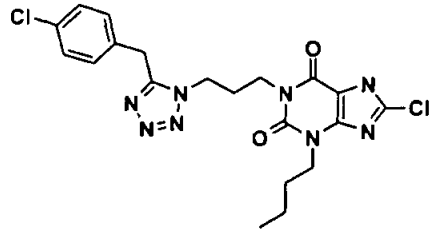
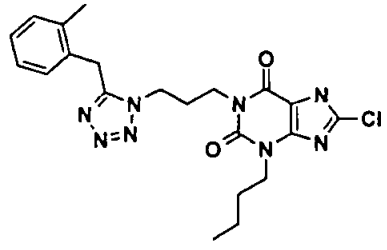
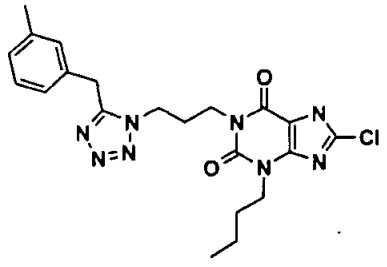
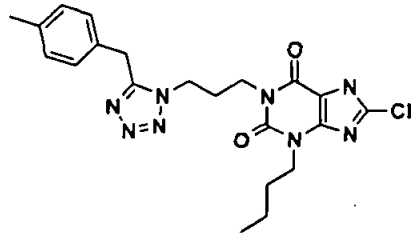
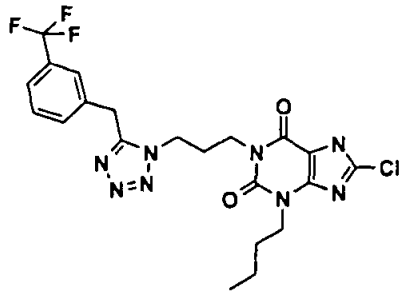
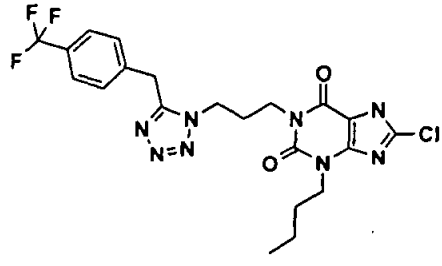
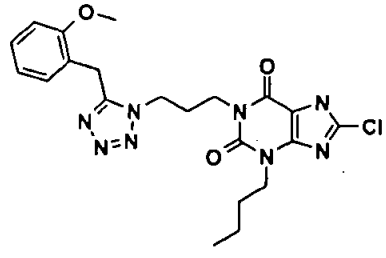
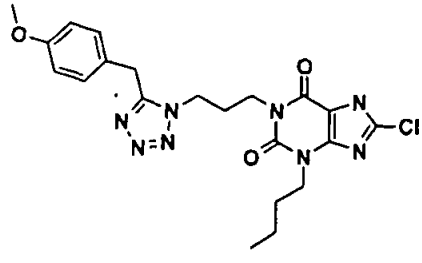
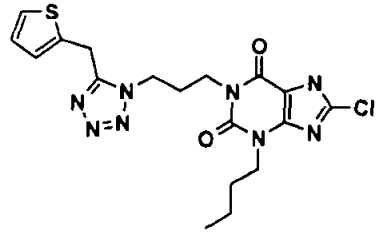
The following compounds (**Table 23**) were prepared using a method analogous to that for **Example 19**, using the appropriate tetrazole and 3-[3-alkyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

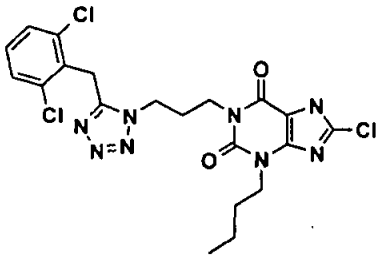
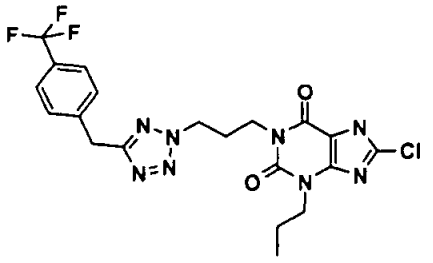
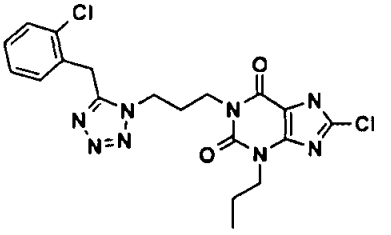
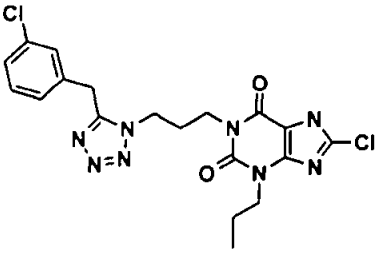
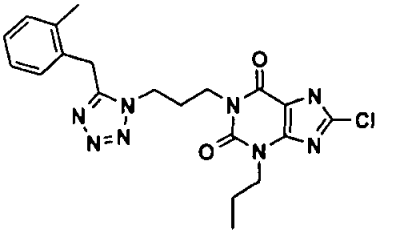
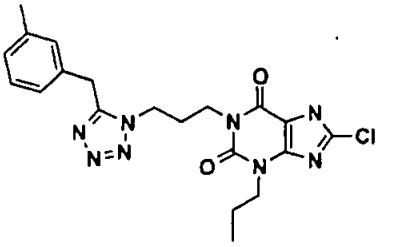
Table 23

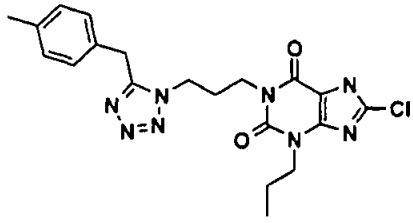
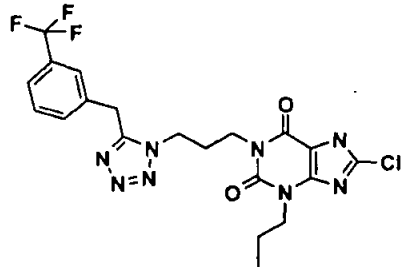
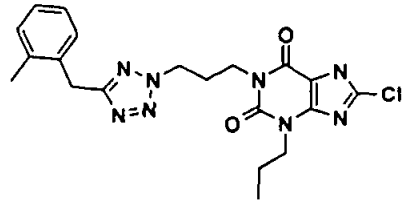
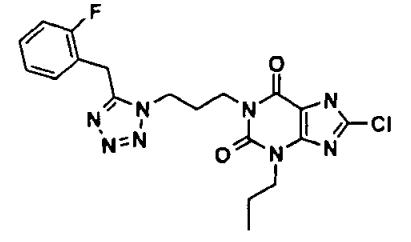
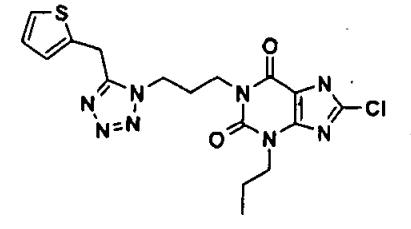
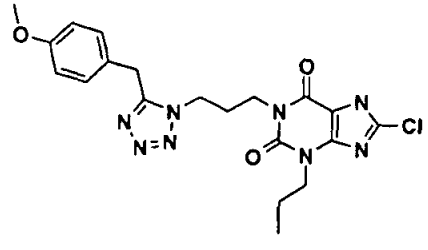
Example	Structure	Name	Yield (mg)	LC/MS
316		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	35.1	m/z 457 $[MH]^+$ RT 3.40min
317		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-	43.6	m/z 511 $[MH]^+$ RT 3.52min

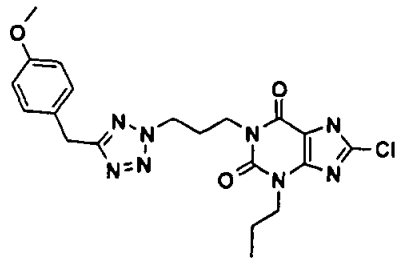
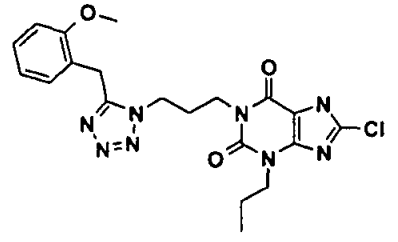
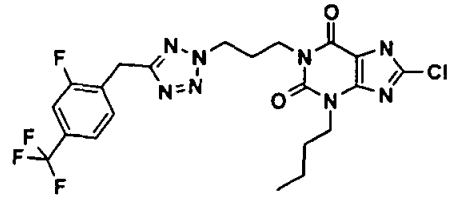
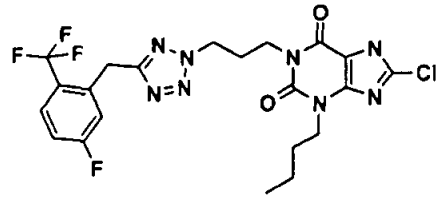
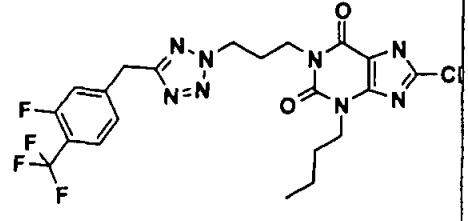
		2,6-dione		
318		3-butyl-8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	38.2	m/z 473 $[MH]^+$ RT 3.24min
319		3-butyl-8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	13.7	m/z 461 $[MH]^+$ RT 3.07min
320		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
321		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
322		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

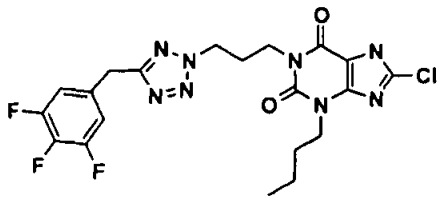
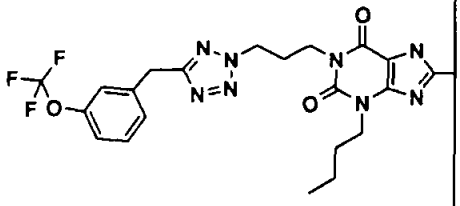
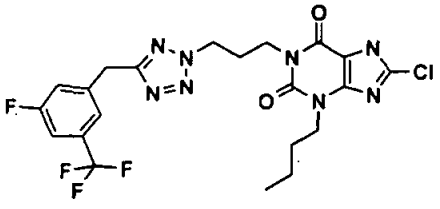
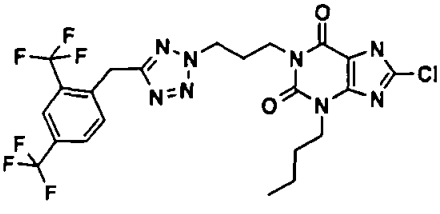
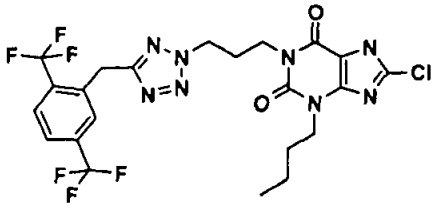
323		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.4	m/z 477 $[MH]^+$ RT 3.23min
324		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0	m/z 477 $[MH]^+$ RT 3.24min
325		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.1	m/z 457 $[MH]^+$ RT 3.15min
326		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
327		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

328		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 3.31m in
329		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 3.33m in
330		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 3.10m in
331		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 3.05m in
332		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 3.02m in

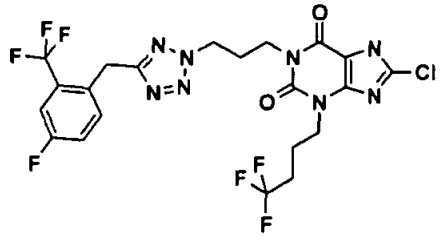
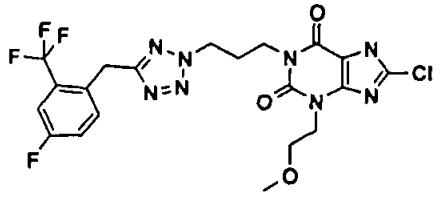
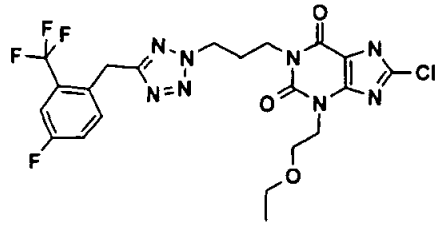
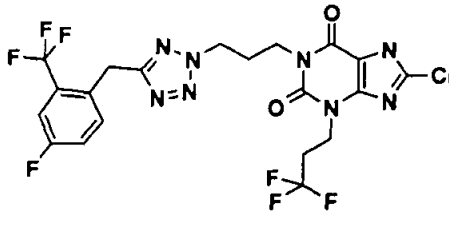
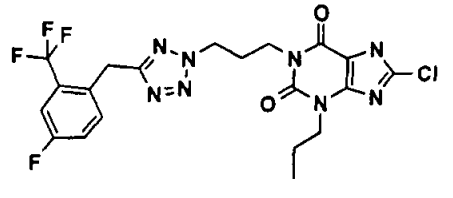
333		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 512 $[MH]^+$ RT 3.27min
334		8-chloro-3-propyl-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 497 $[MH]^+$ RT 3.38min
335		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
336		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
337		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
338		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

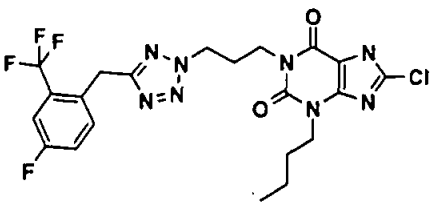
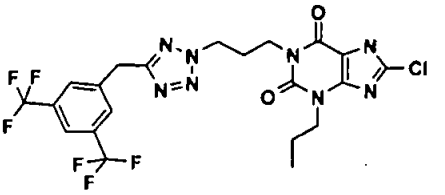
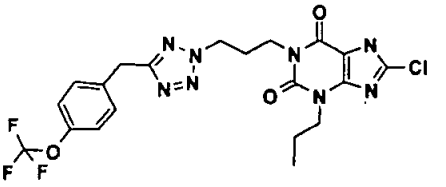
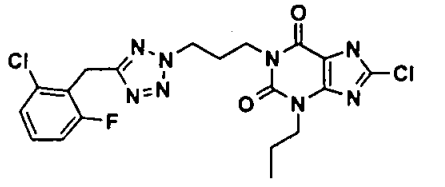
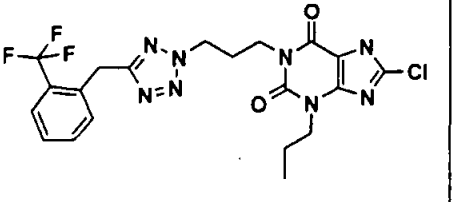
339		8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.5	m/z 443 $[MH]^+$ RT 3.01min
340		8-chloro-3-propyl-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	3.3	m/z 497 $[MH]^+$ RT 3.16min
341		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
342		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
343		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
344		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

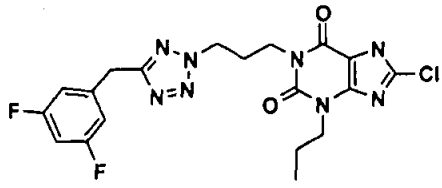
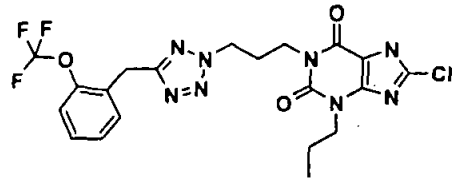
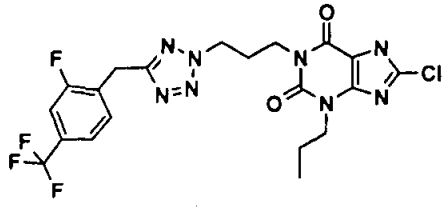
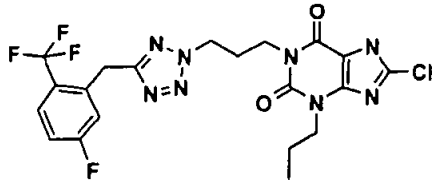
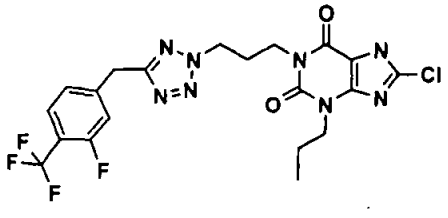
345		8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.7	m/z 459 $[MH]^+$ RT 3.07min
346		8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.9	m/z 459 $[MH]^+$ RT 2.92min
347		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
348		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
349		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

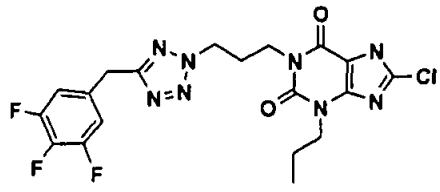
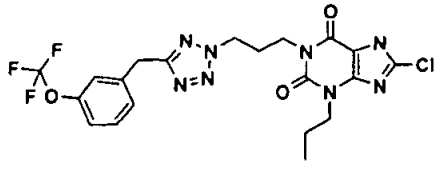
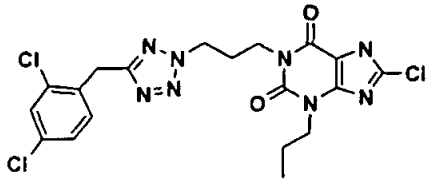
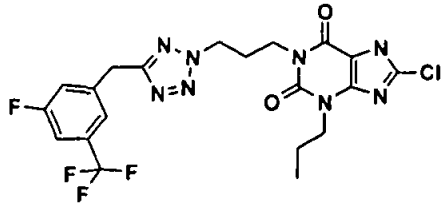
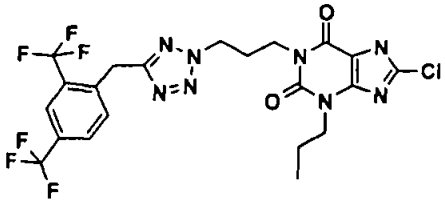
350		3-butyl-8-chloro-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	19.4	m/z 497 $[MH]^+$ RT 3.45min
351		3-butyl-8-chloro-1-{3-[5-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	27.2	m/z 527 $[MH]^+$ RT 3.55min
352		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
353		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
354		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

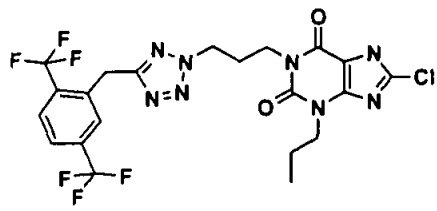
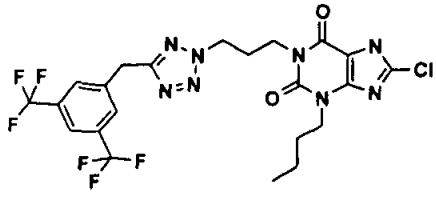
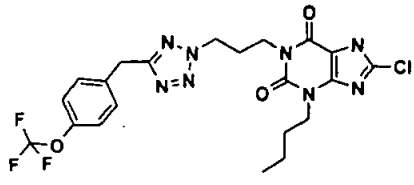
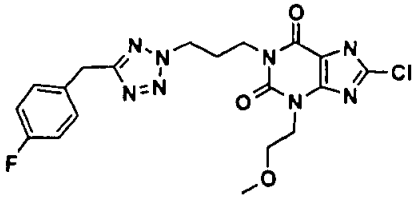
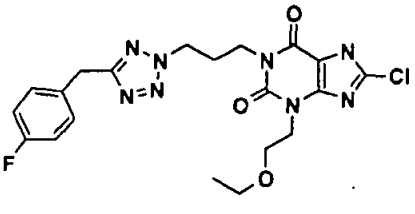
168

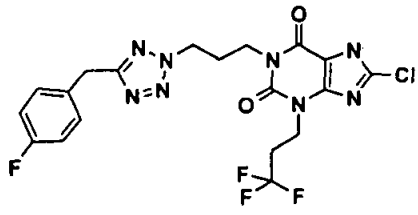
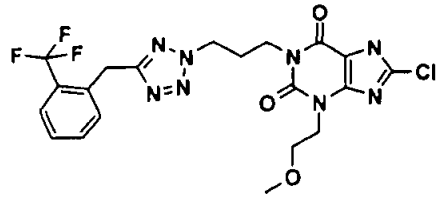
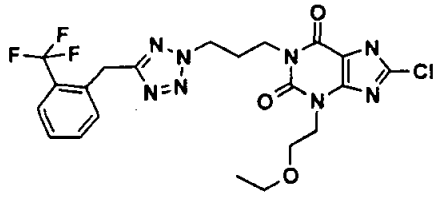
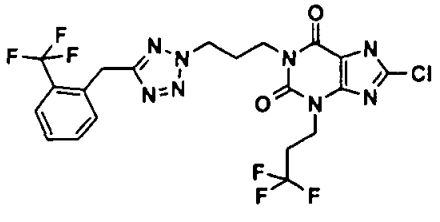
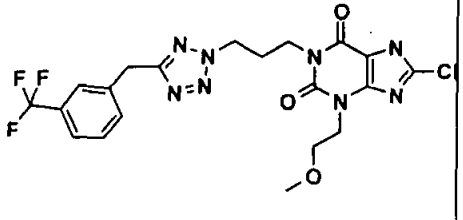
355		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	25.0	m/z 583 $[MH]^+$ RT 3.50min
356		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	23.0	m/z 531 $[MH]^+$ RT 3.16min
357		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
358		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
359		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-	32.0	m/z 515 $[MH]^+$ RT 3.37min

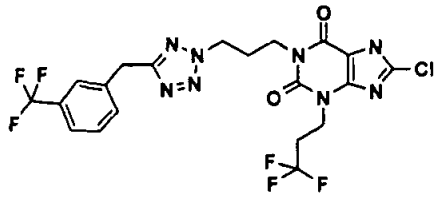
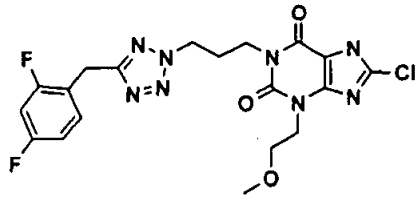
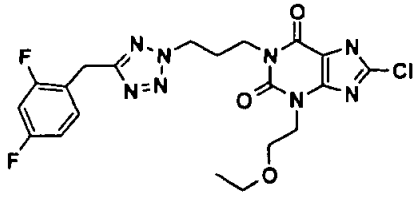
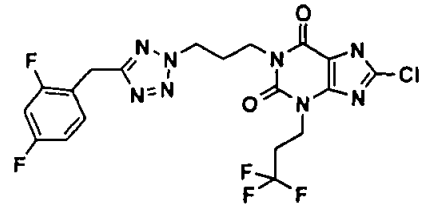
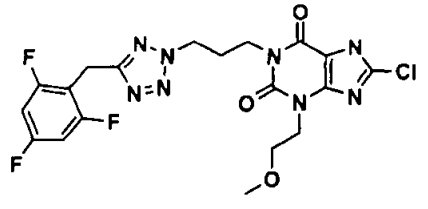
		3,7-dihydro-1H-purine-2,6-dione		
360		3-butyl-8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	30.3	m/z 529 $[MH]^+$ RT 3.53min
361		1-[3-(5-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.9	m/z 565 $[MH]^+$ RT 3.54min
362		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
363		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
364		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

365		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
366		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
367		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
368		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
369		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

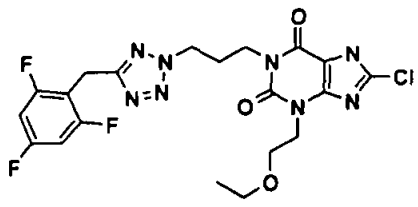
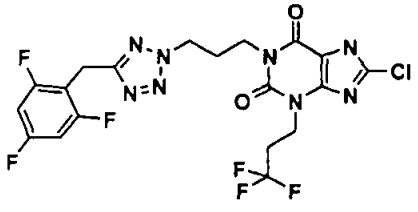
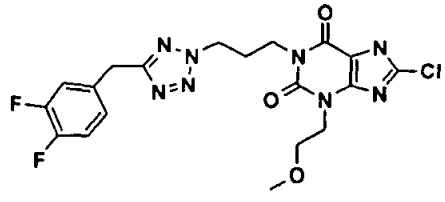
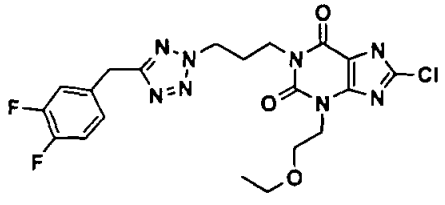
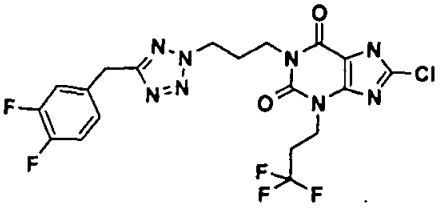
370		8-chloro-3-propyl-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	10.2	m/z 483 $[MH]^+$ RT 3.23min
371		8-chloro-3-propyl-1-{3-[5-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	9.8	m/z 513 $[MH]^+$ RT 3.35min
372		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
373		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
374		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

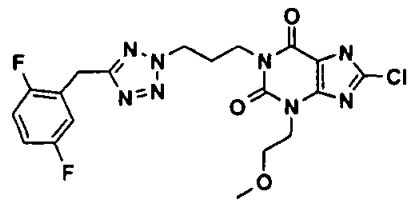
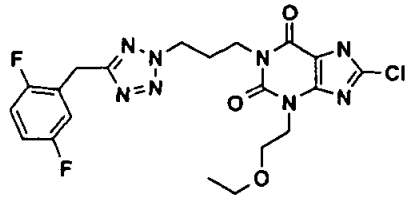
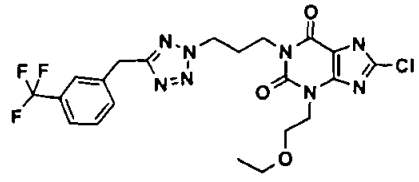
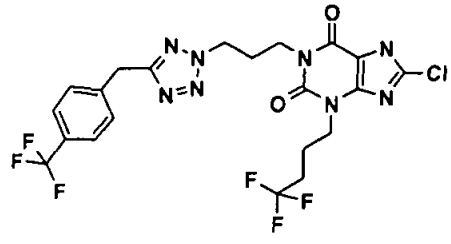
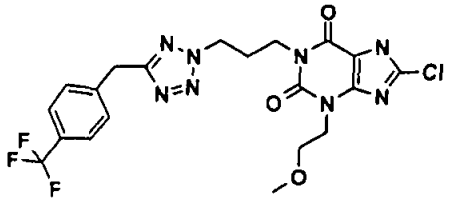
375		1-[3-(5-{[2,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 565 $[MH]^+$ RT 3.50min
376		1-[3-(5-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	28.1	m/z 579 $[MH]^+$ RT 3.68min
377		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
378		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
379		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

380		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 3.21m in
381		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 3.10m in
382		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 3.18m in
383		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 3.35m in
384		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 3.14m in

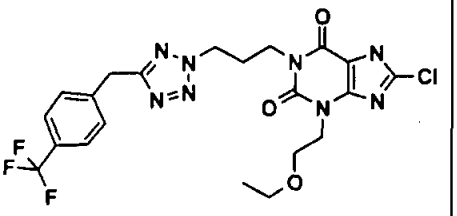
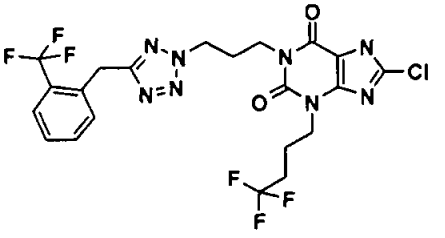
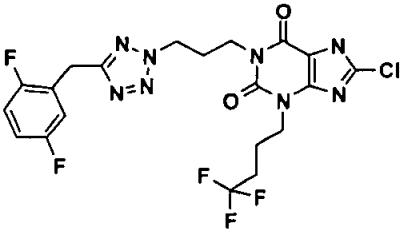
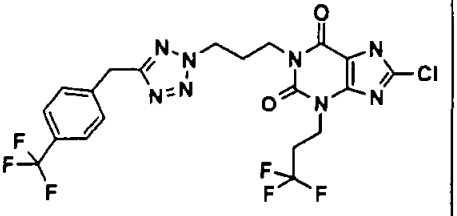
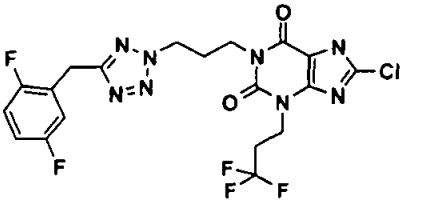
385		8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	29.4	m/z 551 $[MH]^+$ RT 3.42min
386		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.8	m/z 481 $[MH]^+$ RT 2.96min
387		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
388		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
389		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

196

390		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 2.93m in
391		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 3.29m in
392		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 2.97m in
393		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 3.06m in
394		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 3.27m in

395		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
396		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
397		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
398		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
399		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-	17.3	m/z 513 $[MH]^+$ RT 3.17min

148

		2,6-dione		
400		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
401		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	5.8	m/z 565 $[MH]^+$ RT 3.46min
402		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
403		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
404		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-	18.0	m/z 519 $[MH]^+$ RT 3.29min

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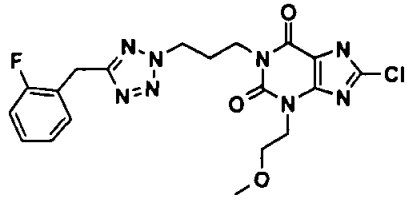
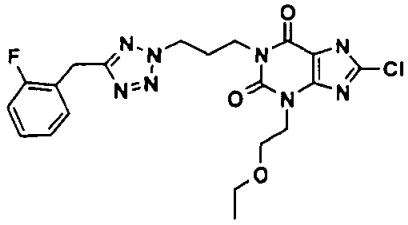
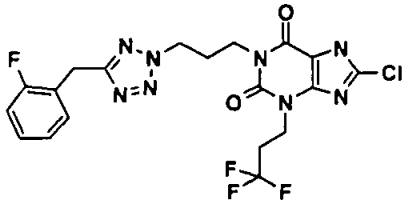
		2,6-dione		
405		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	3.4	m/z 463 $[MH]^+$ RT 2.84min
406		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8.2	m/z 477 $[MH]^+$ RT 2.85min
407		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

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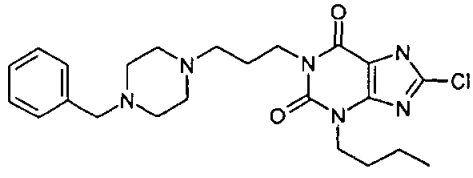
Example 408 : 3-Butyl-8-chloro-1-{3-[4-(phenylmethyl)-1-piperazinyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



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.

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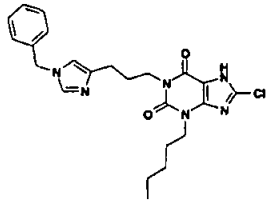
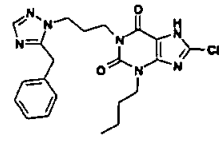
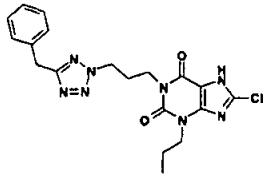
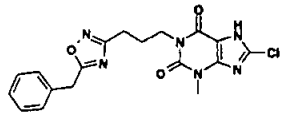
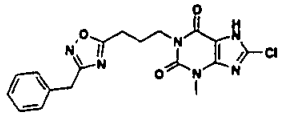
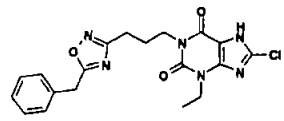
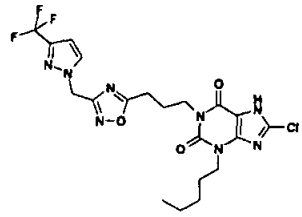
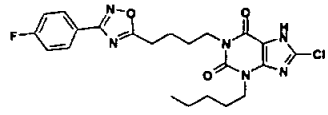
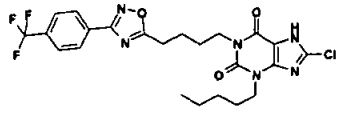
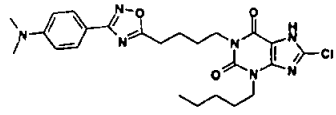
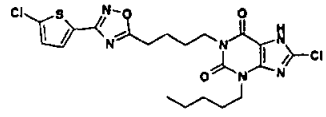
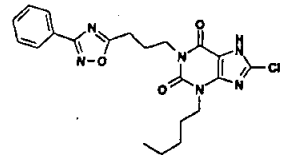
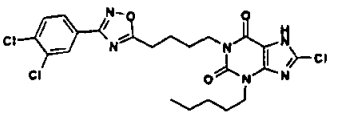
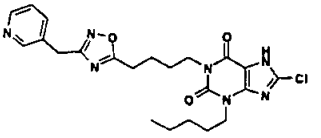
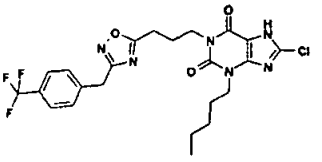
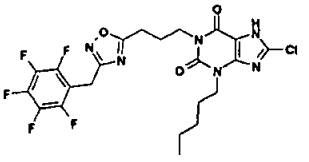
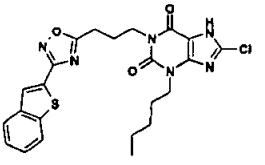
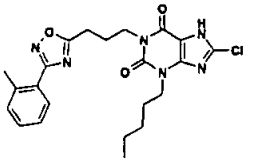
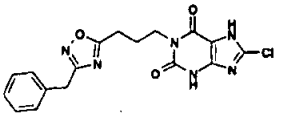
The following compounds (**Table 24**) were prepared by the appropriate general methodology described above.

Table 24

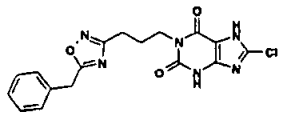
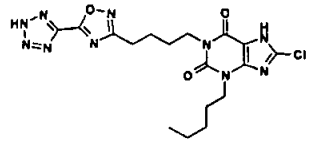
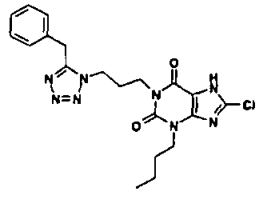
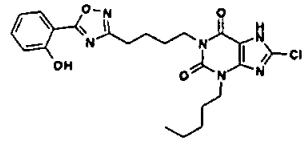
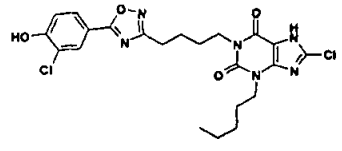
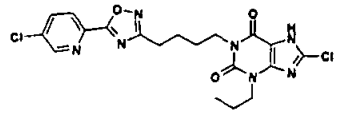
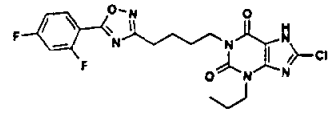
Example	Structure	Name	LC/MS
409		8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 455 $[MH]^+$ RT 2.61min
410		3-butyl-8-chloro-1-{3-[5-(phenylmethyl)-1H-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 442 $[MH]^+$ RT 2.94min
411		8-chloro-1-{3-[5-(phenylmethyl)-2H-tetrazol-2-yl]propyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 429 $[MH]^+$ RT 3.14min
412		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
413		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

414		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
415		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
416		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
417		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
418		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
419		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
420		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

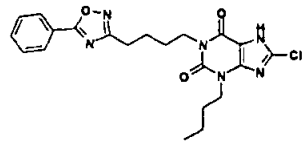
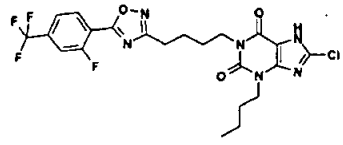
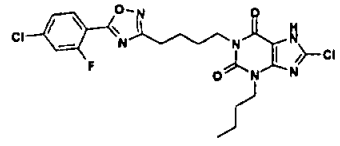
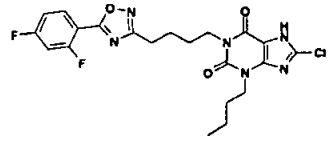
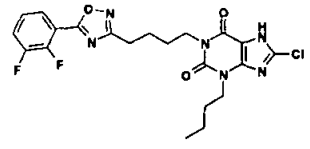
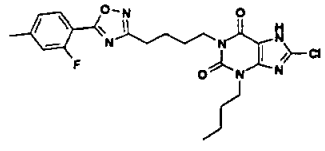
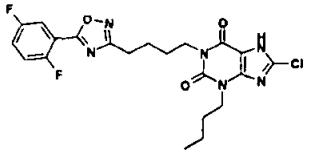
152

421		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
422		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
423		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
424		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
425		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
426		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
427		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

153

428		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
429		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
430		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
431		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
432		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
433		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
434		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

159

435		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
436		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
437		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
438		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
439		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
440		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
441		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

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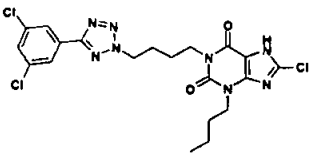
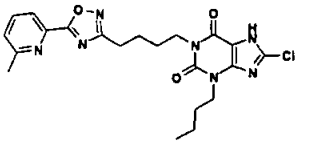
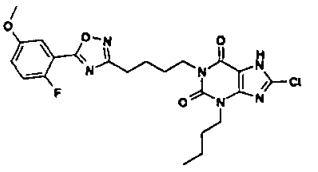
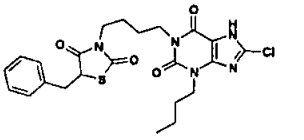
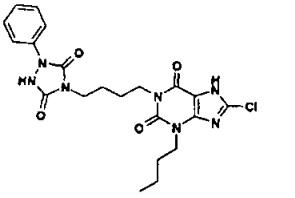
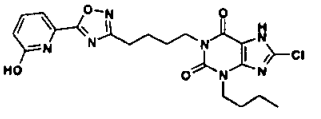
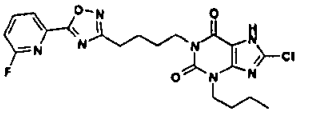
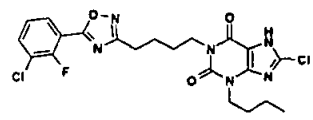
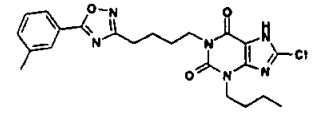
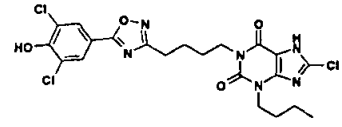
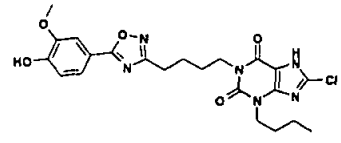
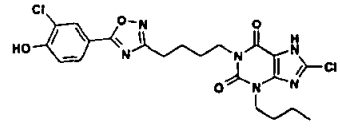
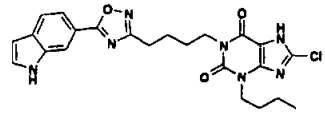
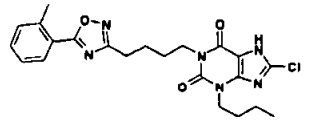
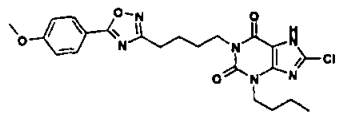
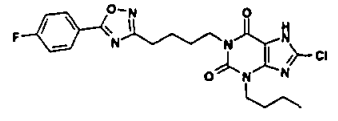
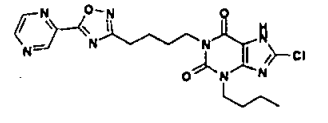
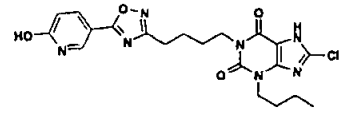
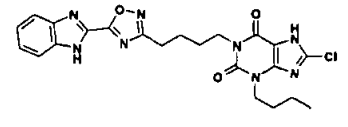
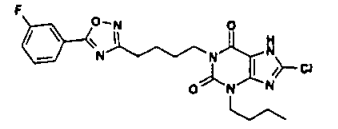
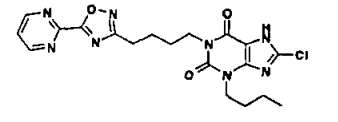
442		3-butyl-8-chloro-1-{4-[5-(3,5-dichlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 511 $[MH]^+$ RT 3.92min
443		3-butyl-8-chloro-1-{4-[5-(6-methylpyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.12min
444		3-butyl-8-chloro-1-(4-{5-[2-fluoro-5-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 $[MH]^+$ RT 3.51min
445		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
446		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
447		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
448		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

156

449		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
450		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
451		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
452		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
453		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
454		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
455		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

456		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
457		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
458		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
459		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
460		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
461		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
462		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

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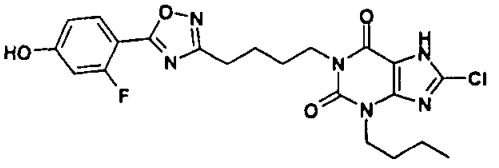
Example 463: 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

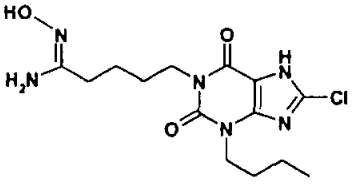
a) 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



159

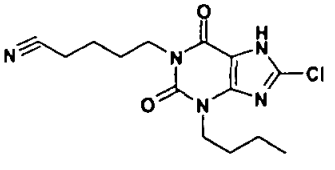
CDI (45mg, 0.28mmol) in anhydrous DMSO (0.5ml) was added to 2-fluoro-4-hydroxybenzoic acid (40mg, 0.25mmol) and stirred at rt for 2h. 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the resulting mixture heated 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

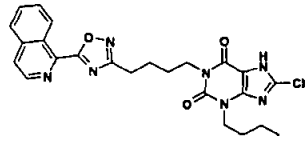
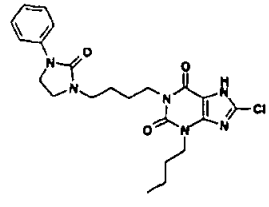
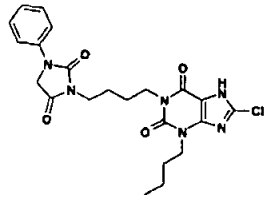
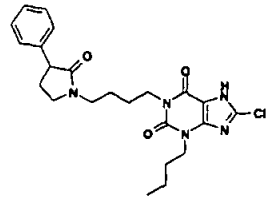


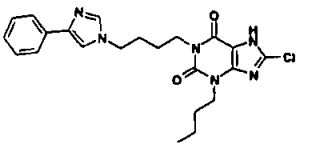
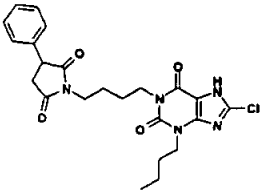
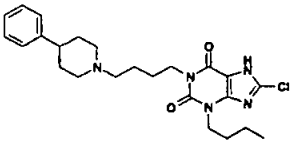
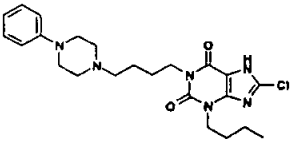
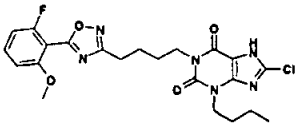
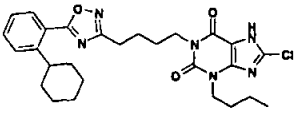
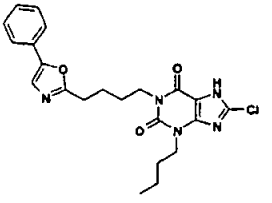
5-Bromopentanenitrile (4.54ml, 39mmol) and cesium carbonate (12.7g) were added to a solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 35mmol) in DMF (100ml) and the mixture stirred under nitrogen at 40°C overnight and allowed to cool.

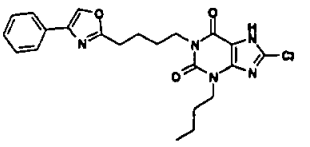
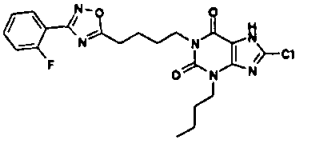
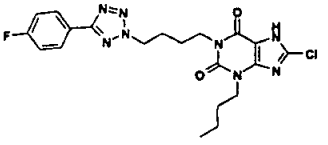
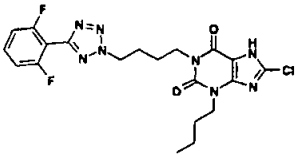
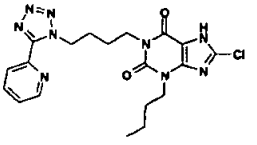
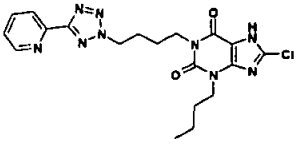
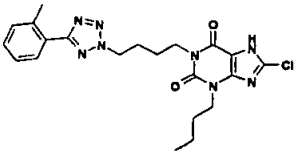
The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (2.86g, 2.5mmol) and morpholine (30.8ml, 350mmol). The mixture was stirred in a nitrogen atmosphere for 3h and then partitioned 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.

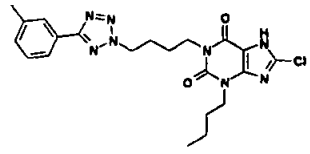
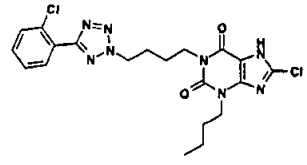
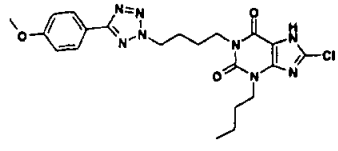
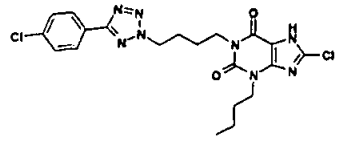
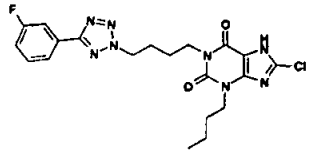
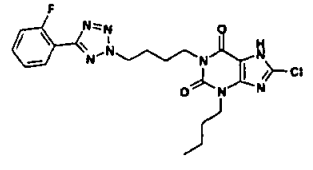
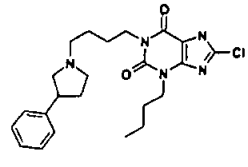
The following compounds (**Table 25**) were prepared using a method analogous to that for **Example 463**, using the appropriate carboxylic acid.

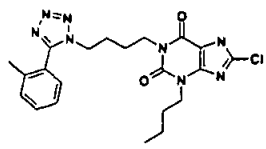
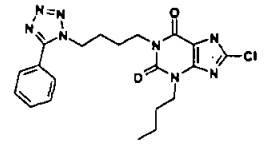
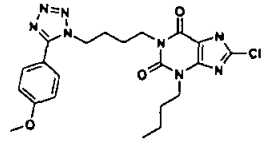
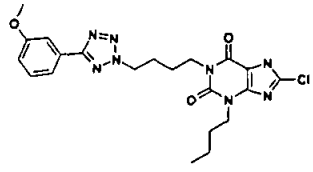
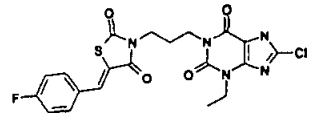
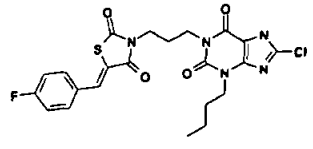
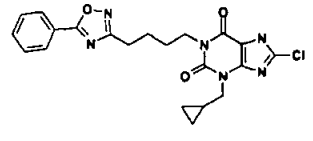
Table 25

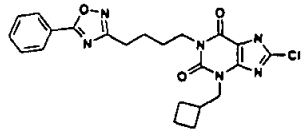
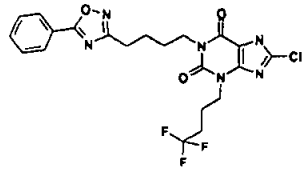
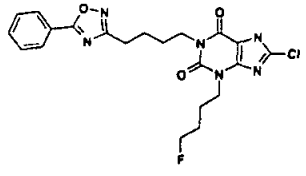
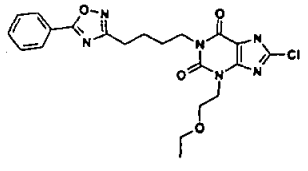
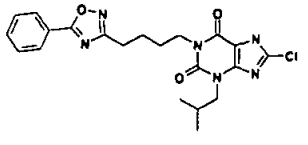
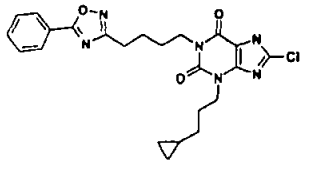
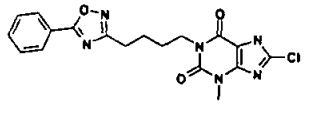
464		3-butyl-8-chloro-1-[4-(5-isoquinolin-1-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 494 $[MH]^+$ RT 3.49min
465		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.23min
466		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.19min
467		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

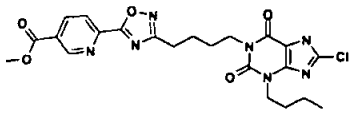
468		3-butyl-8-chloro-1-[4-(4-phenyl-1H-imidazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 441 $[MH]^+$ RT 2.60min
469		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 472 $[MH]^+$ RT 3.20min
470		3-butyl-8-chloro-1-[4-(4-phenylpiperidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 2.56min
471		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
472		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
473		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
474		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

475		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
476		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
477		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
478		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
479		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
480		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
481		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

482		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
483		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
484		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
485		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
486		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
487		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
488		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

489		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
490		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
491		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
492		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
493		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
494		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
495		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

496		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
497		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
498		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
499		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
500		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
501		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
502		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

503		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

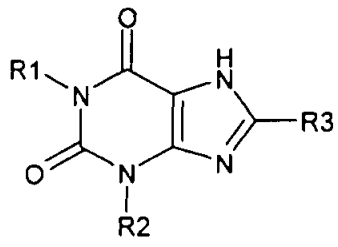
The above starting materials may be purchased commercially and/or made according to processes which are available in the literature.

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)

compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

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

Wherein m and n represent the number of carbon atoms in the alkylene chain;

Wherein X represents a group selected from heteroaryl and heterocyclyl;

Wherein Y represents a group selected from aryl, heteroaryl and O-aryl;
which may be optionally substituted by one or more groups independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, $-(CH_2)_qNR^5R^7$, $-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$, $-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)NR^5R^6$, $-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2NR^5R^6$, $-C_{1-6}$ haloalkyl, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, CN, $-SO_2R^9$, $-(CH_2)_n$heteroaryl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$cycloalkyl, $-(CH_2)_n$cycloalkenyl, and $-(CH_2)_n$aryl;

R^2 represents C_{1-6} alkyl which may be optionally substituted by one or more groups independently selected from cycloalkyl, C_{1-6} haloalkyl, halogen, -CN and $-OR^4$;

R^3 represents halogen;

R^4 represents a group 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 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 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 3 and 4;

n represents an integer selected from 0 and 1;

p represents an integer selected from 0 and 1;

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

t represents an integer selected from 1 and 2.

2. At least one chemical entity according to claim 1 wherein X represents a group selected from heteroaryl.

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 claim 2 or 3 wherein X represents a group selected from heteroaryl comprising a nitrogen heteroatom.

5. At least one chemical entity according to claim 4 wherein X represents oxadiazolyl or tetrazole.

6. At least one chemical entity according to any preceding claim wherein Y represents a group selected from aryl and heteroaryl.

7. At least one chemical entity according to any preceding claim wherein Y is optionally substituted by one or more of halogen and C_{1-6} haloalkyl.

8. At least one chemical entity according to any preceding claim wherein R^3 represents chlorine.

9. At least one chemical entity according to any preceding claim wherein Y represents phenyl and m is 3 and n is 1.

10. At least one chemical entity according to claim 9 wherein X represents tetrazolyl, R^2 represents butyl and R^3 represents chlorine.

11. At least one chemical entity according to claim 8 wherein X represents oxadiazolyl, Y represents piridinyl, R^2 represents butyl, R^3 represents chlorine and m is 4 and n is 0.

12. At least one chemical entity according to any preceding claim for use in human or veterinary medicine.

13. At least one chemical entity according to any one of claims 1 to 11, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.

14. At least one chemical entity according to any one of claims 1 to 11 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.

15. At least one chemical entity according to any one of claims 1 to 11 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.

16. 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 7.

17. A method according to claim 16 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia or an inflammatory disease or condition.

18. A pharmaceutical formulation comprising at least one chemical entity according to any one of claims 1 to 11 and at least one pharmaceutically acceptable diluent, excipient or carrier.

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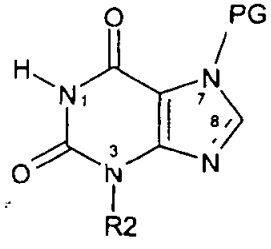
19. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising at least one chemical entity according to any one of claims 1 to 11 together with at least one therapeutically active agent.

20. A pharmaceutical formulation comprising:
    (i) at least one chemical entity according to any one of claims 1 to 11;
    (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.

21. A method for the preparation of at least one chemical entity according to any one of claims 1 to 11 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

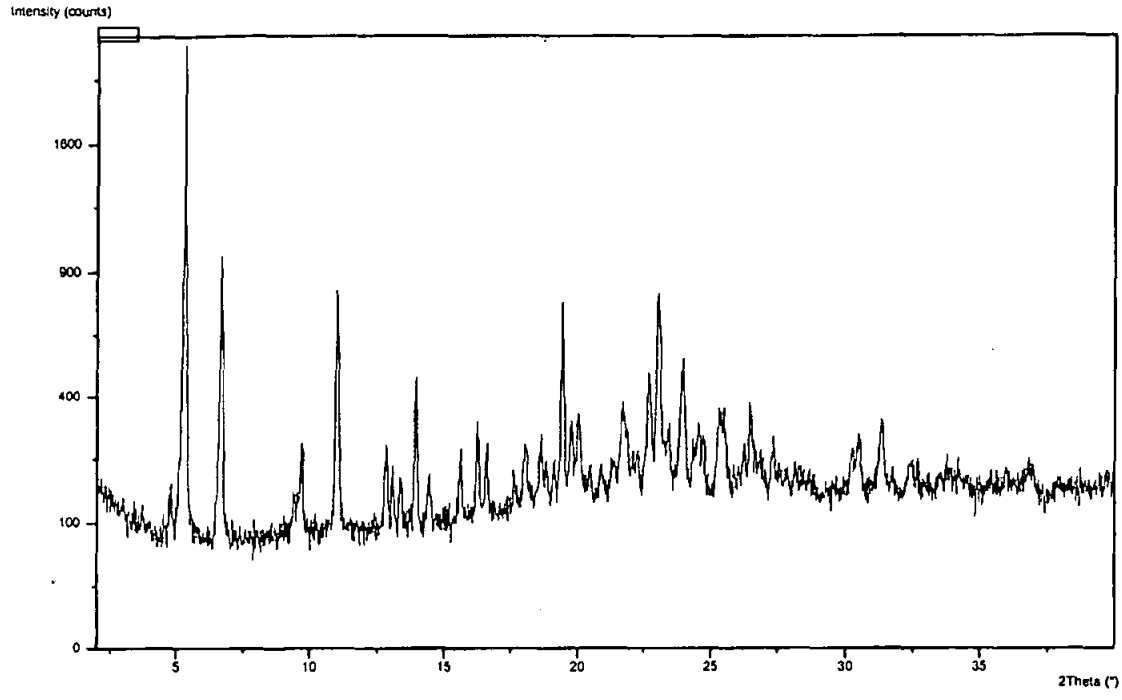


Figure 1: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1.

Figure 2

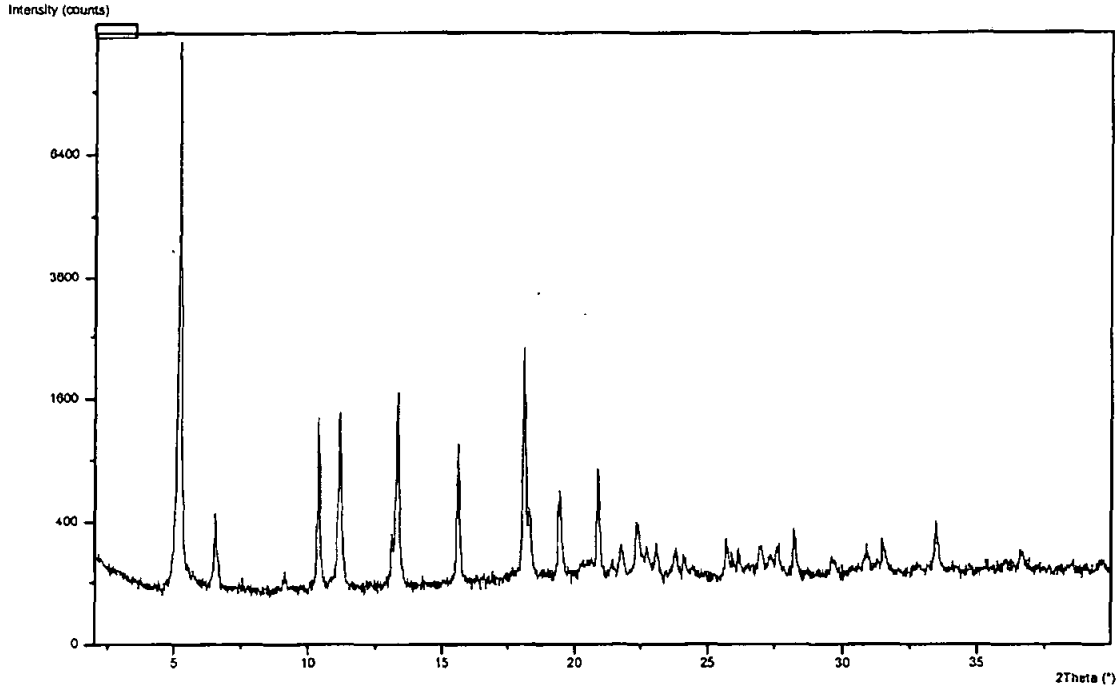


Figure 2: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Figure 3

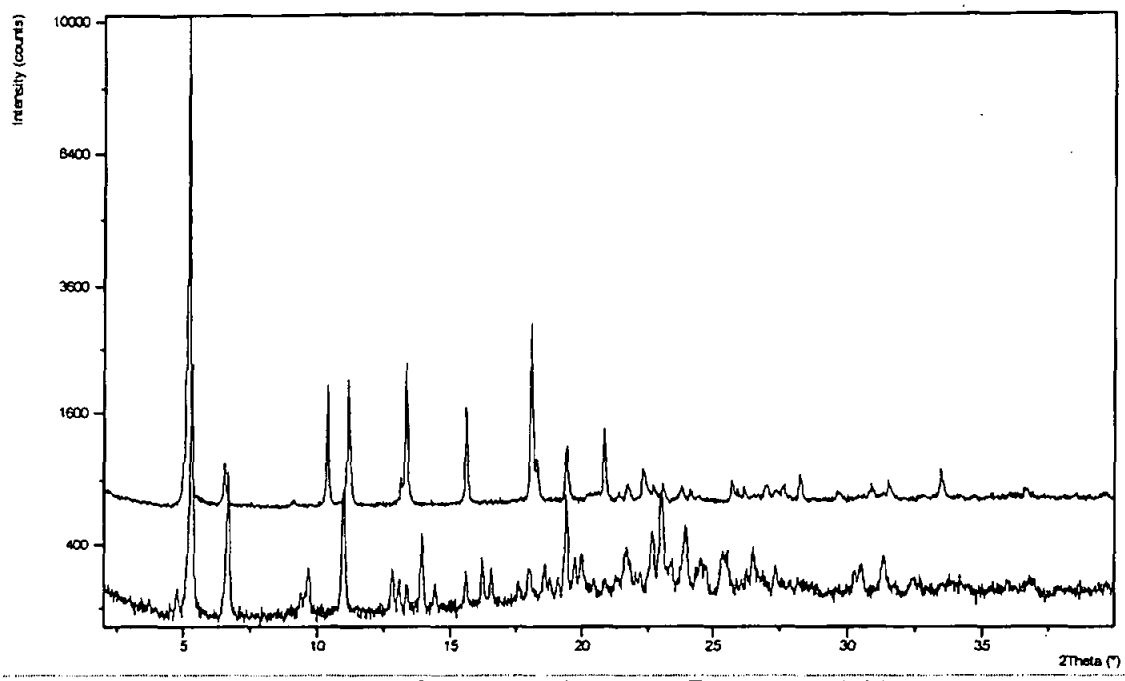


Figure 3 Overlay of XRPD data for Form 1 (bottom), Form 2 (top) (data has been offset for clarity).

DERIVADOS DE XANTINA COMO AGONISTAS SELECTIVOS DE HM74A

La presente invención se refiere a compuestos que son derivados xantina, procedimientos para la elaboración de dichos derivados, formulaciones farmacéuticas que contienen estos compuestos y el uso de los compuestos en la terapia, por ejemplo, en el tratamiento de enfermedades donde sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica.

ANTECEDENTES DE LA INVENCIÓN

La dislipidemia es un término general usado para describir individuos con perfiles de lipoproteína aberrantes. Clínicamente, las clases principales de compuestos usados para el tratamiento de pacientes con dislipidemia, y por tanto en riesgo de enfermedades cardiovasculares son las estatinas, fibratos, resinas de unión a ácido biliar y ácido nicotínico. El ácido nicotínico (niacina, una vitamina B) se han usado clínicamente por alrededor de 40 años en pacientes con varias formas de dislipidemia. El modo primario de acción de ácido nicotínico es a través de la inhibición de triglicérido lipasa sensible a las hormonas (HSL), que resulta en una disminución de ácidos grasos no esterificados de plasma (NEFA) que a su vez altera el metabolismo de grasa hepática para reducir el rendimiento de LDL y VLDL (lipoproteína de densidad baja y muy baja). Se piensa que niveles de VLDL reducidos

disminuyen la actividad de proteína de transferencia de éster de colesterol (CETP) para dar como resultado niveles de HDL incrementados (lipoproteína de alta densidad) que pueden ser la causa de los beneficios cardiovasculares observados. De este modo, el ácido nicotínico produce una alteración muy deseable en perfiles de lipoproteína, reduciendo niveles de VLDL y LDL mientras se incrementa HDL. El ácido nicotínico también ha demostrado que tiene beneficios de modificación de la enfermedad, reduciendo el progreso e incremento de la regresión de lesiones ateroscleróticas y reduciendo el número de eventos cardiovasculares en varias pruebas.

La inhibición observada de HSL por medio de tratamiento con ácido nicotínico es mediada por una disminución en el monofosfato adenosina cíclica celular (cAMP) causada por la inhibición mediada por la proteína G de adenililo ciclasa. Recientemente, los receptores acoplados a proteína G HM74 y HM74A se han identificado como receptores para el ácido nicotínico (solicitud de patente PCT WO02/84298; Wise et al. J Biol Chem., 2003, 278 (11), 9869-9874). La secuencia de ADN de HM74A de humano se puede encontrar en Genbank; con 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 Tunaru lo que ellos denominan HM74 de humano nosotros lo llamamos HM74A y en el documento Soga HM74b es idéntico a HM74A. Las células transfectasa para expresar HM74A y/o HM74 obtienen la capacidad de

producir respuestas mediadas por G_i proteína-G después de la exposición a ácido nicotínico. En ratones que carecen del homologo de HM74A ácido nicotínico (m-PUMA-G) no se reducen os niveles de NEFA en plasma.

Ciertos derivados de xantina se han sintetizado y descrito en la técnica anterior. Por ejemplo, EP0389282 describe derivados de xantina como mediadores potenciales de trastornos cerebro-vasculares. Un intervalo de derivados de xantina se identifican como antagonistas del receptor adenosina por Jacobson et al. en J. Med Chem., 1993, 36, 2639-2644.

Ahora presentamos un grupo de derivados de xantina que son agonistas selectivos del receptor HM74A de ácido nicotínico y por tanto son de potencial beneficio en el tratamiento, profilaxis y supresión de enfermedades donde la sub-activación de este receptor contribuye a la enfermedad o donde la activación del receptor será benéfica.

BREVE DESCRIPCION DE LA INVENCION

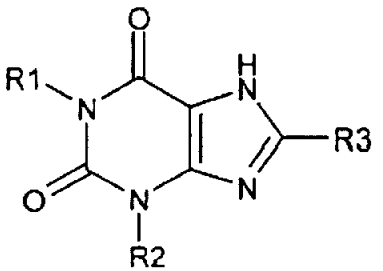
La presente invención provee derivados de xantina y el uso de estos derivados en la terapia, por ejemplo, en el tratamiento de enfermedades donde la sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica. Por ejemplo, en el tratamiento de enfermedades de metabolismo lipídico incluyendo dislipidemia o hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo

aterosclerosis, arteriosclerosis, e hipertrigliceridemia. Como tal, los compuestos también se encuentran favorables como terapéuticos para enfermedad de arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía, así como las indicaciones cardiovasculares asociadas con diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad. Los compuestos también se pueden usar en el tratamiento de enfermedades o condiciones inflamatorias, como se establece posteriormente.

Intermedios, formulaciones, métodos y procedimientos descritos en la presente forman modalidades adicionales de la invención.

DESCRIPCION DETALLADA DE LA INVENCION

De acuerdo a un aspecto de esta invención proveemos al menos una entidad química seleccionada de los compuestos de fórmula (I)



(I)

y derivados farmacéuticamente aceptables de los mismos, en donde

R^1 representa -(alquileno)$_m$-X-(alquileno)$_n$-Y;

en donde m y n representan el número de átomos de carbono en

la cadena alquileno;

en donde X representa un grupo seleccionado de heteroarilo y heterociclilo;

en donde Y representa un grupo seleccionado de arilo, heteroarilo y O-arilo;

que se puede sustituir opcionalmente por uno o más grupos seleccionados independientemente de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, $-(CH_2)_qNR^5R^7$,

$-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$,

$-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)NR^5R^6$,

$-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2NR^5R^6$,

-haloalquilo 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;

R^2 representa alquilo de C_{1-6} que se puede sustituir opcionalmente por uno o más grupos seleccionados independientemente de cicloalquilo, haloalquilo de C_{1-6}, halógeno, -CN y $-OR^4$;

R^3 representa halógeno;

R^4 representa un grupo seleccionado 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 alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_t$ cicloalquilo, $-(CH_2)_t$ cicloalquenilo, $-(CH_2)_t$ heterociclilo, $-(CH_2)_t$arilo, y $-(CH_2)_t$ heteroarilo;

R^8 representa 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 número entero seleccionado de 3 y 4;

n representa un número entero seleccionado de 0 y 1;

p representa un número entero seleccionado de 0 y 1;

q representa un número entero seleccionado de 0, 1 y 2; y

t representa un número entero seleccionado de 1 y 2.

Se piensa que el o los compuestos son de uso en el tratamiento de enfermedades donde la sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica. Por ejemplo en el tratamiento de enfermedades de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardíaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia. Como tal, los compuestos también se encuentran favorables como terapéuticos para enfermedad de arteria coronaria,

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trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía, así como las indicaciones cardiovasculares asociadas con diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad. Como tal los compuestos también se pueden usar como agonistas o agonistas parciales de HM74A. Los compuestos también se pueden usar en el tratamiento de enfermedades o condiciones inflamatorias, como se establece posteriormente.

En una modalidad de la presente invención, X representa un heteroarilo. En otra modalidad X representa un heteroarilo que comprende un heteroátomo de nitrógeno, por ejemplo, triazolilo, furazanilo, oxadiazolilo, tetrazolilo, imidazolilo o pirazolilo. En una modalidad adicional X representa un grupo seleccionado de oxadiazolilo y tetrazolilo.

En una modalidad adicional, 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 representa un grupo opcionalmente sustituido seleccionado de arilo y heteroarilo. En una modalidad Y se selecciona de arilo.

En una modalidad de la presente invención, Y se puede sustituir opcionalmente por uno o más de: alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, NH_2,

$-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$,

$-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)NR^5R^6$,

$-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2NR^5R^6$,

-haloalquilo 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;

En una modalidad adicional, Y se sustituye 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, haloalquilo de C_{1-6}, por ejemplo CF_3 o CH_2CF_3, OCF_3, R^8CN, 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 adicional todavía y se sustituye por uno más grupos seleccionados de OR^5, halógeno, haloalquilo de C_{1-6} y $-(CH_2)_q-N(R^5)C(O)R^8$.

En otra modalidad, Y se sustituye por uno o más grupos seleccionados de halógeno, y haloalquilo de C_{1-6}.

Aún en otra modalidad, Y no se sustituye adicionalmente.

En una modalidad de la presente invención, X y Y representan cada uno independientemente un heteroarilo que comprende un heteroátomo de nitrógeno. En una modalidad adicional X representa oxadiazolilo y Y representa piridinilo. En otra modalidad X representa tetrazolilo y Y representa fenilo. En otra modalidad adicional de la presente invención X representa oxadiazolilo y Y representa fenilo.

En una modalidad de la invención, m es 4 y n es 0. en una modalidad adicional, m es 3 y n es 1.

En una modalidad de la presente invención, R^2 se selecciona de alquilo de C_{3-6}, por ejemplo butilo o pentilo, por ejemplo n-butilo o n-pentilo.

En una modalidad adicional de la presente invención, R^3 se selecciona de cloro y bromo. En otra modalidad, R^3 representa cloro.

En una modalidad de la presente invención R^7 representa un grupo seleccionado de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, -$(CH_2)_t$ cicloalquilo, -$(CH_2)_t$ cicloalquenilo, -$(CH_2)_t$ heterociclilo, -$(CH_2)_t$arilo, y -$(CH_2)_t$ heteroarilo;

En una modalidad de la presente invención X representa oxadiazolilo, Y representa fenilo, R^2 es butilo, R^3 representa cloro y m es 4 y n es 0.

Con respecto a estereisómeros, los compuestos de fórmula (I) pueden tener uno o más átomos de carbono asimétricos y pueden ocurrir como racematos, mezclas racémicas y como enantiómeros individuales o diastereómeros. Todas las formas isoméricas se incluyen dentro de la presente invención, incluyendo mezclas de las mismas.

Cuando un compuesto de fórmula (I) contiene un grupo alquenilo o alquenilo, isomerismo cis (E) y trans (Z) también puede presentarse. La presente invención incluye los estereoisómeros individuales del compuesto de la invención y, cuando sea apropiado, las formas tautoméricas de los mismos, junto con sus mezclas.

La separación de diastereoisómeros o isómeros cis o trans se puede lograr por medio de técnicas convencionales, por ejemplo, por medio de cristalización fraccional, cromatografía o HPLC de una mezcla estereoisomérica del agente también se puede preparar de un intermedio óptimamente puro correspondiente usando un soporte quiral adecuado o por medio de cristalización fraccional de las sales diastereoisoméricas formadas por reacción del racemato correspondiente con un ácido o base óptimamente activo, según sea apropiado.

Además, algunas de las formas cristalinas de los compuestos de 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.

Se entiende 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" son para ser interpretadas de manera inclusive. Es decir, estas palabras pretenden portar la posible inclusión de otros elementos o enteros no recitados específicamente, 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 indique lo contrario, que contiene el número especificado de átomos de carbono. Por ejemplo, alquilo de C_3-C_6 se refiere a una cadena de hidrocarburo recta o ramificada que contiene al menos 3 y a lo más 6 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" como se usa aquí se refiere a una cadena saturada o insaturada recta o ramificada, o grupos enlazadores de hidrocarburo saturados cíclicos. Ejemplos de grupos alquileno incluyen metileno (-CH_2-), etileno (-CH_2CH_2-), eteno (-CH=CH-), o ciclopropileno y lo similar. Por ejemplo, como se usa aquí, -$(alquileno)_m$-, donde m es 3 representa -$(CH_2)_3$-, -$C(CH_3)_2$-, -CH_2CH=CH-, o -ciclopropileno- y lo similar. Por ejemplo como se usa aquí, -$(alq)_m$- donde m es 4 representa -$(CH_2)_4$-, -$CH_2C(CH_3)_2$-, -CH_2CH=$CHCH_2$-, o -CH_2ciclopropileno- y lo similar. Por ejemplo, como se usa aquí -$(alquileno)_n$ donde n = 1 se refiere a -CH_2-. Como se usa aquí -$(alquileno)_n$ donde n = 0 significa que no hay enlace alquileno en esta posición.

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 enlaces dobles.

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 enlaces triples.

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 y ciclooctilo.

El término "cicloalquenilo" como se usa aquí se refiere a un anillo hidrocarburo monocíclico no aromático insaturado de 3 a 8 átomos de carbono que contiene uno o más enlaces dobles carbono-carbono. Ejemplos de dichos grupos incluyen ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo y lo similar.

El término "arilo" como se usa aquí se refiere a un anillo hidrocarburo monocíclico, bicíclico o tricíclico de C_{6-12} en donde al menos un anillo es aromático. Ejemplos de dichos grupos incluyen fenilo, naftilo o tetrahidronaftalenilo y lo similar.

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 a 10 miembros fusionado, que contiene 1 a 4 heteroátomos, cada uno seleccionado independientemente de oxígeno, nitrógeno y azufre. Puede existir uno o más sustituyentes oxo opcionales en los átomos de carbono del 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 lo similar. Ejemplos de dichos anillos aromáticos fusionados incluyen quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinnolinilo, ftalazinilo, naftiridinilo,

indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, furopiridinilo, benzofuranilo, isobenzofuranilo, benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y lo similar.

El término "heterociclilo" como se usa aquí se refiere a un anillo monocíclico de 4-7 miembros o un anillo bicíclico de 8 a 12 miembros fusionado que puede ser saturado o parcialmente saturado que contiene 1 a 4 heteroátomos cada uno seleccionado independientemente de oxígeno, nitrógeno o azufre. Puede haber uno o más sustituyentes oxo opcionales en los átomos de carbono del anillo. Ejemplos de dichos anillos monocíclicos incluyen pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo y lo similar. Ejemplos de dichos anillos bicíclicos incluyen indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H- 3-benzazepina, tetrahidroisoquinolinilo y lo similar.

Los términos "halógeno" o "halo" como se usa aquí se refiere a, por ejemplo, un átomo de flúor, cloro, bromo o yodo.

El término "haloalquilo de C_{1-6}" como se usa aquí se refiere a un grupo alquilo de C_{1-6} como se define en la presente en donde al menos un átomo de hidrógeno se reemplaza con halógeno. Ejemplos de dichos grupos

incluyen fluoroetilo, trifluorometilo, trifluoroetilo y lo similar.

Como se usa aquí, cuando un grupo es referido como siendo "sustituido" por otro grupo o teniendo "uno o más sustituyentes" a menos que una posición particular para dicha sustitución sea especificada se debe 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 durante la administración 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 aquellos con experiencia en la técnica, sin experimentación indebida, y con referencia a la enseñanza de Burger's Medicinal Chemistry And Drug Discovery, 5a Edición, Vol 1: Principles And Practice, que se incorpora en la presente para referencia.

Como se usa aquí, el término "farmacéuticamente aceptable" usado en relación a un ingrediente (ingrediente activo, diluyente o portador) que se puede incluir en una formulación farmacéutica para administración a un paciente, se refiere a que el ingrediente es aceptable en el sentido de ser compatible con cualquiera de otros ingredientes presentes en la formulación farmacéutica y no siendo nocivo a su receptor.

Como se usa aquí, el término "solvato" se refiere a un complejo de estequiometría variable formada por medio de un soluto (en esta invención,

un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo y un solvente. Dichos solventes para los propósitos de la presente invención no pueden interferir con la actividad biológica del soluto. El solvente usado puede ser un solvente farmacéuticamente aceptable. Ejemplos de solventes farmacéuticamente aceptables incluyen agua, etanol y ácido acético. Un ejemplo de un solvente que puede usarse es agua, en dicho caso el solvato se puede referir como un hidrato del soluto en cuestión.

Se apreciará que, para uso farmacéutico, la "sal o solvato" referido anteriormente será una sal o solvato farmacéuticamente aceptable. Sin embargo, otras sales o solvatos pueden encontrar uso, por ejemplo, en la preparación de una sal o solvato farmacéuticamente aceptable del mismo.

Las sales farmacéuticamente aceptables incluyen aquellas descritas por Berge, Bighley and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. Las sales farmacéuticamente aceptables adecuadas incluyen sales de metal alcalino formadas 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 sales de magnesio, sales de amonio; o sales con bases orgánicas tales como etanolamina, trietanolamina, etilen diamina, trietilamina, colina y meglumina; o sales con aminoácidos tales como arginina, lisina e histidina.

Esteres pueden ser activos por sí mismos y/o ser hidrolizables bajo condiciones *in vivo* en el cuerpo humano. Grupos éster hidrolisables *in*

vivo farmacéuticamente aceptables adecuados incluyen aquellos que se rompen fácilmente en el cuerpo humano para dejar el ácido o su sal de origen. Un éster se puede formar en un grupo ácido carboxílico (-(O)OH), por medio de los métodos bien conocidos que involucran la reacción con el alcohol correspondiente. Por ejemplo, ésteres pueden ser ésteres de alquilo de C_{1-6}, por ejemplo, ésteres metílicos, ésteres etílicos, y lo similar.

Como se usa aquí, el término "compuestos de la invención" se refiere a los compuestos de acuerdo a la fórmula I y sus derivados farmacéuticamente aceptables. El término "un compuesto de la invención" se refiere a cualquiera de los compuestos de la invención como se define antes.

Como se usa en la presente el término "al menos una entidad química" significa al menos una sustancia química seleccionada del grupo de compuestos que consisten de compuestos de fórmula I y derivados farmacéuticamente aceptables de los mismos.

En un aspecto de la invención se provee la forma I 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1 H-purina-2,6-diona sustancialmente cristalina. En otro aspecto de la invención se provee la forma 2 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina.

Análisis terminal en muestras de formas 1 y 2 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalinas. De este modo, se provee (forma 1 o forma 2) 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1-H-

purina-2,6-diona sustancialmente cristalina que tiene un punto de fusión inicial por DSC (± 0.5°C) de: 160 °C o más y 147°C o más, respectivamente. 190

Muestras de forma 2 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purine-2,6-diona sustancialmente cristalina, y forma 2 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1 H-puriae-2,6-diona, preparadas como se describe en adelante, proporcionan patrones de difracción de polvo en rayos X de las figuras 1-2. El patrón de difracción de rayos X es único para la forma cristalina. Las formas cristalinas sustancialmente exhiben patrones de difracción con un único conjunto de picos de difracción que se puede expresar en ángulos 2 theta (°).

Los ángulos de difracción 2 theta cuentan para las pociones de varios picos en el patrón de difracción de rayos X. variaciones ligeras en ángulos 2 theta observados se esperan con base en el difractómetro específico empleado 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-purina-2,6-diona se pueden identificar por la presencia de un pico de ángulo 2 theta característico, o por múltiples ángulos 2 theta que son razonablemente característicos de las 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-purina-2,6-diona (forma 1) sustancialmente cristalina, estos picos ocurren en las siguientes posiciones, expresadas en ángulos 2 theta (± 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-purina-2,6-diona (forma 2) sustancialmente cristalina, estos picos ocurren en las siguientes posiciones, expresadas en ángulos 2 theta (±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 al menos uno de los ángulos 2 theta anteriores se emplean para identificar 3-Butil-8- cloro-1 -{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona forma 1 sustancialmente cristalina y 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4- oxadiazol-3-il]butil}-3,7-dihidro-1 H-purina-2,6-diona forma 2 sustancialmente cristalina. En otras modalidades al menos 2, 3, 4 o 5 (donde sea aplicable) de los ángulos 2 theta anteriores se emplean para identificar 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3- il]butil}-3,7-dihidro-1 H-purina-2,6-diona forma 1 sustancialmente criistalina, 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1 H-purina-2,6-diona sustancialmente cristalina.

Algún margen de error está presente en cada una de las asignaciones de ángulo 2 theta. El margen de error en los ángulos 2 theta anteriores es aproximadamente ±0.1 grados para cada una de las asignaciones de pico anteriores.

Ya que algún margen de error es posible en la asignación de ángulos 2 theta, el método preferido de comparación de los patrones de difracción de polvo en rayos X con el fin de identificar la forma cristalina particular es superponer el patrón de difracción de polvo en rayos X de la forma desconocida sobre el patrón de difracción de polvo en rayos X de una forma conocida. Por ejemplo, una persona con experiencia en la técnica

puede superponer un patrón de difracción de polvo en rayos X 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- purina-2,6-diona, obtenida usando los métodos descritos aquí, ver por ejemplo la figura 3, y determinar fácilmente si el patrón de difracción de polvo en rayos X de la forma no identificada es sustancialmente el mismo como el patrón de difracción de polvo en rayos X de 3-Butil-8-cloro-1 -{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona forma 1 sustancialmente cristalina. Si el patrón de difracción de polvo en rayos X es sustancialmente el mismo al mostrado en cualquiera de las figuras 1-2, la forma previa se puede identificar fácilmente y exactamente.

Como se usa aquí, el término "forma sustancialmente cristalina" se refiere a que está sustancialmente libre de forma amorfa 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona. Por "sustancialmente libre" se refiere a que contiene menos del 50% de la forma amorfa, en un aspecto menos de 20% de la forma amorfa, en otro aspecto menos de 10% de la forma forma, 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 S-Butil-[delta]-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-illbutil}-3,7-dihidro-1H-purina- 2,6-diona sustancialmente cristalina como se describe aquí.

Los compuestos de fórmula (I) son de beneficio terapéutico potencial en el tratamiento y mejoramiento de los síntomas de muchas

enfermedades de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia, tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad. Como tal, los compuestos pueden ser favorables como terapéuticos para enfermedad de la arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía.

Se ha reportado que los receptores de HM74 y HM74A están involucrados 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 las células inflamatorias tales como monolitos, neutrófilos y granulocitos en los tejidos. Esto se asocia normalmente con la función de barrera endotelial reducida es referida como inflamación crónica. Dicha inflamación crónica puede manifestarse a través de los síntomas de la enfermedad. El objetivo de la terapia anti-inflamatoria es por tanto reducir esta inflamación crónica y permitir el progreso del proceso fisiológico de la curación y reparación del tejido.

Ejemplos de enfermedades o condiciones inflamatorias para las cuales los compuestos de la presente invención pueden demostrar utilidad incluyen aquellos de la articulación, por ejemplo artritis (por ejemplo, artritis reumatoide, osteoartritis, deficiencia de articulación prostética), o el tracto gastrointestinal (por ejemplo, colitis ulcerativa, enfermedad de Crohn, y otras

enfermedades del intestino inflamatorio y gastrointestinales, gastritis e inflamación de la mucosa que resulta de infección, la enteropatía provocada por fármacos no esteroidales y anti-inflamatorios), del pulmón (por ejemplo, síndrome de distress respiratorio adulto, asma, fibrosis cística, o enfermedad pulmonar obstructiva crónica) del corazón (por ejemplo, miocarditis), de tejido nervioso (por ejemplo esclerosis múltiple), del páncreas, (por ejemplo, inflamación asociada con diabetes mellitus y sus complicaciones), del riñón (por ejemplo, glomerulonefritis), de la piel (por ejemplo, dermatitis, psoriasis, eczema, urticaria, lesión por quemadura), del ojo (por ejemplo glaucoma) así como de órganos transplantados (por ejemplo, rechazo) y enfermedades multi-órganos (por ejemplo, eritematosis lupus sistémica, sepsis) y secuelas inflamatorias de infecciones virales o bacterianas y condiciones inflamatorias asociadas con aterosclerosis y después de insultos hipóxicos o isquémicos (con o sin reperfusión), por ejemplo en el cerebro o en la enfermedad cardiaca isquémica.

En una modalidad, los compuestos de esta invención son útiles en el tratamiento y prevención de inflamación, diabetes y enfermedades cardiovasculares o condiciones que incluyen aterosclerosis, arterosclerosis, hipertrigliceridemia y dislipidemia mixta.

El ácido nicotínico tiene un perfil de efecto lateral significante, posiblemente porque se dosifica en un alto nivel (cantidades en gramos diariamente). El efecto lateral más común es un enjuague cutáneo intenso. En ciertas modalidades de la presente invención los compuestos pueden exhibir

efectos laterales reducidos en comparación a ácido nicotínico. HM74A se han identificado como un receptor de alta afinidad para ácido nicotínico mientras HM74 es un receptor de afinidad baja. Los compuestos de la presente invención muestran una afinidad mayor para HM74A que para HM74 por tanto puede encontrar uso como agonistas HM74A selectivas o agonistas parciales.

El potencial para los compuestos de fórmula (I) para activar HM74A se puede demostrar, por ejemplo, usando los siguientes ensayos de célula completa *in vitro*:

Prueba *in vitro*

Para transfecciones transitoria, células HEK293T (células HEK293 que expresan de manera estable el antígeno T largo SV40) se mantienen en DMEM que contiene suero de ternero fetal al 10% y glutamina 2mM. Las células se siembran en platos de cultivo 90mm y crecen a confluencia de 60-80% (18-24h) antes de la transfección. HM74A humano (GenBank(TM) número de acceso AY148884) se sub-clona en un vector de expresión mamífero (pcDNA3; Invitrogen) y transfecta usando reactivo Lipofectamine™. Para transfección, 9 μg de ADN se mezcla con 30 μl de Lipofectamina en 0.6ml de Opti-MEM (Life Technologies Inc.) y se incuba a temperatura ambiente durante 30 minutos antes de la adición de 1.6ml de Opti-MEM. Las células se exponen a la mezcla Lipofectamina/ADN durante 5 horas y 6 ml de suero de ternero fetal al 20% (v/v) en DMEM entonces se añade. Las células se colectan 48 horas después de transfección. Tratamiento

de toxina de tos ferina se realiza por medio de suplementación en medio a 50 $ngml^{-1}$ durante 16 horas. Todos los estudios de transfección transitoria involucran la co-transfección de receptor junto con la proteína $G_{i/0}$ G, $G_{01\alpha}$.

Para la generación de líneas celulares estables el método anterior se usa para transfectar células CHO-K1 sembradas en seis platos con pozos crecen a confluencia de 30%. Estas células se mantienen en medio DMEM-Ham's F-12 (disponible de Invitrogen) que contiene suero de ternero fetal al 10% y 2mM de glutamina. 48 horas post-transfección el medio se complementa con 400 μg/ml Geneticin (G418, Gibco) para selección de células resistentes a antibióticos. Líneas celulares CHO-K1 que expresan de manera estable HM74A se confirman por mediciones de unión [^{35}S]-GTP$_\gamma$S, después de la adición de ácido nicotínico.

Preparación de membrana P2 - fracciones particuladas P2 que contienen membrana de plasma se preparan de pastas celulares congeladas -80°C después de la recolección. Todos los procedimientos se realizan a 4°C. Las pellas celulares se resuspenden en 1 ml de Tris-HCL 10mM y EDTA 0.1 mM, pH 7.5 (regulador de pH A) y por homogeneización durante 20 segundos con un Ultra Turrax seguido por el paso (5 veces) a través de un aguja de calibre 25. Los lisados celulares se centrifugan a 1,000 g durante 10 minutos en una microcentrífuga para formar en pellas los núcleos y células no fragmentadas y fracciones particuladas P2 se recuperan por medio de microcentrifugación a 16,000 g por 30 minutos. Las fracciones particuladas P2 se resuspenden en regulador de pH A y se almacenan a -80°C hasta que se

requiera.

Unión [^{35}S]-GTP$_\gamma$S - se realizan ensayos a temperatura ambiente en formato de 384 pozos con base en métodos descritos anteriormente, (Wieland, T. y Jakobs, K.H. (1994) Methods Enzymol. 237, 3-13). Brevemente, la dilución de compuestos estándar o de prueba se prepara y añade a una placa de 384 pozos en un volumen de 10 µl. Las membranas (HM74A o HM74) se diluyen en regulador de pH de ensayo (20 mM HEPES, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4) complementado con saponina (60 µg/ml), perlas Leadseeker WGA (Amersham; 250 µg/pozo) y 10 µM GDP, de modo que el volumen 20 µl añadido a cada pozo que contiene 5 µg de membranas. [^{35}S]-GTP$_\gamma$S (1170 Ci/mmol, Amersham) se diluye (1:1500) en regulador de pH de ensayo y 20 µl se añaden a cada pozo. Después de la adición del radioligando, las placas se sellan, giran por impulso y se incuban durante 4 horas a temperatura ambiente. Al final del periodo de incubación las placas se leen en una máquina Leadseeker (VIEWLUX PLUS; Perkin-Elmer) para determinar los niveles de unión específica.

Estos ensayos se refinan al reducir el volumen de ensayo final a 10 µl. Para este ensayo de 10 µl se usa un protocolo revisado. Esto involucra el uso de solamente 100 nl de compuesto estándar o de prueba por pozo de una placa de 384 pozos y 1.5 µg de membrana y 100 µg de perlas Leadseeker WGA. Para el protocolo de volumen bajo, membrana, perlas y [^{35}S]- GTP$_\gamma$S se mezclan en conjunto y después 10 µl de esta mezcla se dispensan a cada pozo. La incubación y la lectura de placa son identicas para

los ensayos 10 µl y 50 µl.

Todos los compuestos ejemplificados se analizan en uno o ambos de los ensayos de unión [^{35}S]- GTP$_\gamma$S descritos anteriormente (es decir, los ensayos 10 µl y 50 µl).

Los datos se analizan por medio de ajuste de la curva como se realiza usando una ecuación logística de cuatro parámetros usando el paquete de software XC50 (máx 2 puntos suprimidos de cualquiera curva). La unión específica se expresa como pEC_{50} y como % de eficiencia en comparación a la respuesta máxima de unión de ácido nicotínico.

Prueba *in vitro*

Los compuestos de la invención se pueden analizar en ratas Spague-Dawley macho (200-250 g) que han estado en ayunas por al menos 12 horas antes del estudio. Los compuestos se dosifican de manera intravenosa en 1 o 3 mg/kg (5 ml/kg) o por medio de alimentación por sonda oral en dosis que varían de 1-30 mg/kg (10 mg/kg). Las muestras de sangre (0.3 ml de sangrado de la vena de la cola) se pueden tomar en pre-dosis y en tres veces post-dosis (el tiempo variando de 15 minutos a 6 horas post-dosis). Cada muestra de sangre se transfiere a un tubo de heparina (Becton Dickinson Microtainer, PST LH) y centrifuga (10,000g durante 5 minutos) para producir una muestra de plasma. Las muestras de plasma se analizan para niveles de ácidos grasos no esterificados (NEFA) usando un equipo comercialmente disponible (Randox). La inhibición de niveles de NEFA en

plasma, en relación a niveles de pre-dosis, se usa como un sustituto para actividad de agonista de HM74A.

Con el fin de determinar si los compuestos de la invención exhiben la respuesta del lavado asociada con ácido nicotínico se pueden dosificar a conejillos de Indias concientes. Los conejillos de Indias Dunkin Hartley (300-600 g; n=10-20 por grupo) se mantienen en ayunas por al menos 12 horas, pero no en exceso de 24 horas antes de la experimentación. Las muestras de sangre pre-estudio (0.5 ml) se toman de cada animal por pinchazo cardiaco bajo anestesia de recuperación (Isoflurano 3.5% con O2 adicional (1L/min)). Se toman mediciones de la temperatura de la oreja al colocar la oreja izquierda de cada animal sobre una sonda de temperatura infla-roja. Mediciones se toman en un intervalo de 5 minutos de pre-dosis a 30 minutos post-dosis. Las mediciones de temperatura se toman en intervalos de 15 minutos hasta 2 horas post-dosis. Los animales reciben los compuestos de prueba por medio de alimentación por sonda oral (5 ml/kg). Las muestras de sangre (0.5 ml) se toman por pinchazo cardiaco 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. Las muestras de sangre completas se colocan en un rodillo de sangre durante 5 minutos y entonces se almacenan en hielo hasta el final del estudio. Después de la centrifugación (12000 g durante 5 minutos) el plasma se transfiere en tubos frescos y se almacena a -20°C hasta que se analice para concentraciones de NEFA.

Algunos compuestos de acuerdo a la fórmula (I) se han

sintetizado (ver ejemplos sintéticos posteriores) y se analizan en los ensayos de unión [^{35}S]-GTP$_\gamma$S discutidos antes.

Algunos compuestos de acuerdo a la fórmula (I) incluyendo:

8-cloro-3-(3,3-dimetilbutil)-1-[2-(etiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona; tienen utilidad como intermedios en la producción de otros compuestos de acuerdo a la fórmula (I).

Los compuestos ejemplificados (ejemplos 1-512) tienen una pEC$_{50}$ de 4.3 (+/- 0.3 unidad log) o mayor y una eficacia de 30% o mayor (en relación a ácido nicotínico) en los ensayos de unión a [^{35}S]- GTP$_\gamma$S discutidos anteriormente, en donde se analizaron.

Purificación general y métodos analíticos

LC/EM: método

HPLC analítico se conduce en una columna Supelcosil™ ABZ+PLUS (Supelco) (3 μm, 3.3 cm x 4.6 mm ID) fluyendo con 0.1% HCO_2H y 0.01 M acetato de amonio en agua (solvente A), y 95% MeCN y 5% agua (que contiene 0.5% HCO_2H) (solvente B), usando el siguiente gradiente de elusión 0-0.7 minutos 0% B, 0.7-4.2 minutos 0 -> 100% B, 4.2-4.6 minutos 100% B, 4.6-4.8 min 100 -> 0% B a un caudal de 3 ml/min. La detección de UV con arreglo de diodos se realiza en el intervalo de 215 a 330nm. Los espectros de masas (EM) se registran en un espectrómetro de masas Waters ZQ usando modos de ionización positiva por electro-rociado mas [(ES+ve para

proporcionar MH^+ y $M(NH_4)^+$ iones moleculares] o ionización negativa por electro-rociado [(ES-ve para proveer $(M- H)^-$ ion molecular]. Únicamente el ion de origen de isotopos entrecomillado.

Los espectros ^1H RMN se registran usando un espectrómetro Bruker DPX 400MHz usando tetrametilsilano como el estándar.

Cromatografía Biotage™ se refiere a purificación usando los sistemas Flash 40i o Flash 150i, comercializados por Biotage AB, usando cartuchos pre-empacados con KPSil (sílice).

El sistema Companion™ se refiere al sistema de purificación Teledyne Isco Combiflash Companion™. Este es un sistema de purificación con gradiente controlado con detección de UV de longitud de onda variable e integral con la capacidad de disparar la colección de fracción automatizada por el umbral de UV.

La auto-preparación dirigida por masa (MDAP) se refiere a métodos donde el material se purifica por cromatografía líquida de alta resolución usando una columna de Supelcosil™ ABZ+ 5 μm (10cm x 20mm i.d.) o una columna Supelcosil™ ABZ+ 10 μm (15cm x 30mm i.d.) con un gradiente adecuado de solvente A: 0.1% HCO_2H en agua y solvente B: 95% MeCN, 5% agua (que contiene 0.5% HCO_2H). El inyector/colector Waters 2767 se dispara por medio de un espectrómetro de masas MicroMass ZQ en la detección de la masa de interés (usando un software Micromass MassLynx).

HPLC preparativa (HPLC auto-preparativa o Autoprep) se refiere

a métodos donde el material se purifica por cromatografía líquida de alta resolución en una columna de Supelcosil™ ABZ+ 5 μm (10cm x 20mm i.d.) con un gradiente adecuado de 0.1% HCO_2H en agua y MeCN (que contiene 0.5% HCO_2H). El colector de fracción Gilson 233 es disparado por detección de UV.

SPE (extracción de fase sólida) se refiere al uso de cartuchos de polietileno que se pre-empacan con sorbente usado para la purificación. El sorbente contenido en estos cartuchos se especificará. Ejemplos usados se detallan posteriormente:

C18 SPE se refiere al uso de cartuchos pre-empacadas con 40 μM C18 sorbente de sílice funcionalizada (comercializado por Varian Inc.). El compuesto se carga, normalmente en 50:50 DEMO / MeOH, en un cartucho condicionado previamente con MeCN y equilibrado con 5% MeCN en agua. El producto se eluye con un gradiente adecuado de 0.1% HCO_2H en agua y MeCN (0.5% HCO_2H).

Aminopropil SPE o columna se refiere al uso de cartuchos pre-empacados con 40 μm-120 μm de sílice funcionalizada con aminopropilo (comercializado por Varian Inc.). El producto crudo se carga normalmente en mezclas DCM/MeOH en un cartucho condicionado previamente con MeOH. Los componentes neutrales se eluyen con MeOH y/o DCM (volúmenes de columna 3 o 4) y los componentes ácidos eluyen normalmente con un eluyente que contiene una proporción de AcOH (2-20%).

Cartuchos Oasis™/Oasis™ SPE se refieren a los cartuchos SPE

empacados con un sorbente polimérico fabricado por Waters Corporation. Estos normalmente se condicionan con 3 volúmenes columna de MeOH y equilibrados con agua antes de que la muestra sea cargada. Sales e inorgánicos se eluyen con agua y el producto normalmente se eluye con MeOH or MeCN.

GreenHouse™ se refiere a una plataforma de sintetizador paralelo de reacción 24 disponible de RDT Ltd, RU.

Como se indicó anteriormente, los compuestos de fórmula (I) pueden encontrar uso en la medicina huma o veterinaria, por ejemplo, como activadores de HM74A, en el manejo de dislipidemia e hiperlipoproteinemia.

De este modo, se provee como otra modalidad de la presente invención al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en la medicina humana o veterinaria, por ejemplo en el tratamiento de trastornos de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia, tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad. Como tal, los compuestos también se proveen para usarse en el tratamiento de la enfermedad de arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía.

Se provee como una modalidad adicional de la presente

invención al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en la elaboración de un medicamento para el tratamiento de trastornos de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia, tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad. Como tal, los compuestos también se proveen para usarse en el tratamiento de la enfermedad de arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía.

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 al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en el tratamiento de trastornos de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia. Por ejemplo, el uso se provee de al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo en el tratamiento de dislipidemia diabética, dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad, enfermedad de arteria coronaria, trombosis, angina, deficiencia

renal crónica, apoplejía y enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis y hipertrigliceridemia

Se entiende que esta modalidad de la presente invención incluye cualquier combinación de modalidades particulares y cubre todas las combinaciones de sustituyentes particulares descritos aquí para los compuestos de fórmula (I)

Adicionalmente, la presente invención provee el uso de al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en la elaboración de un medicamento para el tratamiento de enfermedades o condiciones inflamatorias de la articulación, por ejemplo artritis (por ejemplo, artritis reumatoide, osteoartritis, deficiencia de articulación prostética), o del tracto gastrointestinal (por ejemplo, colitis ulcerativa, enfermedad de Crohn, y otras enfermedades del intestino inflamatorio y gastrointestinales, gastritis e inflamación de la mucosa que resulta de infección, la enteropatía provocada por fármacos no esteroidales y anti-inflamatorios), del pulmón (por ejemplo, síndrome de distress respiratorio adulto, asma, fibrosis cística, o enfermedad pulmonar obstructiva crónica) del corazón (por ejemplo, miocarditis), de tejido nervioso (por ejemplo esclerosis múltiple), del páncreas, (por ejemplo, inflamación asociada con diabetes mellitus y sus complicaciones), del riñón (por ejemplo, glomerulonefritis), de la piel (por ejemplo, dermatitis, psoriasis, eczema, urticaria, lesión por quemadura), del ojo (por ejemplo, glaucoma) así como de órganos transplantados (por ejemplo, rechazo) y enfermedades multi-órganos (por

ejemplo, eritematosis lupus sistémica, sepsis) y secuelas inflamatorias de infecciones virales o bacterianas y condiciones inflamatorias asociadas con aterosclerosis y después de insultos hipóxicos o isquémicos (con o sin reperfusión), por ejemplo en el cerebro o en la enfermedad cardiaca isquémica.

En una modalidad adicional o alternativa se provee un método para el tratamiento de un sujeto humano o animal con una condición donde la sub-activación del receptor HM74A contribuye a la condición o donde la activación del receptor será benéfica, dicho método comprende la administración a dicho sujeto humano o animal de una cantidad efectiva de al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

Nuevamente, se entiende que esta modalidad de la presente invención incluye cualquier combinación de modalidades particulares y cubre todas las combinaciones de sustituyentes particulares descritas aquí para los compuestos de fórmula (I).

En una modalidad, la presente invención provee un método para el tratamiento de trastornos de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia, tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad, dicho método comprende la administración a dicho sujeto humano o

animal de una cantidad efectiva de al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo. Como tal, estos compuestos también pueden ser favorables en métodos para el tratamiento de la enfermedad de arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica y apoplejía, dichos métodos comprenden la administración a dicho sujeto humano o animal de una cantidad efectiva de al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

La cantidad de un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo que se requiere para lograr el efecto biológico deseado, por supuesto, dependerá en 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, normalmente 0.1 mg - 100 mg/kg. Una dosis intravenosa puede, por ejemplo, estar en el intervalo de 0.01 mg a 0.1 g/kg, normalmente 0.01 mg - 10 mg/kg, que puede ser de manera conveniente administrada 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. De este modo las ampolletas para inyección pueden contener, por ejemplo, de 0.01 μg a 1 g y formulaciones de dosis unitaria oralmente administrable, 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 fórmula (I) o un derivado farmacéuticamente aceptable del mismo se puede emplear como el compuesto per se en el tratamiento de una enfermedad donde la sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica, un ejemplo de esto es cuando un compuesto de la presente se presenta con un portador aceptable en la forma de una formulación farmacéutica. El portador debe, por supuesto, ser aceptable en el sentido de ser compatible con los otros ingredientes de la formulación y no debe se nocivo para el receptor. El portador 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 la administración oral, rectal, tópica, bucal (por ejemplo, sublingual) y parenteral (por ejemplo, subcutánea, intramuscular, intradérmica o intravenosa).

Se provee también de acuerdo a la invención un procedimiento para la preparación de dicha composición farmacéutica que comprende el mezclado de los ingredientes.

Formulaciones adecuadas para la administración oral se puede presentar en unidades discretas, tales como cápsulas, sellos, pastillas o tabletas, cada una conteniendo una cantidad predeterminada de un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo; como un polvo o gránulos; como una solución o una suspensión en un

líquido acuoso o no acuoso; o como una emulsión aceite en agua o agua en aceite. En general, las formulaciones se preparan por medio de mezclado de manera uniforme e íntima del compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, con un líquido o portador sólido finamente dividido, o ambos, y entonces, si es necesario, la formación del producto. Por ejemplo, una tableta se puede preparar al comprimir o moldear un polvo o gránulos del compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo opcionalmente con uno o más ingredientes adicionales. Las tabletas comprimidas se pueden preparar al comprimir, en una máquina adecuada, el compuesto en una forma de flujo libre, tal como un polvo o gránulos opcionalmente el mezclado con un aglutinante, lubricante, diluyente inerte y/o agente o agentes superficialmente activos/dispersantes. Las tabletas moldeadas se pueden hacer al moldear, en una máquina adecuada, el compuesto en polvo humedecido con un diluyente líquido inerte.

Las tabletas y cápsulas para la administración oral pueden contener excipientes convencionales tales como agentes aglutinantes, por ejemplo, jarabe, acacia, gelatina, sorbitol, trgacanto, mucilago de almidón o polivinil pirrolidona; sustancias de relleno, por ejemplo, lactosa, celulosa microcristalina, azúcar, almidón de maiz, fosfato de calcio o sorbitol; lubricantes, por ejemplo, estearato de magnesio, ácido esteárico, talco, polietilen glicol o sílice; desintegrantes, por ejemplo, almidón de papa, croscarmelosa de sodio o glicolato almidón de sodio; o agentes de

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humectación tales como sulfato lauril de sodio. Las tabletas se pueden recubrir de acuerdo a métodos bien conocidos en la técnica. Las preparaciones líquidas orales pueden estar en la forma de, por ejemplo, suspensiones acuosas o aceitosas, soluciones, emulsiones, jarabes o elíxires, o se pueden presentar 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, metil celulosa, jarabe de glucosa/azúcar, gelatina, hidroximetil celulosa, hidroxipropilmetil celulosa, carboximetil celulosa, gel de estearato de aluminio o grasas comestibles hidrogenadas; agentes de emulsionamiento, por ejemplo, lecitina, sorbitán mono-oleato o acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo aceite de almendras, aceite de coco fraccionado, ésteres aceitosos, propilen glicol o alcohol etílico; o conservadores, por ejemplo, metil o propil p-hidroxibenzoatos o ácido sórbico. Las preparaciones también pueden contener sales reguladoras de pH, saborizantes, agentes de color y/o edulcorantes (por ejemplo, mannitol) como sea apropiado.

Formulaciones adecuadas para la administración bucal (sublingual) incluyen tabletas que comprenden un compuesto de la invención en una base de sabor, normalmente 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 la

administración parenteral comprenden de manera conveniente preparaciones acuosas estériles de un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, la formulación puede ser isotónica con la sangre del receptor propuesto. Estas preparaciones se pueden administrar de manera intravenosa, aunque la administración también puede ser efectuada por medio de inyección subcutánea, intramuscular, o intradérmica. Estas preparaciones se pueden preparar de manera conveniente al mezclar el compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo con agua y haciendo la solución resultante estéril e isotónica con la sangre. Composiciones inyectables de acuerdo a la invención generalmente contendrán de 0.1 a 5% p/p del compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

De este modo, las formulaciones de la presente invención adecuadas para la administración parenteral que comprenden un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo se pueden formular para la administración parenteral por medio de inyección de bolo o infusión continua y puede ser presentada en 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 tomar tales formas como soluciones, suspensiones o emulsiones en vehículos acuosos o no acuosos, y pueden contener agentes formuladotes tales como anti-oxidantes, reguladores de pH, agentes anti-microbianos y/o agentes de ajuste de toxicidad. Ejemplos

de formulaciones adecuadas para la administración oral incluyen formulaciones que comprenden un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en DEMO al 10% y carbonato ácido de sodio al 90% en solución salina estéril. Ejemplos de formulaciones adecuadas para administración intravenosa incluyen formulaciones que comprenden un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en DEMO al 5% o 10% y carbonato ácido de sodio al 95% o 90% en agua estéril. Alternativamente, el agente terapéuticamente activo puede estar en forma de polvo para constitución con un vehículo adecuado, por ejemplo, agua estéril, libre de pirógeno, antes de usarse. La presentación sólida seca se puede preparar por medio de llenado de un polvo estéril de manera aséptica en contenedores estériles individuales o por medio del llenado de una solución estéril de manera aséptica en cada contenedor y secado por congelamiento.

Formulaciones adecuadas para administración rectal se puede presentar como supositorios de dosis unitaria. Estos se pueden preparar por mezclado de un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo con uno o más portadores sólidos convencionales, por ejemplo, manteca de cacao o glicéridos y después la formación de la mezcla resultante.

Las formulaciones adecuadas para aplicación tópica a la piel pueden tomar la forma de un ungüento, crema, loción, pasta, gel, pulverizador, aerosol, o aceite. Los portadores que se pueden usar incluyen

vaselina, lanolina, polietilen glicoles, alcoholes, y combinaciones de dos o más de estos. El compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo generalmente está 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, incluimos la administración por medio de insuflación e inhalación. Ejemplos de varios tipos de preparación para administración tópica incluyen ungüentos, cremas, lociones, polvos, pesarios, pulverizadores, aerosoles, cápsulas, o cartuchos para usarse en un inhalador o insuflador o gotas (por ejemplo, gotas para ojos o nariz).

Ungüentos y cremas pueden, por ejemplo, formularse con una base acuosa o aceitosa con la adición de agentes espesantes y/o gelificantes y/o solventes. Dichas bases pueden de este modo, por ejemplo, incluir 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 polietilen glicol.

Agentes de espesamiento que se pueden usar incluyen parafina suave, estearato de aluminio, alcohol cetoestearílico, polietilen glicoles, cera microcristalina y cera de abeja.

Lociones se pueden formular con una base acuosa o aceitosa y en general contendrán uno o más agentes de emulsionamiento, agentes de estabilización, agentes de dispersión, agentes de suspensión o agentes de espesamiento.

Polvos para aplicación externa se pueden formar con la ayuda

de cualquier base en polvo adecuada, por ejemplo, talco, lactosa o almidón. Las gotas se pueden formular con una base acuosa o no acuosa que comprende también uno o más agentes de dispersión, agentes de solubilización o agentes de suspensión.

Las composiciones para pulverización se pueden formular, por ejemplo, como soluciones acuosas o suspensiones o como aerosoles suministrados de paquetes presurizados, con el uso de un propulsor adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, 1,1,1,2,3,3,3-heptafluoropropano, 1,1,1,2-tetrafluoretano, dióxido de carbono u otro gas adecuado.

Cápsulas y cartuchos para usarse en un inhalador o insuflador, de por ejemplo gelatina, se puede formular conteniendo una mezcla en polvo de un compuesto de la invención y una base en polvo adecuada tal como lactosa o almidón.

Las composiciones farmacéuticas de acuerdo a la invención también se pueden usar en combinación con otras clases de fármacos dislipidémicos (por ejemplo, estatinas, fibratos, resinas de unión a ácido biliar o ácido nicotínico).

Los compuestos de la presente invención se pueden usar en combinación con uno o más agentes terapéuticamente activos diferentes, por ejemplo, en combinación con otras clases de fármacos dislipidémicos, por ejemplo, inhibidores de reductasa A 3-hidroxi-3-metilglutaril-coenzima (estatinas) o fibratos o resinas de unión a ácido biliar o ácido nicotínico. De

este modo la invención provee, en una modalidad adicional, el uso de dicha combinación en el tratamiento de enfermedades donde la sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica y el uso de al menos de un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo en la elaboración de un medicamento para la terapia de combinación de trastornos de metabolismo lipídico incluyendo dislipidemia o hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa 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 de manera separada, consecutivamente o simultáneamente por cualquier ruta conveniente.

Las combinaciones referidas anteriormente se pueden presentar convenientemente para usarse en la forma de una formulación farmacéutica y de este modo formulaciones farmacéuticas que comprenden una combinación como se definió anteriormente óptimamente junto con un portador o excipiente farmacéuticamente aceptable comprende una modalidad adicional de la invención. Los componentes individuales de dichas combinaciones se pueden administrar en conjunto o de manera separada, consecutivamente o simultáneamente en formulaciones farmacéuticas separadas o combinadas.

Cuando se combina en la misma formulación se apreciará que los dos componentes deben ser estables y compatibles uno con otro y los otros componentes de la formulación y se pueden formular para administración. Cuando se formulan de manera separada se pueden proveer en cualquier formulación conveniente, de manera conveniente en dicha manera como es conocido para dichos compuestos en la técnica.

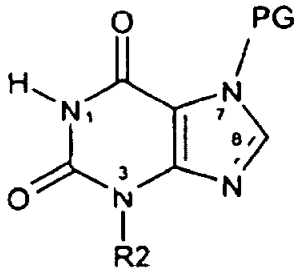
Cuando está en combinación con un segundo agente activo terapéutico contra la misma enfermedad, la dosis de cada componente puede diferir de aquel cuando el compuesto se usa solo. Las dosis apropiadas se apreciarán fácilmente por aquellos con experiencia en la técnica.

De esta manera la invención provee, en una modalidad adicional, una combinación que comprende al menos un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo junto con otro agente terapéuticamente activo.

La combinación referida anteriormente se puede presentar de manera conveniente para usarse en la forma de una formulación farmacéutica y así las formulaciones farmacéuticas que comprenden una combinación como se definió anteriormente junto con un portador farmacéuticamente aceptable de la misma representa una modalidad adicional de la invención.

Los compuestos de la presente invención y derivados farmacéuticamente aceptables de los mismos se pueden preparar por medio de metodología descrita en adelante, constituyendo una modalidad adicional de esta invención.

En una modalidad la presente invención provee un método para la preparación de compuesto o compuestos de fórmula (I) de un material de inicio apropiado, por ejemplo compuesto o compuestos de fórmula (II):



(II)

En donde PG= grupo protector, el método comprendiendo

(i) alquilación en N1 de una xantina N7 protegida;

(ii) alquilación en N3 de una xantina N7 protegida;

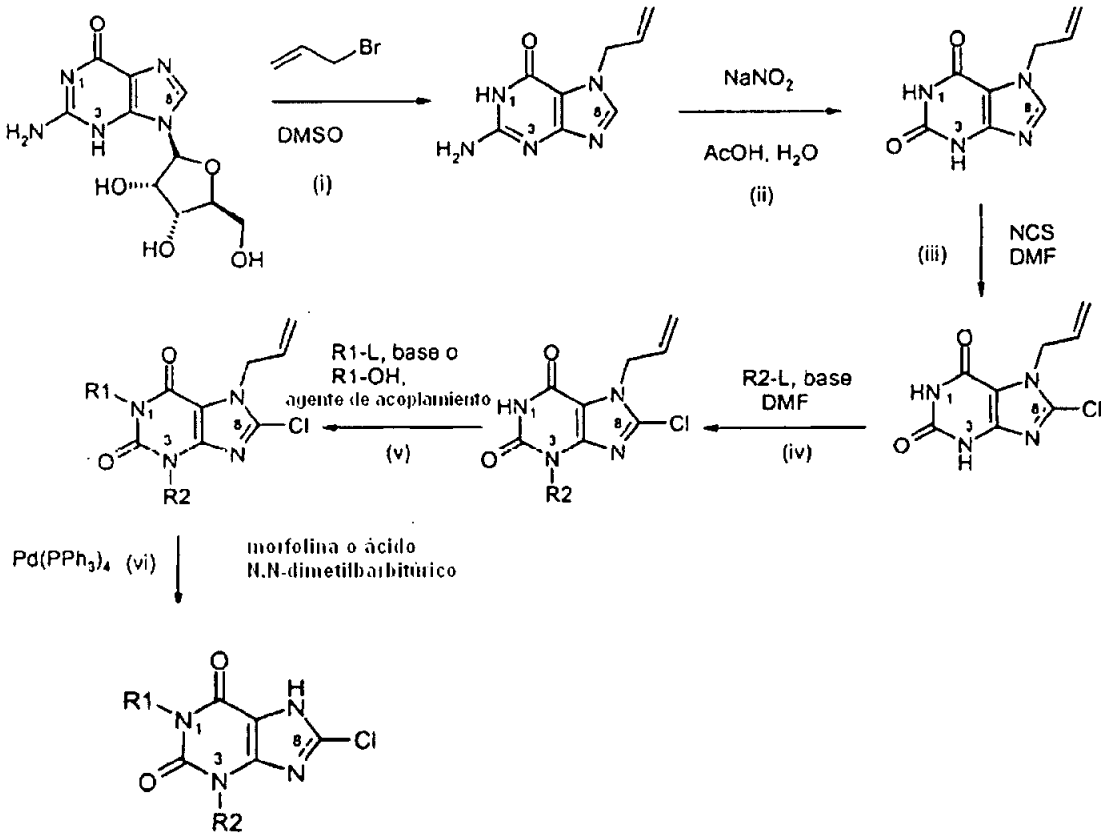
(iii) halogenación en C8; y

(iv) desprotección de N7;

en cualquier orden que provee desprotección se realiza después de la alquilación.

Procedimiento 1:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde R1 incorpora un heterociclilo, heteroarilo o arilo y R1 representa Cl.



i) alquilación de guanina con bromuro de alilo

ii) diazotisación con nitrito de sodio seguido por hidrólisis para formar la xantina

iii) cloración

iv) alquilación en N3 (ejemplos de bases adecuadas incluyen Na_2CO_3, Cs_2CO_3, K_2CO_3)

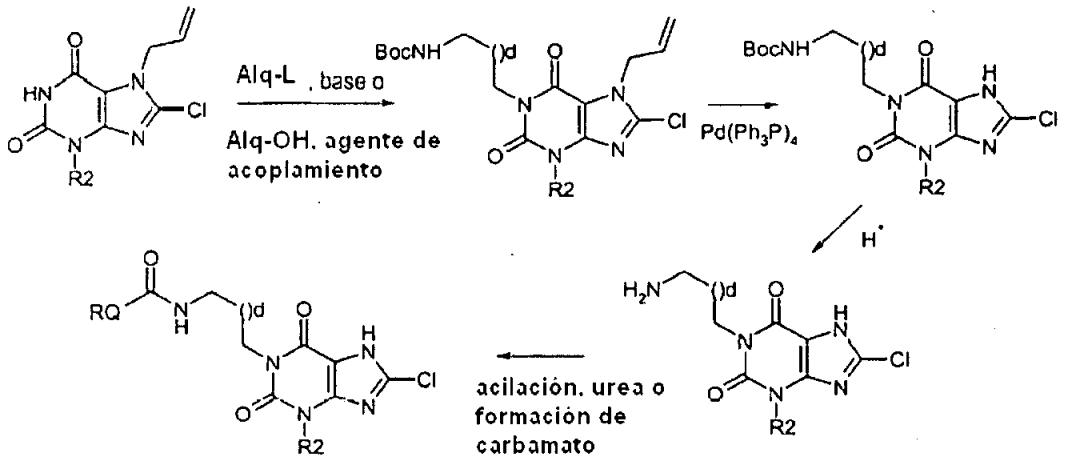
v) alquilación en N1 (ejemplos de bases adecuadas incluyen Na_2CO_3, Cs_2CO_3, K_2CO_3)

vi) remoción catalizada con paladio del grupo alilo

en donde L representa un grupo saliente, por ejemplo halógeno.

Procedimiento 2:

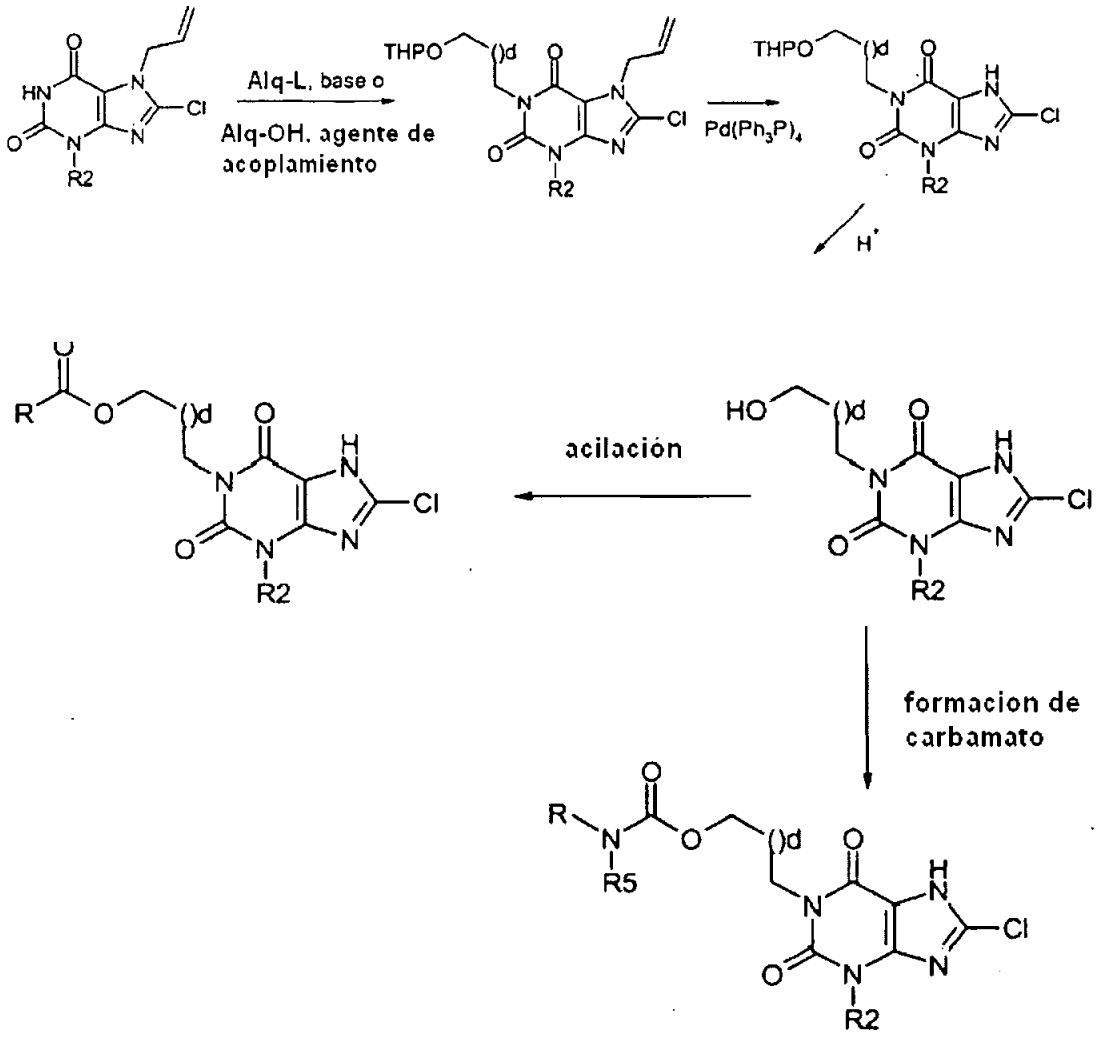
Un procedimiento de acuerdo a la invención para la preparación de intermedios en donde R1 incorpora una amida, carbamato o urea, que puede ser útil para la producción de compuesto o compuestos de fórmula (I).



En donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1) (es decir, d junto con el metileno precedente = m), R representa -(alquileno)$_n$-Y y Q puede o no estar presente, y si está presente representa O o NR5.

Procedimiento 3:

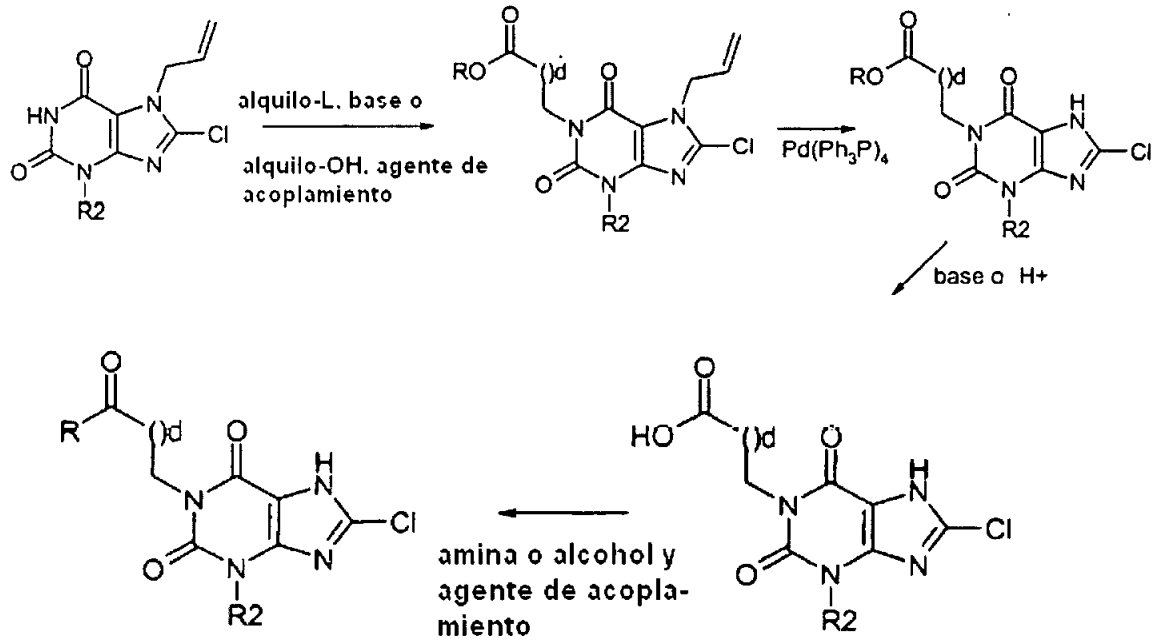
Un procedimiento para la preparación de intermedios en donde R1 incorpora un carbamato o éster "inverso", que puede ser útil para la producción de compuesto o compuestos de fórmula (I).



en donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1), y R representa -$(alq)_n$-Y.

Procedimiento 4:

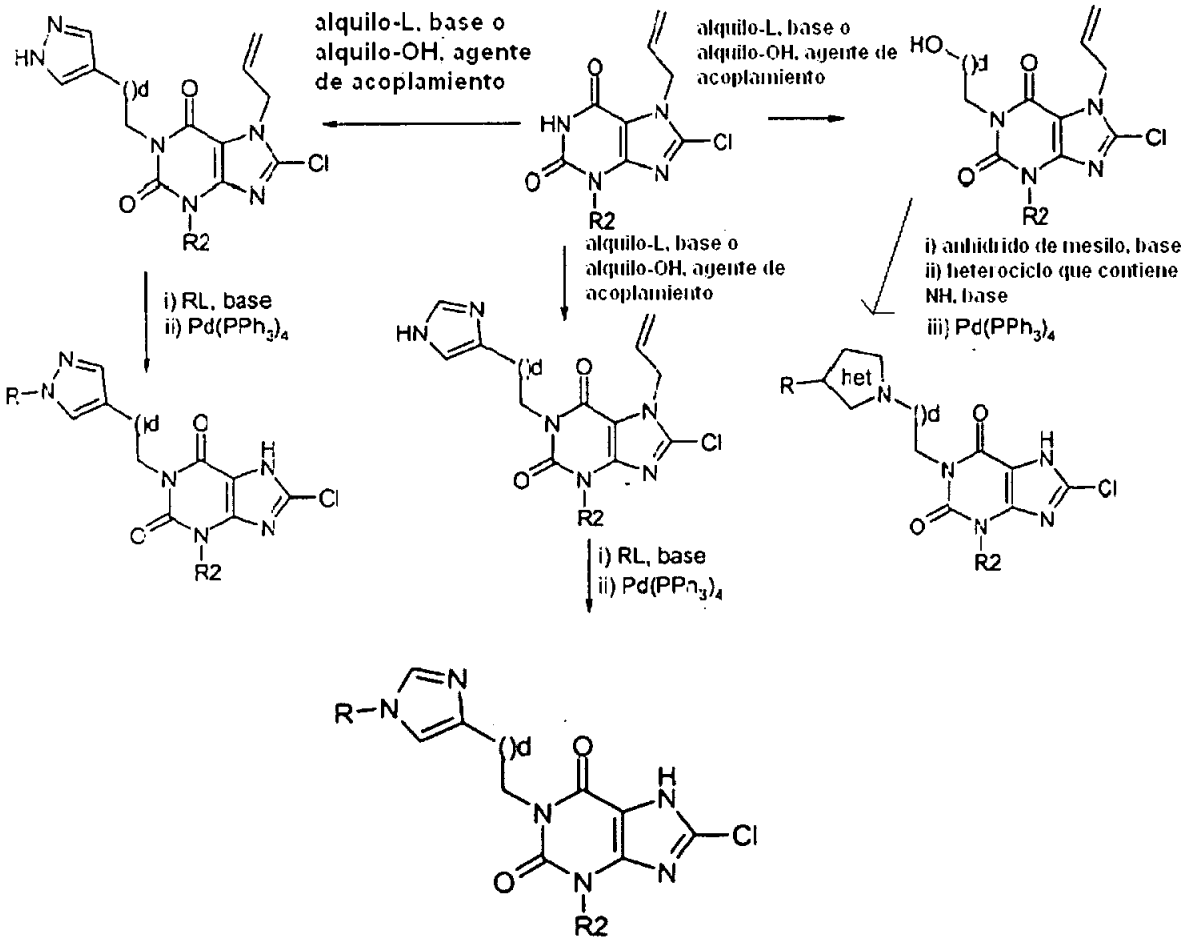
Un procedimiento de acuerdo a la invención para la preparación de intermedios en donde R1 incorpora un éster o amida, que puede ser útil para la producción de compuesto o compuestos de fórmula (I).



en donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1), y R representa $-NR^5R^7$ u OR^5.

Procedimiento 5:

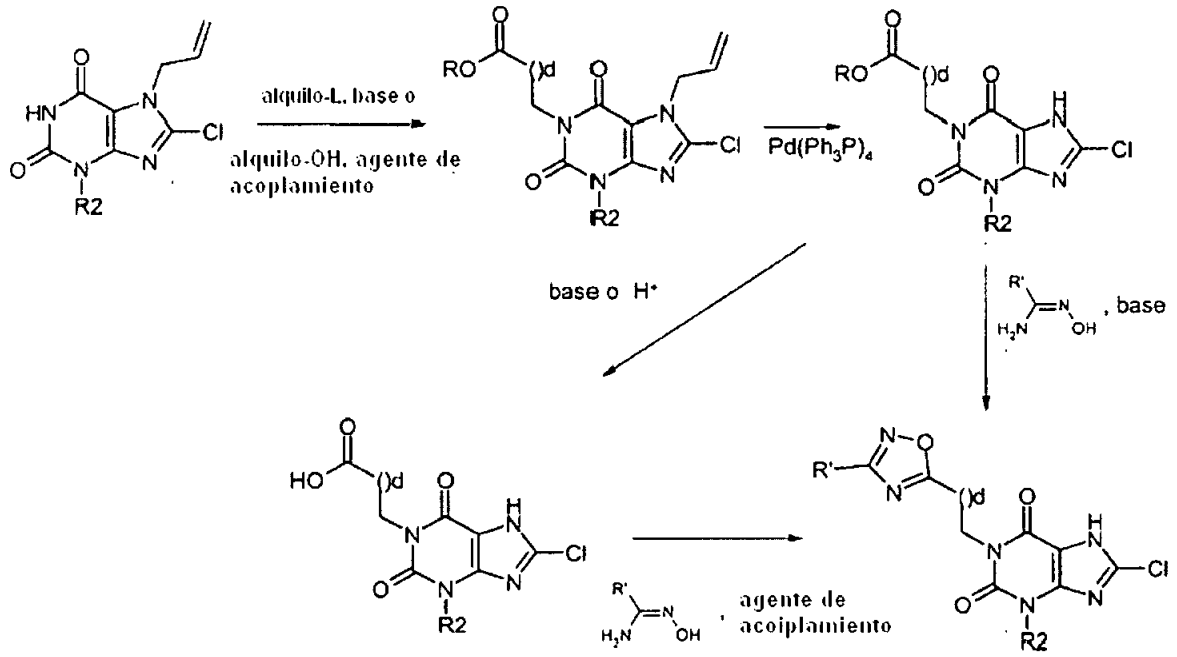
Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde X incorpora un pirazol, imidazol o tetrazol.



En donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1), y R representa $-(alq)_n-Y$.

Procedimiento 6:

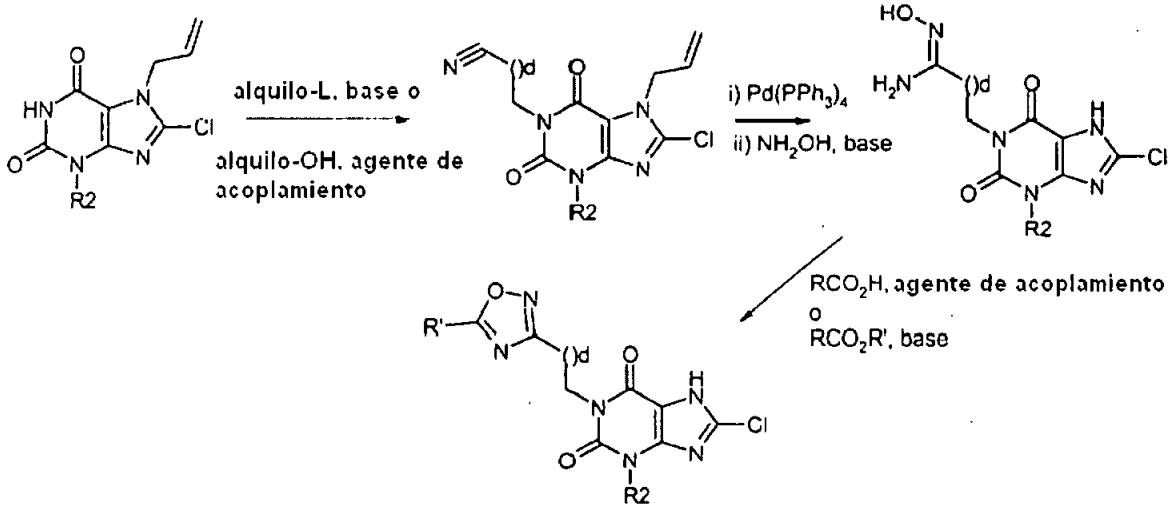
Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde x incorpora un oxadiazol.



En donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1), R representa un grupo alquilo y R' representa -(alq)$_n$-Y.

Procedimiento 7:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde X incorpora un oxadiazol

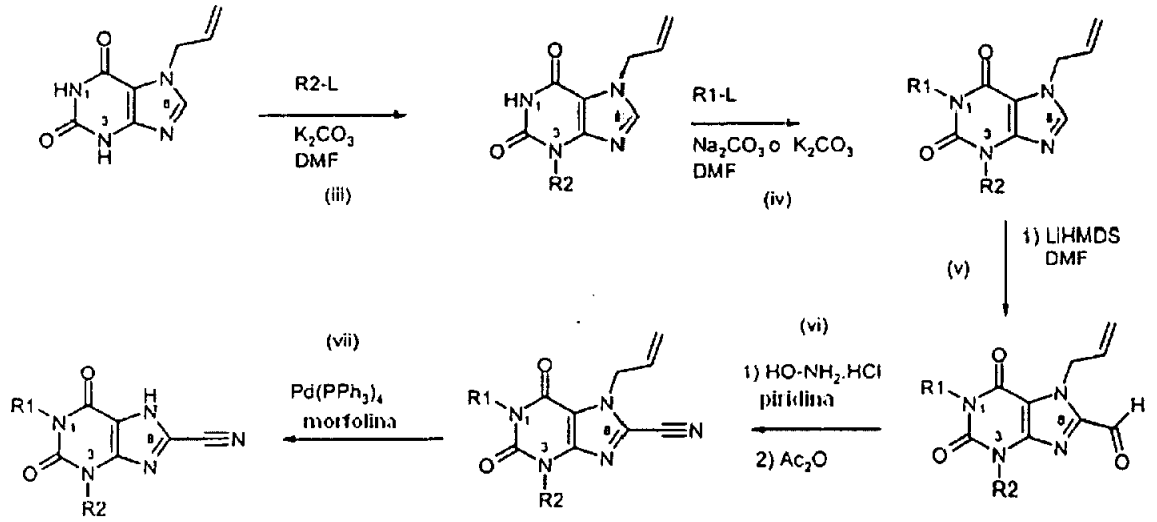


En donde L representa un grupo saliente, por ejemplo halógeno, d representa (m-1), R representa un grupo alquilo y R' representa -$(alq)_n$-Y.

Procedimiento 8

Un procedimiento de acuerdo a la invención para la preparación de intermedios en donde R^3 es CN, que puede ser útil para la preparación de compuesto o compuestos de fórmula (I).

Este comprende etapas (i) y (ii) del procedimiento 1 seguido por:



iii) alquilación en N3

iv) alquilación en N1

v) formación del aldehído en C8 por medio de litiación con LiHMDS y templado con DMF

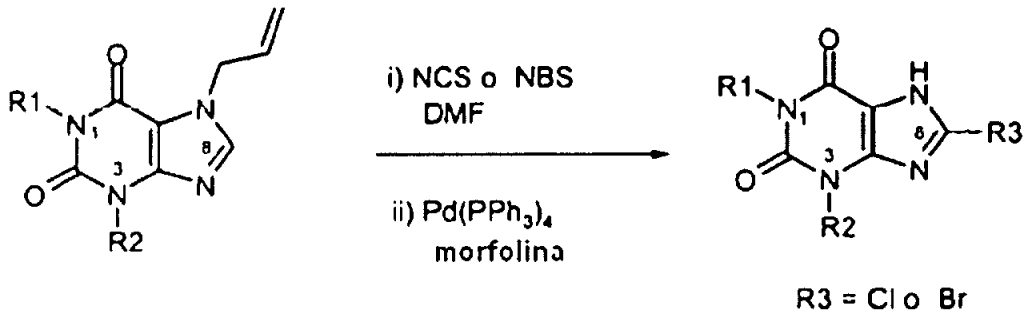
vi) conversión del aldehído al nitrilo

vii) remoción catalizada con paladio del grupo alilo

en donde L representa un grupo saliente.

Procedimiento 9:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde R^3 es Cl o Br comprende las etapas (i) a (iv) seguido por:

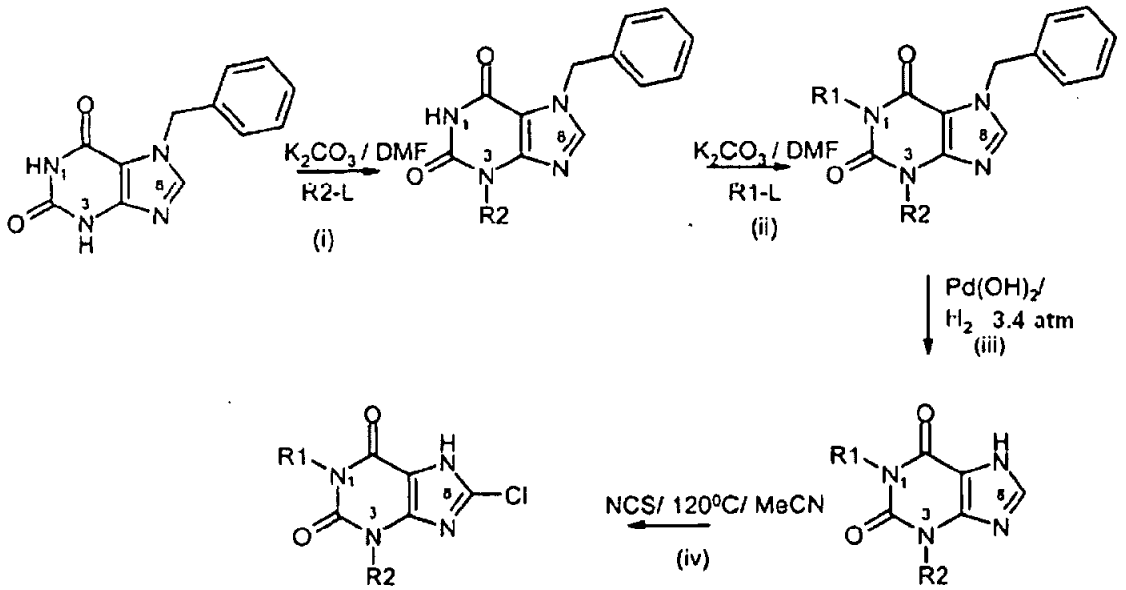


i) halogenación en C8 usando NCS o NBS

ii) remoción catalizada con paladio del grupo alilo

Procedimiento 10:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde R^3 es Cl comprende:



i) alquilación en N3

ii) alquilación en N1

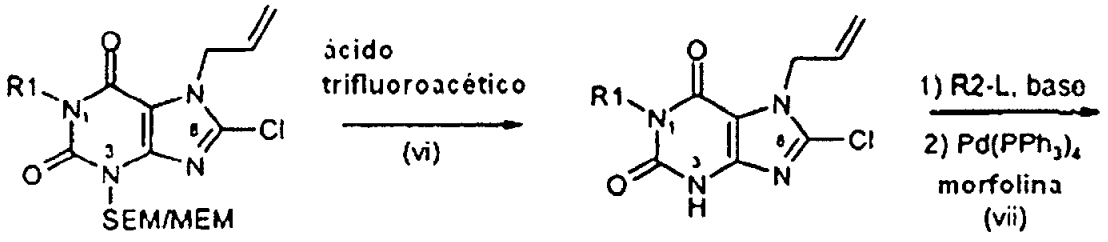
iii) debencilación

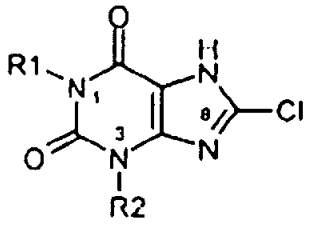
iv) cloración en C8

en donde L representa un grupo saliente

Procedimiento 11:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde R^1 difiere de R^2 y R^3 es Cl comprende las etapas (i) a (v) del procedimiento 1 (donde R^2 del procedimiento 1 es específicamente SEM o MEM) seguido por:





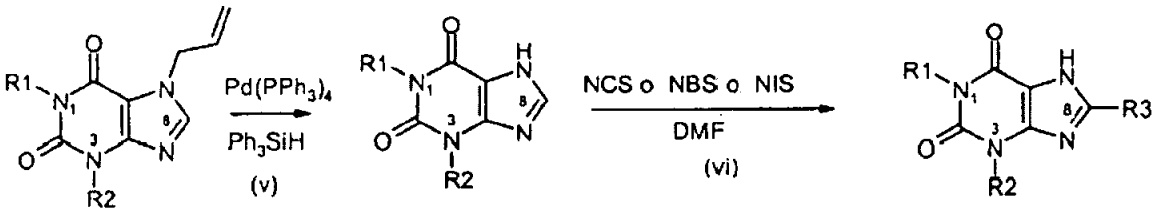
vi) escisión de MEM o grupo protector SEM

vii) alquilación de N3 seguido por remoción catalizada con paladio del grupo alilo

en donde L representa un grupo saliente

Procedimiento 12

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I) en donde R^3 es Cl, Br o I comprende las etapas (i) a (v) del procedimiento 8 seguido por:

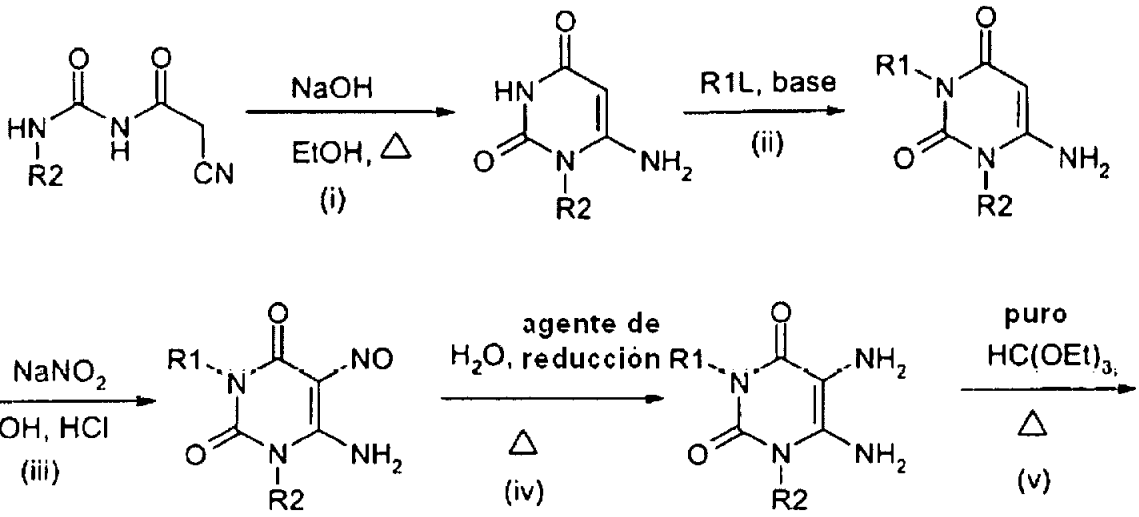


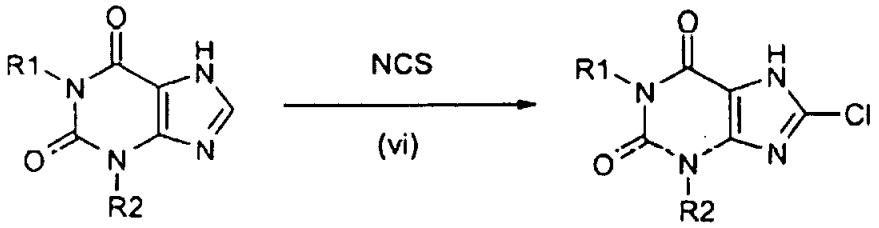
v) remoción catalizada con paladio de grupo alilo

vi) halogenación en C8 usando NCS, NBS o NIS

Procedimiento 13:

Un procedimiento de acuerdo a la invención para la preparación de compuestos de fórmula (I) comprende:





i) formación de pirimidinadiona

ii) alquilación en N1

iii) nitrosación

iv) reducción usando $Na_2S_2O_4$ o un agente de reducción similar

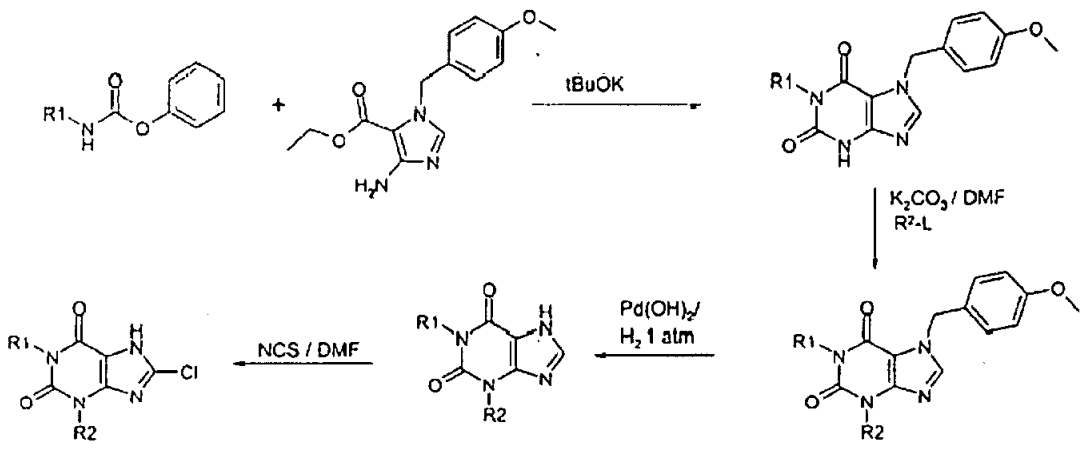
v) formación de xantina

vi) halogenación en C8 usando NCS

en donde L representa un grupo saliente

Procedimiento 14:

Un procedimiento de acuerdo a la invención para la preparación de compuesto o compuestos de fórmula (I):



En donde L representa un grupo saliente.

Como una etapa adicional a los procedimientos generales descritas anteriormente, y en particular para usarse en la preparación de los ejemplos posteriores, existen varias formas de compuestos resultantes de purificación, uno o más de los cuales pueden ser de uso en la presente invención, por ejemplo el uso de MDAP, por medio de recristalización de uno o más solventes adecuados tales como acetato de etilo, etanol absoluto, acetonitrilo o metanol, o por el uso de purificación en columna tal como cartuchos Silica Redisep™ y elusión posterior con un solvente adecuado tal como diclorometano que contiene acetato de etilo.

Cuando se desee o se necesite, como una etapa final en cualquiera de los procedimientos sintéticos anteriores, un compuesto resultante de fórmula (I) se puede convertir en un derivado farmacéuticamente aceptable, por ejemplo un compuesto resultante de fórmula (I) se puede convertir en una forma salina o viceversa o conversión de una forma de sal en otra forma de sal farmacéuticamente aceptable. Estos procedimientos serán conocidos por una persona con experiencia en la técnica.

Abreviaciones

AcOH	ácido acético
atm	atmósfera
br	amplio (RMN)
CDI	carbonildiimidazol
d	doblete (RMN)

230

DBAD	di-t-butilazodicarboxilato
DCM	diclorometano
DIPEA	diisopropiletilamina
DMSO	dimetilsulfóxido
DMF	N,N-dimetilformamida
EtOAc	Acetato de etilo
EtOH	etanol
h	hora(s)
IPA	alcohol isopropílico
m	multiplete (RMN)
MDAP	masa dirigida autoprep
MeCN	acetonitrilo
MeOH	metanol
Min	minutos
NCS	N-clorosuccinimida
NBS	N-bromosuccinimida
NIS	N-yodosuccinimida
q	cuartete (RMN)
rt	temperatura ambiente
RT	tiempo de retención
s	singlete (RMN)
SPE	cartucho de extracción de fase sólida
t	tiempo

TFA	ácido trifluoroacético
THF	tetrahidrofurano
DMEM	medio de Tagle modificado de Dulbecco
HEPES	ácido 4-(2-hidroxietil)piperazina-1-etanosulfónico
LiHMDS	hexametildisilano de litio
Δ	calor
SEM	2-(trimetilsilil)etoximetil
MEM	2-metoxietoximetilo
Boc	t-butoxicarbonilo
THP	tetrahidropirano

BREVE DESCRIPCION DE LOS DIBUJOS

Figura 1: datos de XRPD de forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina.

Figura 2: datos de XRPD de forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina.

Figura 3: sobreposición de datos de XRPD para la forma 1 y forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina.

Los siguientes ejemplos no limitantes ilustran la presente

invención

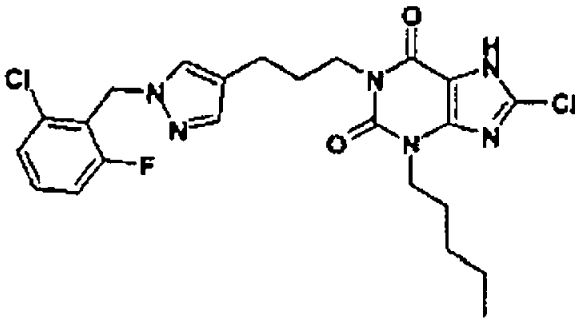
EJEMPLOS SINTETICOS

Se debe notar que la asignación de (Z)-estereoquímica expuesta en los compuestos ejemplificados posteriormente no se han confirmado por datos experimentales. La persona con experiencia en la técnica reconocerá que puede existir interconversión entre isómeros E & Z. (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. La barrera rotacional carbono-nitrógeno como una prueba estreoquímica de benzamidoximas. Journal of Organic Chemistry (1975), 40(20), 2979-80).

EJEMPLO 1

8-cloro-1-(3-{1-[(2-cloro-6-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-1-(3-{1-[(2-cloro-6-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

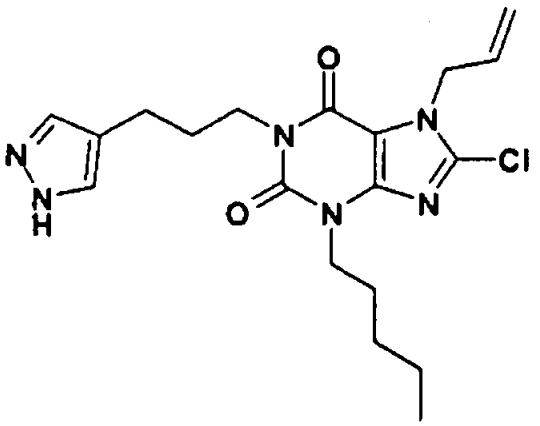


8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-

dihidro-1H-purina-2,6-diona (61 mg, 0.15 mmol) en DMF seco (2 ml) se agita con carbonato de sodio (64 mg, 0.6 mmol) y bromuro 2-cloro-6-fluorobencilo (134 mg, 0.6 mmol) y se calienta a 45°C durante 18h bajo nitrógeno. Después de enfriamiento a temperatura ambiente la mezcla se desgasifica mediante evacuación y readmisión de nitrógeno, y se agita con tetraquis(trifenilfosfina)paladio (0) (35 mg, 0.303 mmol) y morfolina (0.13 ml) durante 5.5 h. La mezcla se divide entre EtOAc y HCl 2M, la fase orgánica se separa y se evapora y el residuo se purifica por SPE de aminopropilo (5 g, se lava con THF-MeOH (1:1) después MeOH puro cerca y finalmente se eluye con DCM-MeOH (1:1)

LC/EM: m/z 507 $[MH]^+$, temperatura ambiente 3.64 minutos.

b) 8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona



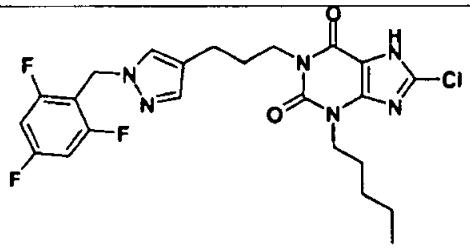
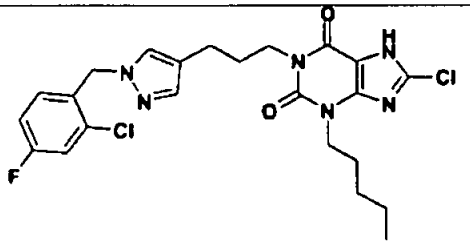
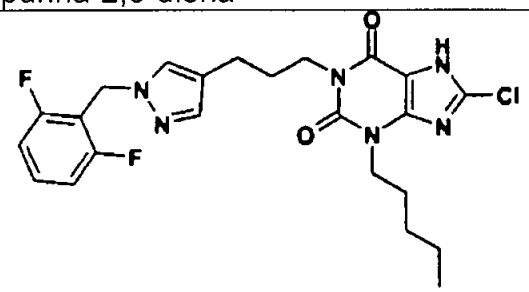
3-pentil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (5 g, 16.86 mmol) y 3-(1H-pirazol-4-il)propan-1-ol (2.12 g, 16.8 mmol) se agitan en THF seco (150 ml) a 3°C. Se añade azodicarboxilato de dibencilo

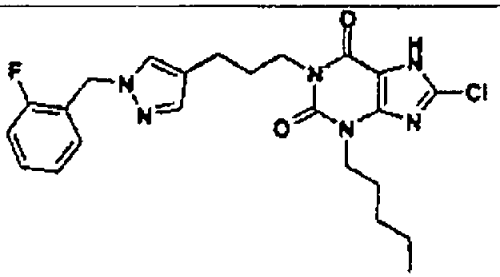
(10.05 g, 33.7 mmol) seguido por la adición gota a gota de trifenilfosfina (8.83 g, 33.7 mmol) en THF seco (70 ml). La mezcla se deja calentar a temperatura ambiente y se agita durante 18 horas. Se añade agua (1 ml) y los solventes se evaporan. El residuo se toma en Et_2O (200 ml) a partir del cual un sólido blanco, principalmente óxido de trifenilfosfina, se cristaliza y se filtra. El filtrado se concentra y los productos secundarios se cristalizan a partir de éter-ciclohexano. El filtrado sobrante se concentra (19.2 g) y se purifica en un sistema Biotage™ (400 g) eluyendo con EtOAc-ciclohexano (2:1) para producir el compuesto del titulo como un sólido blanco (2.89 g).

LC/EM m/z 405 $[M+H]^+$, temperatura ambiente 3.19 minutos.

Los siguientes compuestos (cuadro 1) se preparan usando un método análogo al del ejemplo 1, a partir de haluros de bencilo correspondientes.

CUADRO 1

Ejemplo	Estructura	Rend. (mg)	LC/EM
2	 8-cloro-3-pentil-1-(3-{1-[(2,4,6-trifluorofenil)metil]-1H-pirazol-4-il}-propil)-3,7-dihidro-1H-purina-2,6-diona	68	m/z 509 $[M+H]^+$ RT 3.58 min
3	 8-cloro-1-(3-{1-[(2-cloro-4-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	56	m/z 507 $[M+H]^+$ RT 3.73 min
4	 8-cloro-1-(3-{1-[(2,6-difluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	29	m/z 491 $[M+H]^+$ RT 3.53 min

Ejemplo	Estructura	Rend. (mg)	LC/EM
5	 8-cloro-1-(3-{1-[(2-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	32*	m/z 473 $[M+H]^+$ RT 3.55 min

[a] después de purificación adicional por MDAP

Detalles RMN para ejemplos seleccionados del cuadro 1

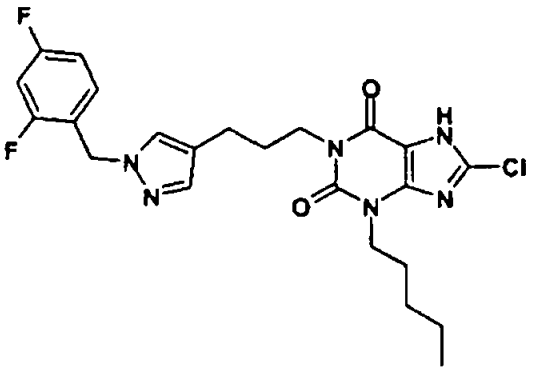
EJEMPLO 2

8-cloro-3-pentil-1-(3-{1-[(2,4,6-trifluorofenil)metil]-1H-pirazol-4-il}propil)-3,7-dihidro-1H-purina-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= 8Hz), 3.83-3.94 (m, 4H), 5.24 (s, 2H), 7.18-7.30 (m, 3H), 7.57 (s, 1H).

EJEMPLO 6

8-cloro-1-(3-{1-[(2,4-difluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

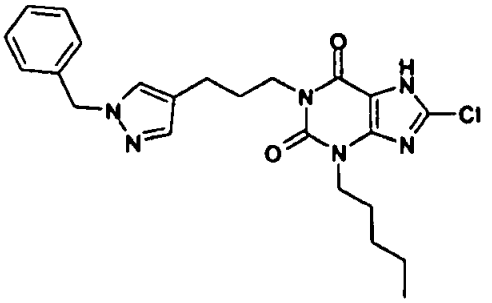
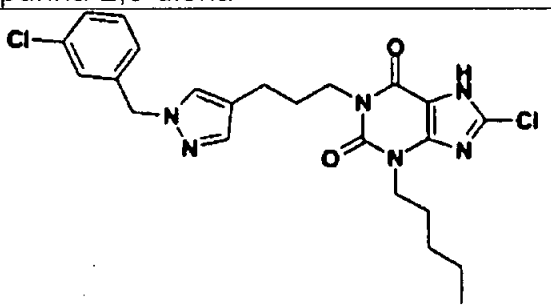
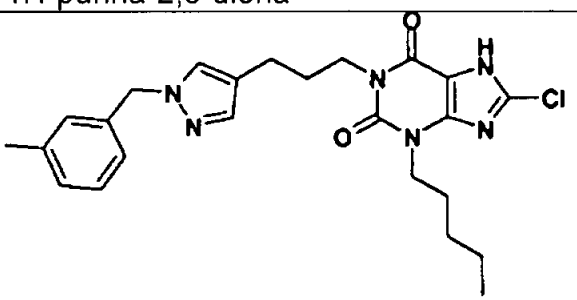


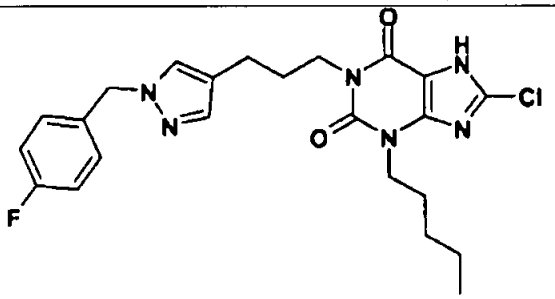
8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona (81 mg, 0.2 mmol) y carbonato de sodio (85 mg, 0.8 mmol) se agita en DMF seco (2 ml) con bromuro de 2,4-difluorobencilo (166 mg, 0.8 mmol) a 45°C durante 18 horas. La mezcla se desgasifica y se agita con tetraquis(trifenilfosfina)paladio (0) (46 mg, 0.04 mmol) y morfolina (176 mg, 2 mmol) a temperatura ambiente durante 6 horas. La reacción se trata y se purifica por SPE de aminopropilo (5 g, se lava con THF-MeOH (1:1) después MeOH puro, se eluye con DCM-MeOH (1:1) con 5% AcOH añadido) para producir el compuesto del titulo (37.7 mg) como un sólido.

LC/EM: m/z 491 $[M+H]^+$, temperatura ambiente 3.42 min.

Los siguientes compuestos (cuadro 1) se preparan usando un método análogo al del ejemplo 1, a partir de los haluros de bencilo correspondientes.

CUADRO 2

Ejemplo	Estructura	Rend. (mg)	LC/EM
7	 8-cloro-3-pentil-1-(3-[1-(fenilmetil)-1H-pirazol-4-il]propil)-3,7-dihidro-1H-purina-2,6-diona	17[a]	m/z 455 $[M+H]^+$ RT 3.52 min
8	 8-cloro-1-(3-{1-[(3-clorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	11.6[a]	m/z 489 $[M+H]^+$ RT 3.52 min
9	 8-cloro-1-(3-{1-[(3-metilfenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	33	m/z 469 $[M+H]^+$ RT 3.54 min

Ejemplo	Estructura	Rend. (mg)	LC/EM
10	 8-cloro-1-(3-{1-[(4-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	42	m/z 473 $[M+H]^+$ RT 3.44 min

[a] después de purificación adicional por MDAP

Detalles RMN para ejemplos seleccionados del cuadro 2

EJEMPLO 6

^{1}H RMN (d^6 DMSO) 0.85 (3H, t, J= 7 Hz), 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)

EJEMPLO 7

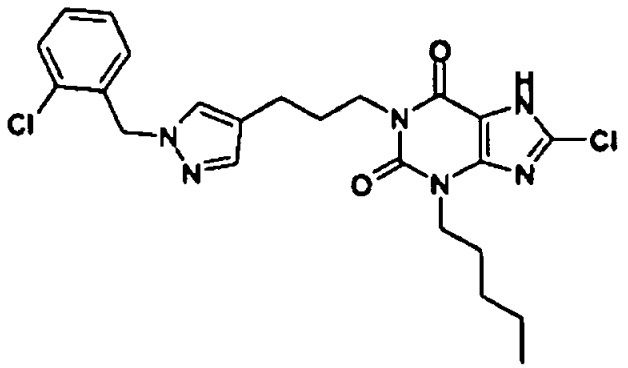
8-cloro-3-pentil-1-{3-[1-(fenilmetil)-1H-pirazol-4-il]propil}-3,7-dihidro-1H-purina-2,6-diona

^{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= 8Hz), 3.83-3.95 (m, 4H), 5.24 (s, 2H), 7.13-7.38 (m, 6H), 7.61 (s, 1H).

240

EJEMPLO 11

8-cloro-1-(3-{1-[(2-clorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



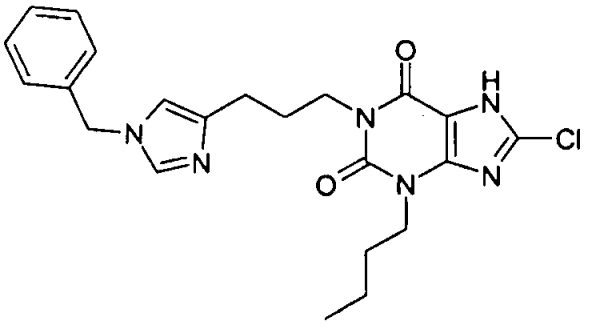
Se prepara por el método para 8-cloro-1-(3-{1-[(2,4-difluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona. Ejemplo 6 pero a partir de bromuro de 2-clorobencilo (164 mg, 0.8 mmol). Sin embargo, a fin de completar la etapa de desprotección se añade tetraquis(trifenilfosfina)paladio (0) (40 mg) y morfolina (0.15 ml) adicionales y la agitación continua por unas 5.5 horas adicionales. La purificación por SPE de aminopropilo anteriormente produce el compuesto del titulo como un sólido (42 mg).

LC/EM: m/z 489 $[MH]^+$, temperatura ambiente 3.67 minutos.

EJEMPLO 12

3-butil-8-cloro-1-{3-[1-(fenilmetil)-1H-imidazol-4-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 3-butil-8-cloro-1-(3-[1-(fenilmetil)-1H-imidazol-4-il]propil)-3,7-dihidro-1H-purina-2,6-diona



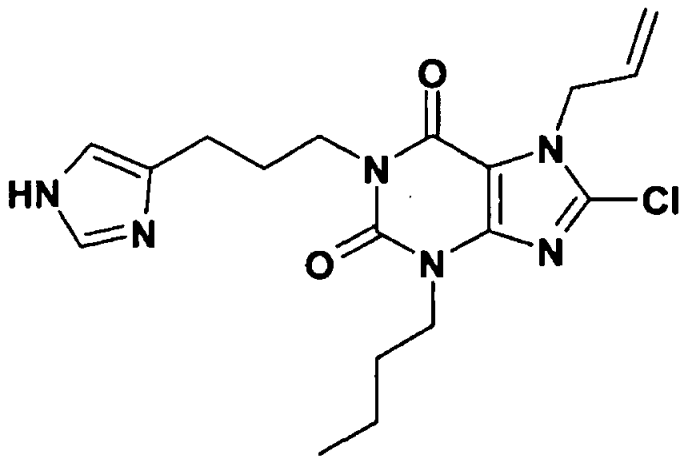
A una solución de 3-butil-8-cloro-1-[4-(1H-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (300 mg, 0.77 mmol) en THF anhidro (5 ml) se trata con bromuro de bencilo (144 mg, 0.84 mmol) y DIPEA (147 µl, 0.84 mmol). La mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 4 días. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El crudo se purifica por una columna SPE de sílice usando un gradiente MeOH/DCM al 0.5-5%. Las fracciones de producto se combinan y se concentran bajo alto vacío. El producto se disuelve en THF (5 ml) después $Pd(PPh_3)_4$, (88 mg, 0.077 mmol) y morfolina (670 µl, 7.67 mmol) se añaden y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 horas. Se añaden 88 mg de $Pd(PPh_3)_4$, (0.077 mmol) y la mezcla se deja

agitar a temperatura ambiente bajo nitrógeno durante 16 horas. La mezcla se divide entre EtOAc y H_2O. La capa orgánica se separa y la capa acuosa se extrae con EtOAc (x2). Las capas orgánicas se combinan, se lavan con salmuera, se secan ($MgSO_4$) y se concentran. El producto crudo se purifica por MDAP para proporcionar el compuesto del titulo como un sólido blanco (9 mg, 2%).

LC/EM: m/z 441 $[MH]^+$, temperatura ambiente 2.50 minutos.

^1H 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 (t traslapado con DMSO, 2H, J= 7.5Hz), 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-(1H-imidazol-4-il)propil]-7-(2-propan-1-il)-3,7-dihidro-1H-purina-2,6-diona

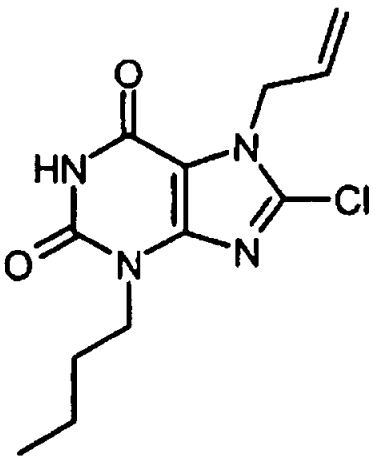


Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (2.8 g, 9.9 mmol) en THF anhidro (60 ml) se trata con 3-(1H-imidazol-4-il)-1-propanol (1.5 g, 12 mmol) en THF anhidro (10 ml) y PPh_3 (3.4

g, 13 mmol). Se añade DBSD (2.9 g, 13 mmol) en una porción y la mezcla se deja agitar a temperatura ambiente, bajo nitrógeno durante 18 horas. La mezcla se divide entre EtOAc y H_2O. La capa acuosa se extrae y se lava con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan ($MgSO_4$) y se concentran. El producto crudo se purifica por un cartucho SPE de sílice usando un gradiente MeOH/EtOAc (0.5%-7% de MeOH). Las fracciones de producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (2.16 g, 55%).

LC/EM: m/z 391 $[MH]^+$, temperatura ambiente 2.40 minutos.

c) 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona



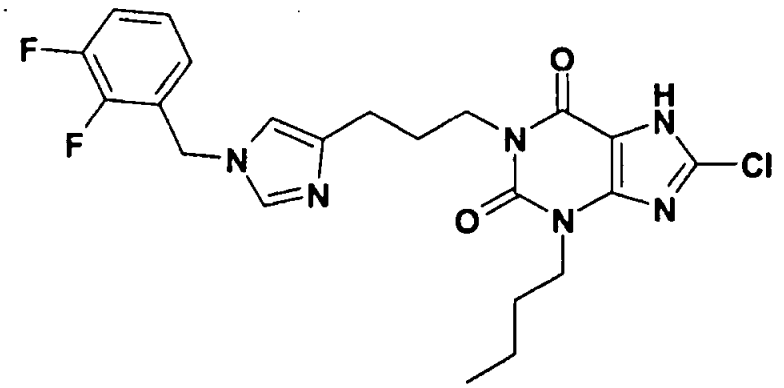
A una solución de 3-butil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (3.34 g, 13.4 mmol) en DMF anhidro (19 ml) se añade NCS (1.97 g, 14.8 mmol) y se deja agita a temperatura ambiente bajo nitrógeno durante 22 horas. La mezcla se concentra *in vacuo* para proporcionar un sólido amarillo

que se filtra y se lava con MeOH para proveer un primer cultivo. El filtrado se concentra a un sólido y se lava con MeOH para proveer un segundo cultivo y se repite dos ocasiones adicionales para proveer el compuesto del titulo. En una lavado final el filtrado se purifica adicionalmente por cartucho SPE (si, 20 g) eluyendo con EtOAc:ciclohexano (1:1). Los sólidos combinados se secan bajo vacio para producir el compuesto del titulo (2.42 g, 64%).

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

EJEMPLO 13

3-butil-8-cloro-1-(3-{1-[(2,3-difluorofenil)metil]-1H-imidazol-4-il}propil)-3,7-dihidro-1H-purina-2,6-diona



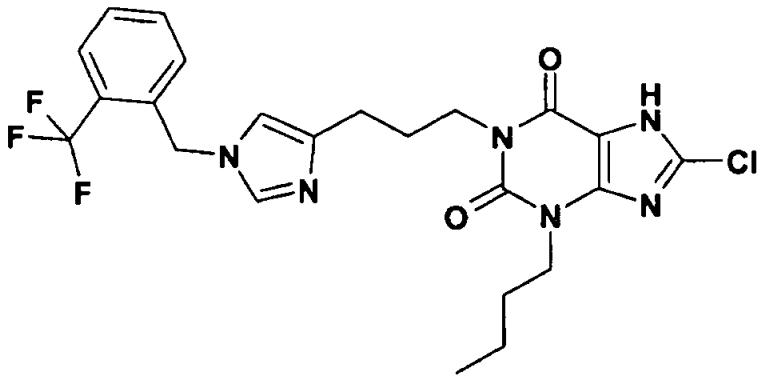
Una solución de 3-butil-8-cloro-1-[4-(1H-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (150 mg, 0.38 mmol) en DMF anhidro (3 ml) se trata con 1-(bromometil)-2,4-difluorobenceno (54 µl, 0.42 mmol) y DIPEA (73 µl, 0.42 mmol). La mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 días. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca

($MgSO_4$) y se concentra. El producto crudo se purifica en una columna de SPE de sílice usando un DCM para cargar el material en la columna y se lava a través de las impurezas después un gradiente de MeOH/DCM 0-5% para eluir el compuesto. Las fracciones de producto se combinan y se concentran y los residuos se disuelven en DMF anhidro (3 ml). La solución se desgasifica después $Pd(PPh_3)_4$, (39 mg, 0.034 mmol) y morfolina (200 µl, 2.3 mmol) se añade y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 horas. El producto crudo se purifica mediante un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y se lava a través de las impurezas después un gradiente de AcOH/MeOH 0-5% para eluir el producto. Las fracciones de producto se combinan y se concentran mediante alto vacío para dejar el compuesto del titulo como un sólido blanco (14 mg, 7%).

LC/EM: m/z 477 $[MH]^+$, temperatura ambiente 2.54 min.

EJEMPLO 14

3-butil-8-cloro-1-[3-(1-{[2-(trifluorometil)fenil]metil}-1H-imidazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona



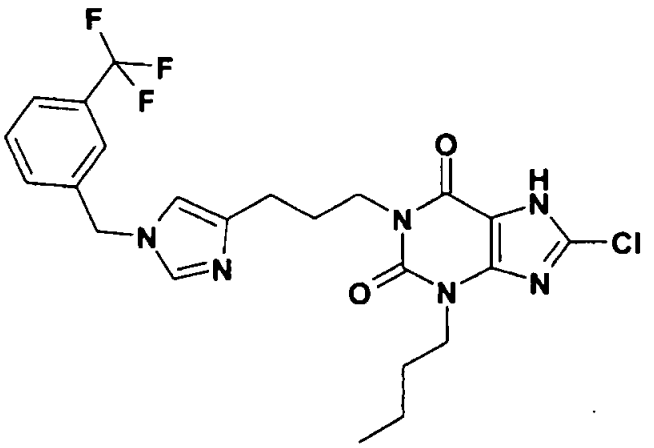
Una solución de 3-butil-8-cloro-1-[4-(1H-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (150 mg, 0.38 mmol) en DMF anhidro (3 ml) se trata con 1-(clorometil)-2-(trifluorometil)benceno (61 µl, 0.42 mmol) y DIPEA (73 µl, 0.42 mmol). La mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 días. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El producto crudo se purifica en una columna SPE de sílice usando DCM para cargar el material dentro de la columna y se lava a través de las impurezas después un gradiente de MeOH/DCM 0-5% para eluir el compuesto. Las fracciones de producto se combinan y se concentran y los residuos se disuelven en DMF anhidro (3ml). La solución se desgasifica después se añade $Pd(PPh_3)_4$, (35 mg, 0.30 mmol) y morfolina (174 µl, 2.0 mmol) y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 horas. El producto crudo se purifica por un SPE de aminopropilo

usando MeOH para cargar el compuesto en la columna y se lava a través de impurezas después un gradiente de AcOH/MeOH 0-5% para eluir el producto. Las fracciones de producto se combinan y se concentran a alto vacío para dejar el compuesto del titulo como un sólido blanco (50 mg, 26%).

LC/EM: m/z 509 $[MH]^+$, temperatura ambiente 2.64 minutos.

EJEMPLO 15

3-butil-8-cloro-1-[3-(1-{[3-(trifluorometil)fenil]metil}-1H-imidazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona



A una solución de 3-butil-8-cloro-1-[4-(1H-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (150 mg, 0.38 mmol) en DMF anhidro (3 ml) se trata con 1-(clorometil)-3-(trifluorometil)benceno (65 µl, 0.42 mmol) y DIPEA (73 µl, 0.42 mmol). La mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 días. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El producto crudo se purifica en una columna de SPE

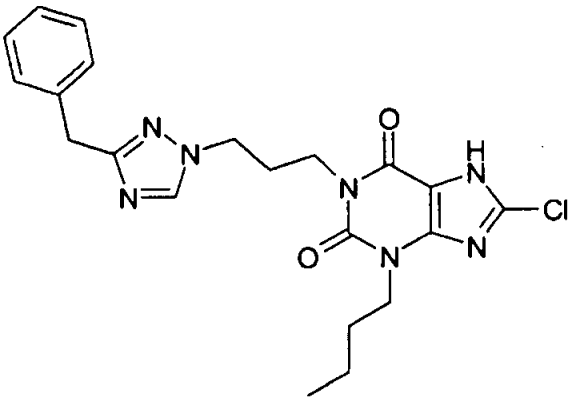
de sílice usando un DCM para cargar el material dentro de la columna y se lava a través de las impurezas después un gradiente de MeOH/DCM 0-5% para eluir el compuesto. Las fracciones de producto se combinan y se concentran y los residuos se disuelven en DMF anhidro (3ml). La solución se desgasifica después se añade $Pd(PPh_3)_4$ (30 mg, 0.027 mmol) y morfolina (156 µl, 1.8 mmol) y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 3 horas. El producto crudo se purifica por un SPE de aminopropilo usando MeOH para cargar el compuesto dentro de la columna y se lava a través de impurezas después un gradiente de AcOH/MeOH 0-5% para eluir el producto. Las fracciones de producto se combinan y se concentran por alto vacío para dejar el compuesto del titulo como un sólido blanco (18 mg, 9%).

LC/EM: m/z 509 $[MH]^+$, temperatura ambiente 2.78 minutos.

EJEMPLO 16

3-butil-8-cloro-1-{3-[3-(fenilmetil)-1H-1,2,4-triazol-1-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 3-butil-8-cloro-1-{3-[3-(fenilmetil)-1H-1,2,4-triazol-1-il]propil}-3,7-dihidro-1H-purina-2,6-diona



Una solución de 3-butil-8-cloro-1-{3-[3-(fenilmetil)-1H-1,2,4-triazol-1-il]propil}-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (669 mg, 1.39 mmol) en THF (7 ml) se desgasifica mediante la aplicación de vacío y después se introduce nitrógeno. $Pd(PPh_3)_4$ (160 mg, 0.14 mmol) se añade y la mezcla se desgasifica una vez más. Se añade morfolina (1.2 ml, 13.9 mmol) y la mezcla se agita bajo nitrógeno durante 18 horas, después se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa y la capa acuosa se extrae nuevamente con EtOAc. Los extractos combinados se lavan con salmuera, se secan ($MgSO_4$) y se concentran, proporcionando un residuo amarillo. Se añade MeOH y se pasa debajo de un SPE de aminopropilo con el producto eluyendo con AcOH/MeOH 2-3%. Las fracciones de producto se combinan y

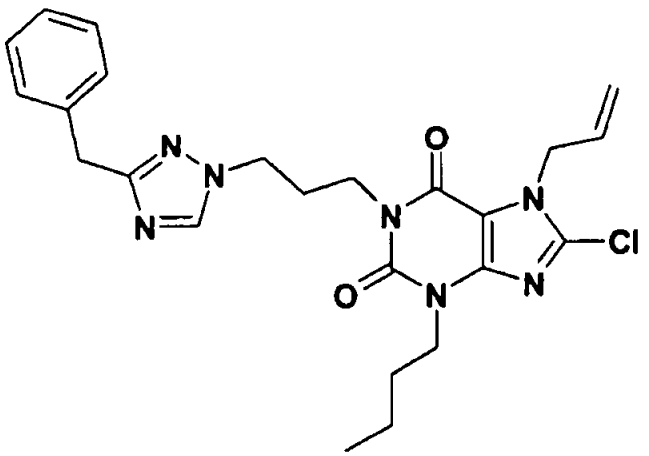
250

se concentran proporcionando un sólido amarillo pálido (380 mg). Aproximadamente un cuarto del material se purifica por HPLC autoprep y el resto se cristaliza a partir de MeOH:DMSO (1:1) proporcionando el compuesto del titulo como un sólido blanco (125 mg, 31%).

LC/EM: m/z 442 $[MH]^+$, temperatura ambiente 3.0 minutos.

^{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)-1H-1,2,4-triazol-1-il]propil}-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona



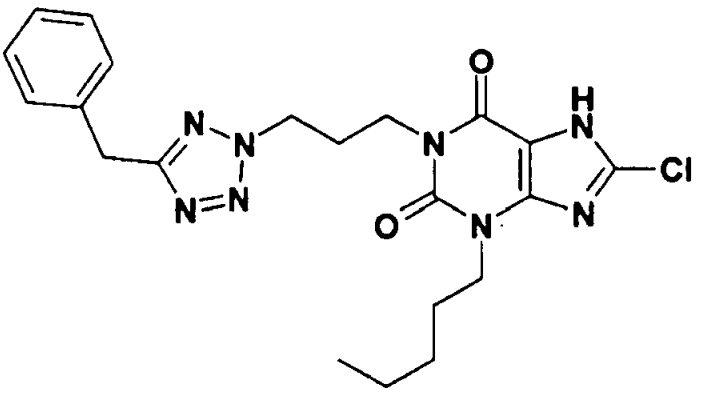
Una solución de 3-(fenilmetil)-1H-1,2,4-triazol (2.1 g, 13.2 mmol) en MeOH (40 ml) se trata con NaOMe 0.5M en MeOH (29 ml) seguido por 1,3-dibromopropano (1.7 ml). Después de la agitación durante 5 horas a 50°C la mezcla se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra, proporcionando un

residuo aceitoso (1.0 g). A esta se añade butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (917 mg, 3.2 mmol) y Cs_2CO_3 (1.2 g, 3.6 mmol), DMF (15 ml) se añade y la mezcla se agita a 50°C durante 20 horas después se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El aceite resultante (1.52 g) se pasa debajo de una columna SPE de sílice (50 g) eluyendo con mezclas de EtOAc/ciclohexano. Dos productos isoméricos del triazol se obtiene como una mezcla 2:1, a favor del compuesto del titulo, como una pasta amarilla (697 mg, 67% basado en la relación de isómeros presentes)..

LC/EM: m/z 482 $[MH]^+$, temperatura ambiente 3.3 minutos.

EJEMPLO 17

8-cloro-3-pentil-1-{3-[5-(fenilmetil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona



Una solución de 5-bencil-1H-tetrazol (1.0 g, 6.24 mmol) en MeOH (5 ml) se trata con 1-cloro-3-yodopropano (1.0 ml, 9.36 mmol) y una solución de NaOMe 0.5M en MeOH (4.7 ml, 9.36 mmol). La reacción se

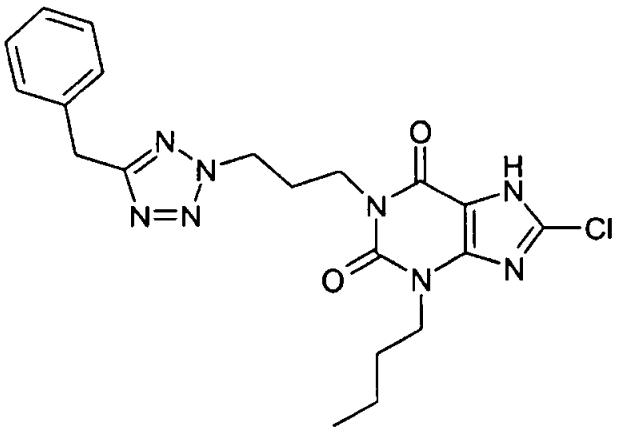
calienta a reflujo durante 18 horas después se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa y la capa acuosa se extrae una vez más con EtOAc. Los extractos combinados se lavan con salmuera, se secan ($MgSO_4$) y se concentran, proporcionando un sólido amarillo (796 mg), 700 mg de este material se hace reaccionar con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (732 mg, 2.47 mmol) y Cs_2CO_3 (967 mg, 3.0 mmol) en DMF (20 ml) a 75°C durante 24 horas. La reacción se deja enfriar a temperatura ambiente y la mezcla se desgasifica mediante la aplicación de vacío y después se introduce nitrógeno. Se añade $Pd(PPh_3)_4$ (428 mg, 0.37 mmol) y la mezcla se desgasifica una vez más. Se añade morfolina (2.1 ml, 24.7 mmol) y la mezcla se agita bajo nitrógeno durante 3 horas, después se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa y la capa acuosa se extrae una vez más. Los extractos combinados se concentran, proporcionando un residuo amarillo. Se añade MeOH y después se pasa debajo de un SPE de aminopropilo, el producto se eluye con AcOH/MeOH 2-3%. Las fracciones de producto se combinan y se concentran después se purifican mediante MDAP para proporcionar el compuesto del titulo como un sólido blanco (35 mg, 3%).

LC/EM: m/z 457 $[MH]^+$, temperatura ambiente 3.5 minutos.

^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 18

3-butil-8-cloro-1-{3-[5-(fenilmetil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona



Una solución de 5-bencil-1H-tetrazol (1.8 g, 11.2 mmol) en MeOH (30 ml) se trata con 1,3-dibromopropano (5.7 ml, 56.2 mmol) y NaOMe 0.5M en MeOH (31.5 ml) después se agita a 40°C bajo nitrógeno durante 60 horas. La mezcla se divide entre HCl 2M (ac) y EtOAC. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. 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) proporciona un aceite (1.98 g, 62% de una mezcla de isómeros, 2:1 a favor de 2-(3-bromopropil)-5-(fenilmetil)-2H-tetrazol) que se toman en crudo en la siguiente etapa.

Una mezcla de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (1.74 g, 6.1 mmol), 2-(3-bromopropil)-5-(fenilmetil)-2H-tetrazol crudo) (1.9 g, 6.8 mmol), Cs_2CO_3 (2.2 g, 6.8 mmol) y DMF (60 ml) se

agita a 45°C bajo nitrógeno durante 24 horas. La mezcla se desgasifica mediante la aplicación de vacío y después se introduce nitrógeno. Se añade $Pd(PPh_3)_4$ (705 mg, 0.61 mmol) y la mezcla se desgasifica una vez más. Se añade morfolina (5.4 ml, 61.4 mmol) y la mezcla se agita bajo nitrógeno durante 4 horas, y después se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra, proporcionando un residuo amarillo. Se añade MeOH y después se pasa debajo de una columna de aminopropilo con el producto eluyendo con AcOH/MeOH 2%. El producto se purifica adicionalmente por el sistema Companion™ usando mezclas de EtOAc/ciclohexano. El sólido resultante se agita con Et_2O en ebullición y se filtra después del enfriamiento a temperatura ambiente. El compuesto del titulo se colecta con un sólido blanco (1.01 g, 37%) y se seca a 50°C bajo vacío.

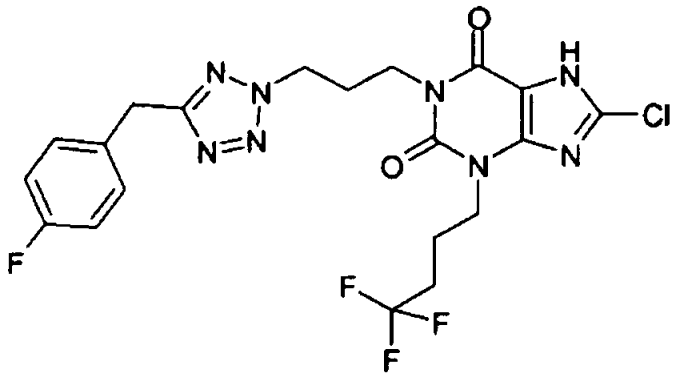
LC/EM: m/z 443 $[MH]^+$, temperatura ambiente 3.3 minutos.

^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 19

8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona



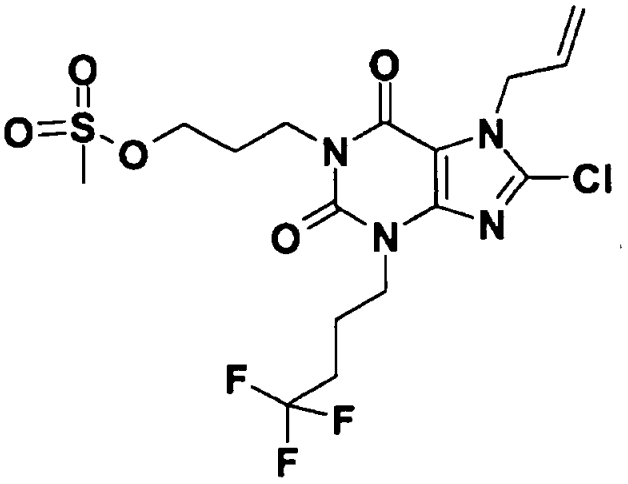
Se trata 5-[(4-fluorofenil)metil]-1H-tetrazol (75 mg, 0.4 mmol) con carbonato de potasio (100 mg, 0.7 mmol) y DMF (3 ml). La mezcla se trata con una solución de metanosulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-2,3,6,7-tetrahidro-1H-purin-1-il]propilo (100 mg, 0.2 mmol) en DMF (0.5 ml). La mezcla se agita y se calienta a 60°C 3 horas después se enfría y se evapora. El residuo se divide entre cloroformo (4 ml) y agua (2 cm^3), 1 cm^3 de bicarbonato de sodio acuoso saturado (3 ml) se añade a cada uno. La mezcla se separa y la fase orgánica se evapora. El residuo se disuelve en THF anhidro (3 ml) y la mezcla se desgasifica mediante aplicación sucesiva cuidadosa de vacío y presión de nitrógeno a la mezcla. La mezcla se trata con tetraquis(trifenilfosfina)paladio (0) (10 mg, 0.008 mmol) y morfolina

(0.2 ml, 2.3 mmol) y después se agita en una atmósfera de nitrógeno durante 2 horas. La mezcla se evapora y se divide entre cloroformo (4 ml) y cloruro de amonio acuoso saturado (3 ml). La mezcla se separa, y la fase acuosa se re-extrae con cloroformo. La fase orgánica se evapora y el residuo se disuelve en MeOH (3 ml). La solución se añade a la parte superior de un SPE de aminopropilo 2 g y se lava con MeOH (15 ml). El producto deseado se eluye a partir del cartucho con una solución al 3% v/v de AcOH en MeOH (20 ml). El producto que contiene fracciones se combina y se evapora y el residuo se somete a purificación mediante cromatografía de columna instantánea (gradiente de elusión de ciclohexano/EtOAc 10:1 a EtOAc). Las fracciones que contienen el producto se combinan y se evaporan para producir el producto como un aceite incoloro. La trituración en dietiléter mínima causa que el producto solidifique y esto se seca completamente para producir el compuesto del titulo como un sólido blanco (18.7 mg, 18%).

LC/EM: m/z 515 $[MH]^+$, temperatura ambiente 3.31 minutos.

^1H 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= 7.0 Hz), 4.70 (t, 2H, J= 7.2 Hz), 6.96 (m, 2H), 7.25 (m, 2H).

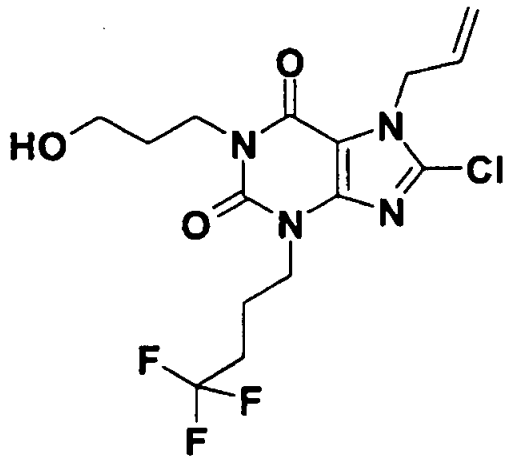
b) metanosulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-2,3,6,7-tetrahidro-1H-purin-1-il]propilo



Una solución de 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona (0.82 g, 2.1 mmol) en DCM (20 ml) se trata con trietilamina (0.42 ml, 3.1 mmol) y anhídrido metanosulfánico (0.40 g, 2.3 mmol). Después de 1 hora la mezcla se trata con bicarbonato de sodio saturado acuoso (20 ml). La mezcla se separa y la fase orgánica se seca ($MgSO_4$), se filtra y se evapora para proporcionar el compuesto del titulo (0.91 g), que se usa sin purificación adicional.

LC/EM: m/z 473 $[MH]^+$, temperatura ambiente 3.17 minutos.

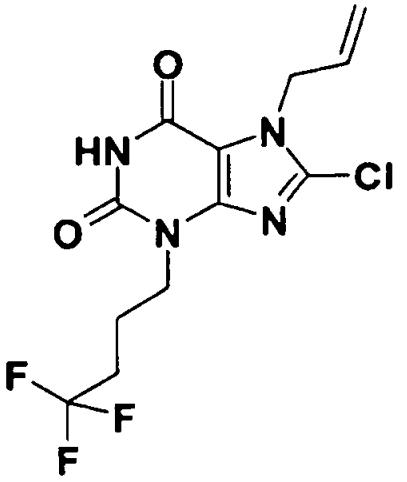
c) 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona (1.0 g, 3.0 mmol) en DMF (15 ml) se trata con carbonato de cesio (1.16 g, 3.6 mmol) y 3-bromo-1-propanol (0.3 ml, 3.3 mmol). La mezcla se calienta a 60°C durante 4 horas y después se enfría y se evapora. El residuo se divide entre EtOAc (50 ml) y agua (50 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se evapora. El producto se purifica mediante cromatografía instantánea usando una elusión de gradiente a partir de ciclohexano a EtOAc. Las fracciones que contienen el producto se combinan y se evaporan para proporcionar el compuesto del titulo como un aceite incoloro (0.82 g, 75%).

LC/EM: m/z 395 $[MH]^+$, temperatura ambiente 2.90 minutos.

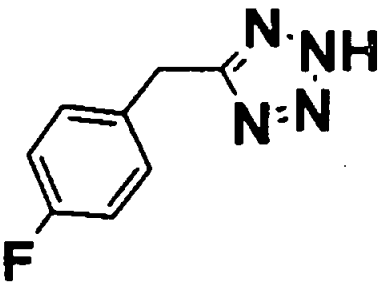
d) 8-cloro-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (2.0 g, 8.8 mmol) en DMF (20 ml) se trata con carbonato de sodio (1.15 g, 10.8 mmol) y 4-bromo-1,1,1-trifluorobutano (1.86 g, 9.7 mmol). La mezcla se agita a 50°C durante 18 horas después se enfría y se evapora. El residuo se divide entre EtOAc (100 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se evapora. El residuo se tritura en una mezcla de dietiléter y ciclohexano después el producto se filtra y se seca para producir el compuesto del titulo como un sólido blanco (1.18 g, 40%).

LC/EM: m/z 337 $[MH]^+$, temperatura ambiente 2.83 minutos.

e) 5-[(4-fluorofenil)metil]-1H-tetrazol



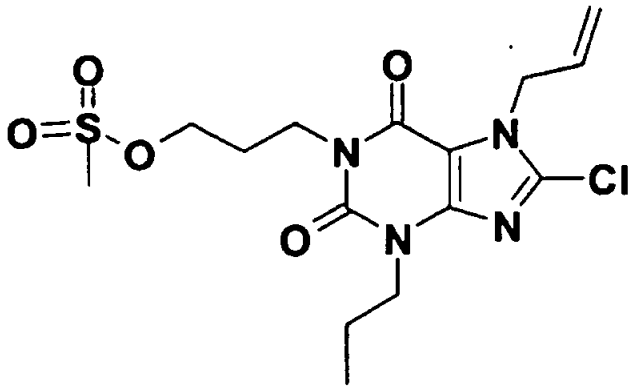
Una mezcla de cloruro de trietilamonio (4.14 g, 30 mmol) y azida de sodio (1.95 g, 30 mmol) se trata con una solución de (4-fluorofenil)acetonitrilo (1.35 g, 10 mmol) en tolueno (14 ml) y la mezcla se agita y se calienta a 100°C durante 5 horas. La mezcla enfriada se trata con agua (10 ml) y la mezcla se separa. La fase acuosa se agita y se trata gota a gota con ácido clorhídrico concentrado hasta que el producto ha precipitado de la solución. El producto precipitado se filtra, se lava con agua y se seca para producir el compuesto del titulo como un sólido blanco (1.27 g, 72%).

LC/EM: m/z 179 $[MH]^+$, temperatura ambiente 2.24 minutos.

Los compuestos en el cuadro 3 se preparan usando un método análogo al del ejemplo 19: 8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona, con el metanosulfonato y tetrazol apropiado. MDAP se emplea para purificar adicionalmente aquellos compuestos insuficientemente puros siguiendo la cromatografía de fase normal.

Intermedios de metanosulfonatos y sus alcoholes de precursor se preparan de acuerdo con los siguientes procedimientos:

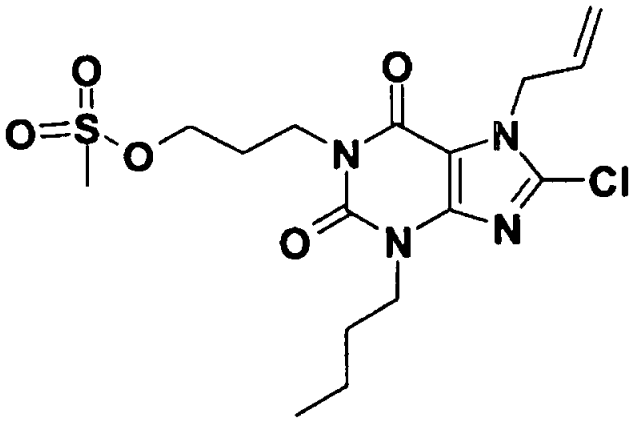
Metanosulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-propil-2,3,6,7-tetrahidro-1H-purin-1-il]propilo



Una solución de 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona (1.99 g, 6.1 mmol) en DCM (50 ml) se trata con trietilamina (1.2 ml, 8.6 mmol) y anhídrido metanosulfónico (1.2 g, 6.9 mmol). Después de 1.5 horas la mezcla se trata con agua (50 ml). La mezcla se separa y la fase acuosa se extrae con DCM (25 ml), las fases orgánicas combinadas se secan ($MgSO_4$), se filtran y se evaporan para proporcionar el compuesto del titulo como un aceite amarillo pálido (2.38 g), que se usa sin purificación adicional.

LC/EM: m/z 405 $[MH]^+$, temperatura ambiente 2.93 minutos.

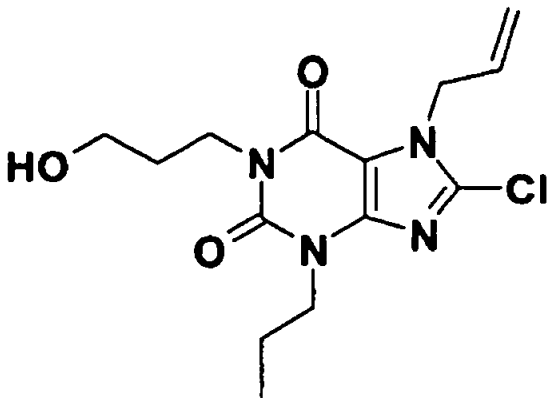
3-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]propilmetanosulfonato



Se prepara de acuerdo con el método usado para metanosulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-propil-2,3,6,7-tetrahidro-1H-purin-1-il]propil para proporcionar el compuesto del titulo como un aceite amarillo pálido (2.44 g).

LC/EM. m/z 419 $[MH]^+$, temperatura ambiente 3.14 minutos.

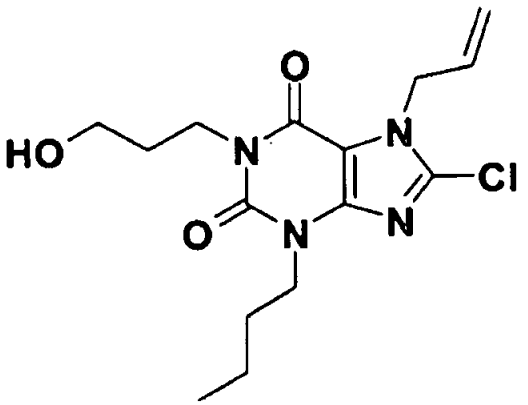
8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona (3.0 g, 11.1 mmol) en DMF (20 ml) se trata con carbonato de cesio (3.7 g, 11.4 mmol) y 3-bromo-1-propanol (1.6 g, 11.5 mmol). La mezcla se calienta a 60°C durante 4 horas y después se enfría y se evapora. El residuo se divide entre EtOAc (60 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase acuosa se extrae con EtOAc (60 ml), las fases orgánicas combinadas se secan ($MgSO_4$), se filtran y se evaporan. El producto se purifica usando el sistema Companion ™ y un gradiente de elusión de ciclohexano a EtOAc. Fracciones que contienen el producto se combinan y se evaporan para proporcionar el compuesto del titulo como un aceite incoloro (2.6 g).

LC/EM: m/z 327 $[MH]^+$, temperatura ambiente 2.62 minutos.

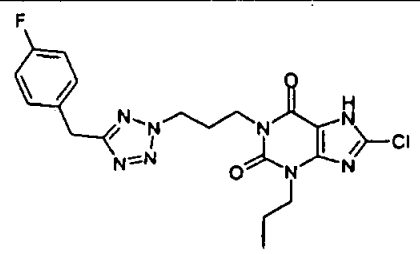
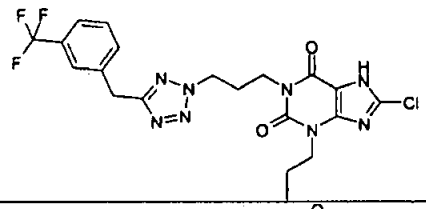
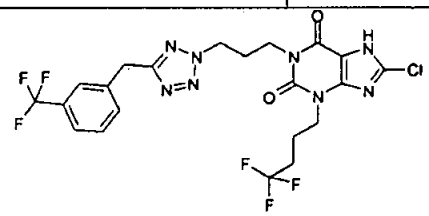
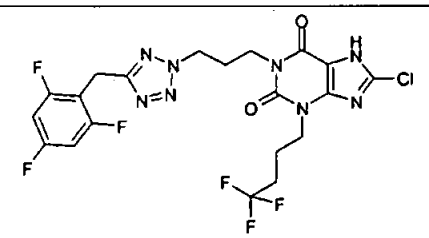
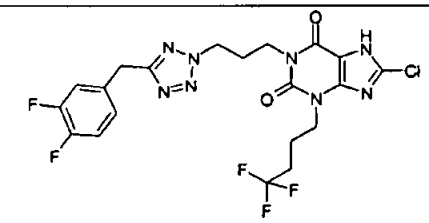
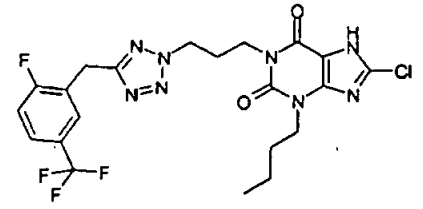
3-butil-8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona

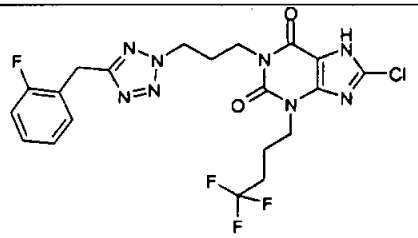
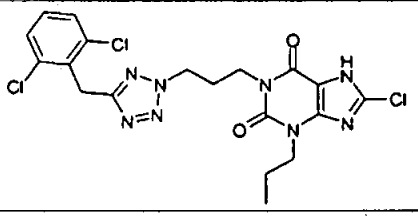
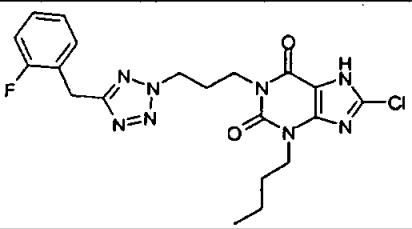
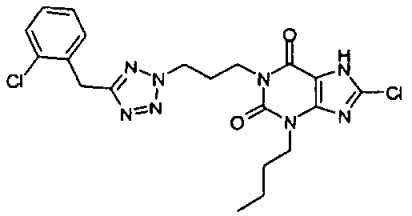
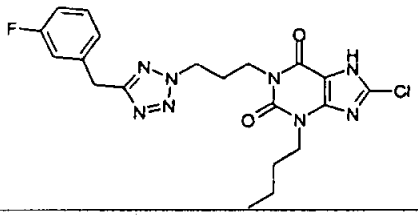
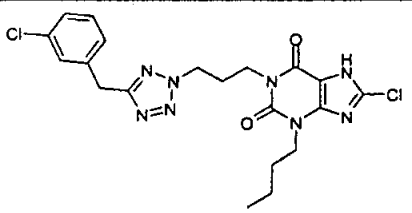
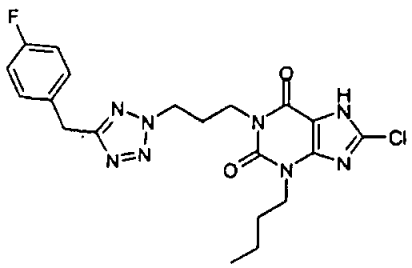


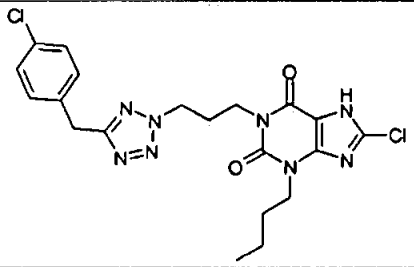
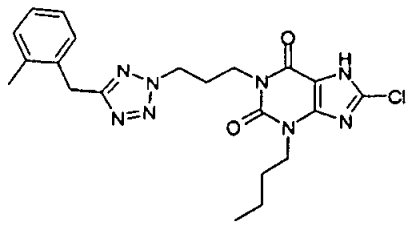
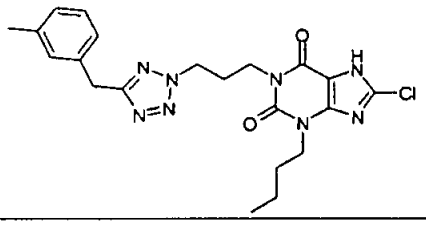
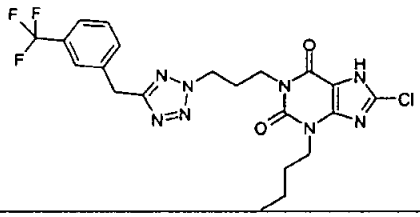
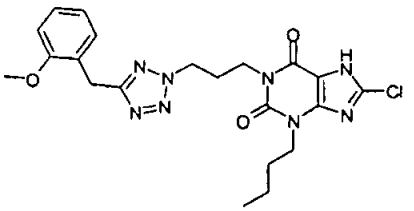
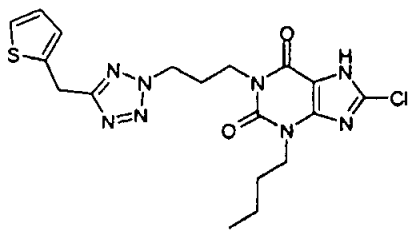
Se prepara de acuerdo con el método usado para 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona para proporcionar el compuesto del titulo como un aceite incoloro (2.3 g).

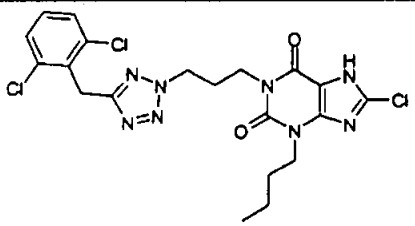
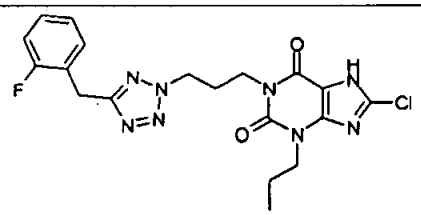
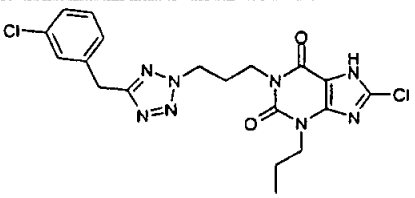
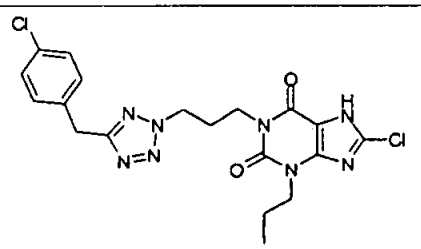
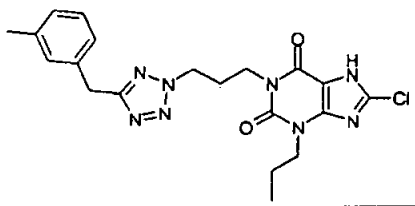
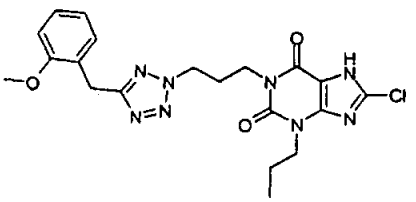
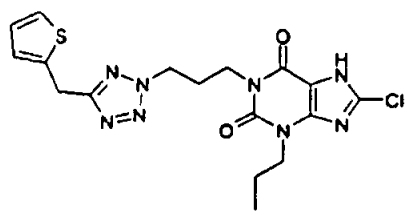
LC/EM: m/z 341 $[MH]^+$, temperatura ambiente 2.85 minutos.

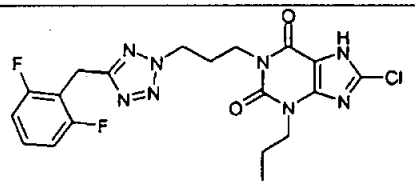
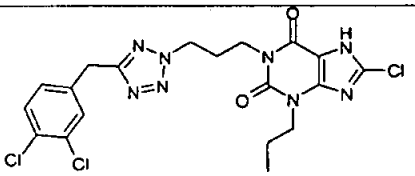
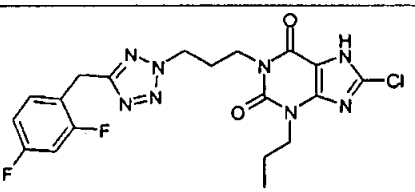
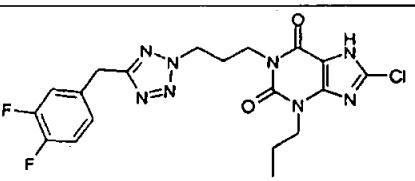
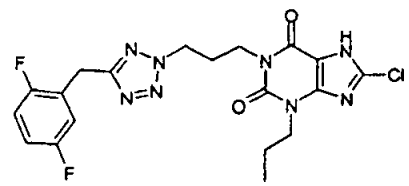
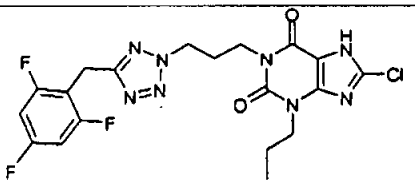
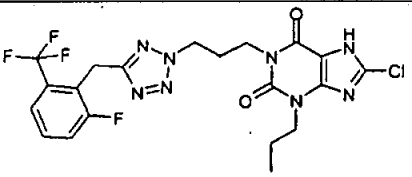
CUADRO 3

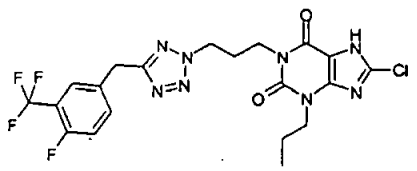
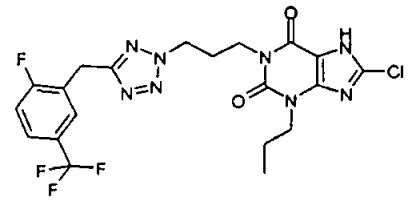
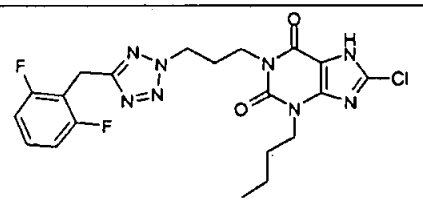
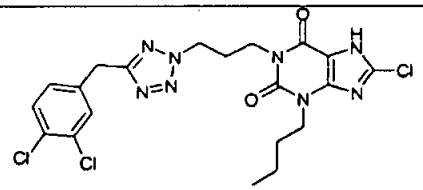
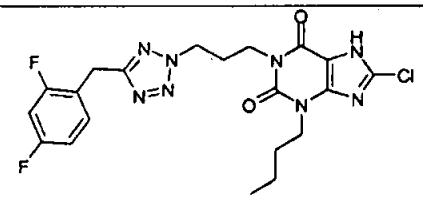
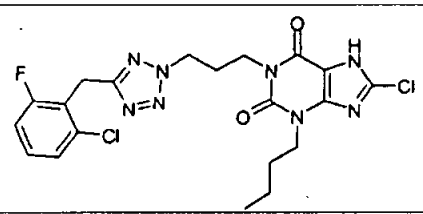
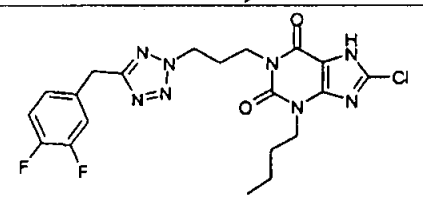
#	Estructura	Nombre	Rend.	LC/EM
20		8-cloro-1-(3-[5-[(4-fluorofenil)metil]-2H-tetrazol-2-il]propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	12.4 mg (14%)	m/z 447 $[MH]^+$ RT 3.14 min.
21		8-cloro-3-propil-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	8.0 mg (8%)	m/z 497 $[MH]^+$ RT 3.36 min.
22		8-cloro-3-(4,4,4-trifluorobutil)-1-[3-(5-{[3-(trifluorometil)fenil]-metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	21.0 mg (19%)	m/z 565 $[MH]^+$ RT 3.34 min.
23		8-cloro-3-(4,4,4,4-trifluorobutil)-1-(3-[5-{(2,4,6-trifluorofenil)metil}-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purina-2,6-diona	17.0 mg (15%)	m/z 551 $[MH]^+$ RT 3.37 min.
24		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona	19.1 mg (18%)	m/z 533 $[MH]^+$ RT 3.36 min.
25		3-butil-8-cloro-1-[3-(5-{[2-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	23.9 mg (23%)	m/z 529 $[MH]^+$ RT 3.50 min.

#	Estructura	Nombre	Rend.	LC/EM
26		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona	19.8 mg (19%)	m/z 515 $[MH]^+$ RT 3.31 min.
27		8-cloro-1-(3-{5-[(2,6-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	50.7 mg (51%)	m/z 497 $[MH]^+$ RT 3.33 min.
28		3-butil-8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il+propil}-3,7-dihidro-1H-purina-2,6-diona	46.4 mg (48%)	m/z 461 $[MH]^+$ RT 3.27 min.
29		3-butil-8-cloro-1-(3-{5-[(2-clorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	25.4 mg (27%)	m/z 477 $[MH]^+$ RT 3.40 min.
30		3-butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	38.5 mg (40%)	m/z 477 $[MH]^+$ RT 3.31 min.
31		3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	38.5 mg (40%)	m/z 461 $[MH]^+$ RT 3.45 min.
32		3-butil-8-cloro-1-(3-[5-[(4-fluorofenil)metil]-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purina-2,6-diona	31.6 mg (34%)	m/z 461 $[MH]^+$ RT 3.31 min.

#	Estructura	Nombre	Rend.	LC/EM
33		3-butil-8-cloro-1-(3-[5-[(4-clorofenil)metil]-2H-tetrazol-2-il]-propil)-3,7-dihidro-1H-purina-2,6-diona	33.1 mg (35%)	m/z 477 $[MH]^+$ RT 3.46 min.
34		3-butil-8-cloro-1-(3-[5-[(2-metilfenil)metil]-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purina-2,6-diona	39.5 mg (43%)	m/z 457 $[MH]^+$ RT 3.37 min.
35		3-butil-8-cloro-1-(3-{5-[(2-metilfenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	36.5 mg (40%)	m/z 457 $[MH]^+$ RT 3.40 min.
36		3-butil-8-cloro-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	43.7 mg (43%)	m/z 511 $[MH]^+$ RT 3.50 min.
37		3-butil-8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	28.6 mg (30%)	m/z 473 $[MH]^+$ RT 3.29 min.
38		3-butil-8-cloro-1-{3-[5-(2-tienilmetil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	33.4 mg (37%)	m/z 449 $[MH]^+$ RT 3.20 min.

#	Estructura	Nombre	Rend.	LC/EM
39		3-butil-8-cloro-1-(3-{5-[(2,6-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	36.4 mg (36%)	m/z 511 $[MH]^+$ RT 3.49 min.
40		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil-3,7-dihidro-1H-purina-2,6-diona	5.6 mg (6%)	m/z 447 $[MH]^+$ RT 3.10 min.
41		8-cloro-1-(3-{5-[(3-clorofenil)metil]-2H-tetrazol-2-il}propil-3-propil-3,7-dihidro-1H-purina-2,6-diona	5.9 mg (6%)	m/z 463 $[MH]^+$ RT 3.29 min.
42		8-cloro-1-(3-{5-[(4--clorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	14.9 mg (16%)	m/z 463 $[MH]^+$ RT 3.30 min.
43		8-cloro-1-(3-{5-[(3-metilfenil)metil]-2H-tetrazol-2-il}propil-3,7-dihidro-1H-purina-2,6-diona	17.5 mg (20%)	m/z 443 $[MH]^+$ RT 3.23 min.
44		8-cloro-1-[3-(5-{(2-(metiloxi)fenil)metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	14.5 mg (16%)	m/z 459 $[MH]^+$ RT 3.12 min.
45		8-cloro-3-propil-1-{3-(5-(2-trienilmetil)-2H-tetrazol-2-il)propil}-3,7-dihidro-1H-purina-2,6-diona	17.0 mg (20%)	m/z 435 $[MH]^+$ RT 3.02 min.

#	Estructura	Nombre	Rend.	LC/EM
46		8-cloro-1-(3-{5-[(2,6-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	18.4 mg (20%)	m/z 465 $[MH]^+$ RT 3.11 min.
47		8-cloro-1-(3-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	19.4 mg (20%)	m/z 497 $[MH]^+$ RT 3.44 min.
48		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	19.1 mg (21%)	m/z 465 $[MH]^+$ RT 3.16 min.
49		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 $[MH]^+$ RT 3.19 min.
50		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	8.5 mg 89%)	m/z 465 $[MH]^+$ RT 3.14 min.
51		8-cloro-3-propil-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.4 mg (18%)	m/z 483 $[MH]^+$ RT 3.09 min.
52		8-cloro-1-[3-(5-{[2-fluoro-6-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	22.3 mg (22%)	m/z 515 $[MH]^+$ RT 3.28 min.

#	Estructura	Nombre	Rend.	LC/EM
53		8-cloro-1-[3-(5-{[4-fluoro-3-(trifluorometi)fenil]-metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	17.2 mg (17%)	m/z 515 $[MH]^+$ RT 3.30 min.
54		8-cloro-1-[[3-(5-{[2-fluoro-5-(trifluorometil)fenil]-metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	18.2 mg (18%)	m/z 515 $[MH]^+$ RT 3.34 min.
55		3-butil-8-cloro-1-(3-[5-[(2,6-difluorofenil)metil]-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purina-2,6-diona	18.2 mg (19%)	m/z 479 $[MH]^+$ RT 3.29 min.
56		3-butil-8-cloro-1-(3-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	20.1 mg (20%)	m/z 511 $[MH]^+$ RT 3.58 min.
57		3-butil-8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	19.3 mg (20%)	m/z 479 $[MH]^+$ RT 3.33 min.
58		3-butil-8-cloro-1-(3-{5-[(2-cloro-6-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	18.9 mg (19%)	m/z 495 $[MH]^+$ RT 3.33 min.
59		3-butil-8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	21.7 mg (23%)	m/z 479 $[MH]^+$ RT 3.33 min.

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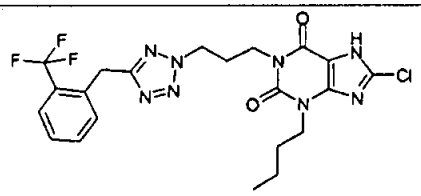
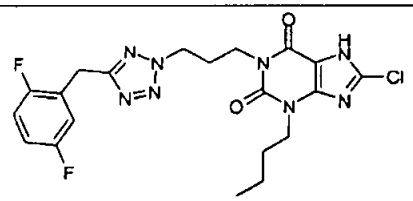
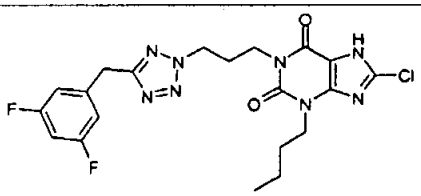
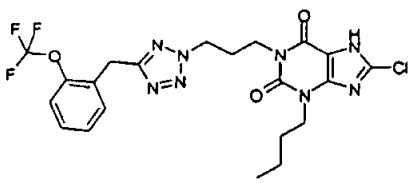
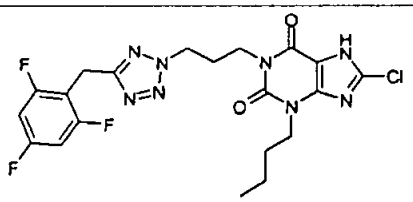
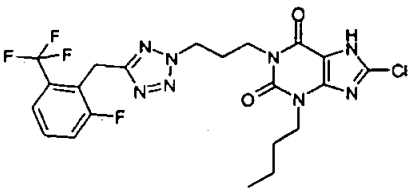
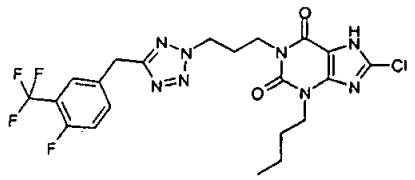
#	Estructura	Nombre	Rend.	LC/EM
60		3-butil-8-cloro-1-[3-(5-{[2-(trifluorometil)fenil]-metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	18.1 mg (18%)	m/z 511 $[MH]^+$ RT 3.32 min.
61		3-butil-8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	24.0 mg (25%)	m/z 479 $[MH]^+$ RT 3.31 min.
62		3-butil-8-cloro-1-(3-{5-[(3,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	15.9 mg (17%)	m/z 479 $[MH]^+$ RT 3.38 min.
63		3-butil-8-cloro-1-[3-[5-({-2-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il]propil]-3,7-dihidro-1H-purina-2,6-diona	32.8 mg (31%)	m/z 527 $[MH]^+$ RT 3.51 min.
64		3-butil-8-cloro-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	20.7 mg (21%)	m/z 497 $[MH]^+$ RT 3.35 min.
65		3-butil-8-cloro-1-[3-(5-{[2-fluoro-6-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	23.9 mg (23%)	m/z 529 $[MH]^+$ RT 3.44 min.
66		3-butil-8-cloro-1-[3-(5-{[4-fluoro-3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	13.9 mg (13%)	m/z 529 $[MH]^+$ RT 3.53 min.

#	Estructura	Nombre	Rend.	LC/EM
67		3-butil-8-cloro-1-(3-{5-[(2,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.5 mg (17%)	m/z 511 $[MH]^+$ RT 3.63 min.

Detalles RMN para ejemplos seleccionados del cuadro 3

EJEMPLO 20

8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-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= 7.5 Hz), 6.96 (m, 2H). 7.26 (m, 2H), 13.15 (br s, 1H).

EJEMPLO 23

8-cloro-3-(4,4,4-trifluorobutil)-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-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=7.1 Hz), 4.20 (s, 2H), 4.24 (t, 2H, J= 6.8 Hz), 4.68 (t, 2H, J= 7.3 Hz), 6.67 (t, 2H, J= 8.1 Hz), 13.04 (br s, 1H).

EJEMPLO 24

^{1}H RMN ($CDCl_3$) δ 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= 7.1 Hz), 4.71 (t, 2H, J=7.1 Hz), 7.00-7.13 (m 3H), 13.06 (bs, 1H).

EJEMPLO 27

^{1}H RMN ($CDCl_3$) δ 0.99 (t, 3H, J=7.5 Hz), 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 28

^{1}H RMN ($CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz), 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), 4.66-4.71 (m, 2H), 7.02 -7.09 (m, 2H), 7.20-7.26 (m, 2H), 13.14 (bs, 1H).

EJEMPLO 29

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

EJEMPLO 30

3-butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-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= 7.5 Hz), 4.21 (s, 2H), 4.26 (t, 2H, J= 6.5 Hz), 4.70 (t, 2H, J=7.5 Hz), 6.90 (m, 1H), 6.99 (m, 1H), 7.07 (m, 1H), 7.25 (m, 1H), 13.25 (br s, 1H).

EJEMPLO 31

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

EJEMPLO 32

3-butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona

^{1}H RMN ($CDCl_3$) δ 0.99 (t, 3H, J= 7 Hz), 1.43 (m, 2H), 1.77 (m, 2H9, 2.48 (m, 2H), 4.12 (t, 2H, J= 7.5 Hz), 4.20 (s, 2H), 4.27 (t, 2H, J= 7.5 Hz), 6.98 (m, 2H), 7.27 (m, 2H), 13.35 (br s, 1H).

EJEMPLO 33

3-butil-8-cloro-1-(3-{5-[(4-clorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona

^{1}H RMN ($CDCl_3$) δ 1.02 (t, 3H, J= 7.5 Hz), 1.45 (m, 2H), 1.79 (m, 2H), 2.50 (m, 2H), 4.14 (t, 2H, J= 7.5 Hz), 4.22 (s, 2H), 4.29 (t, 2H, J= 7Hz), 4.75 (t, 2H, J= 7.5 Hz), 7.27 (s, 4H), 13.35 (br s, 1H).

EJEMPLO 48

8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-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= 7.5 Hz) 6.80 (m, 2H), 7.23 (m, 1H).

EJEMPLO 51

8-cloro-3-propil-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-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= 6.5 Hz), 4.67 (t, 2H, J= 7.3 Hz), 6.68 (t, 2H, J= 8.1 Hz).

EJEMPLO 52

^{1}H RMN ($CDCl_3$) δ 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= 7.1 Hz), 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 59

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

EJEMPLO 61

^{1}H RMN ($CDCl_3$) δ 0.96 (t, 3H, J= 7.2 Hz), 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 64

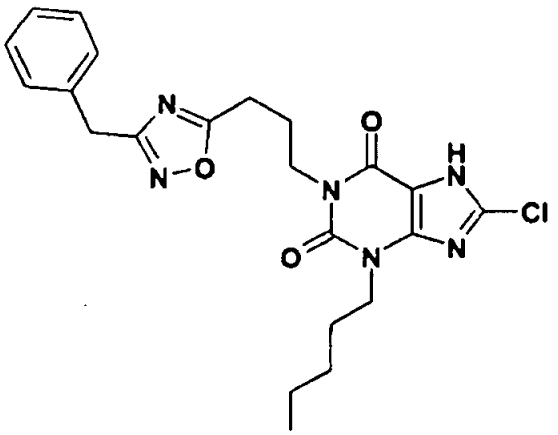
3-butil-8-cloro-1-[3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil]-3,7-dihidro-1H-purina-2,6-diona

^{1}H RMN ($CDCl_3$) δ 0.97 (t, 3H, J= 7.3 Hz), 1.41 (m, 2H), 1.75 (m, 2H), 2.44 (m, 2H), 4.10 (t, 2H, J= 7.5 Hz), 4.20 (s, 2H), 4.25 (t, 2H, J= 6.5 Hz), 4.67 (t, 2H, J= 7.4 Hz), 6.67 (t, 2H, J= 8.0 Hz), 13.25 (br s, 1H).

EJEMPLO 68

8-cloro-3-pentil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-3-pentil-1-(3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1H-purina-2,6-diona



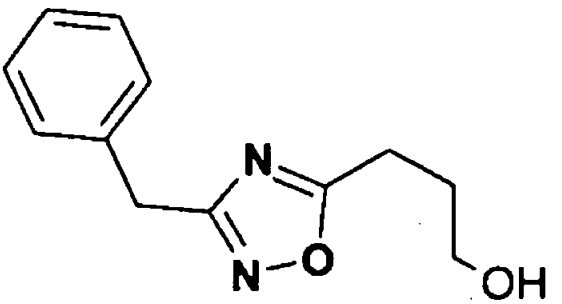
Una solución de 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (88 mg, 0.4 mmol) en THF (4 ml) se trata con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (100 mg, 0.34 mmol) y PPh_3 (115 mg, 0.44 mmol) bajo nitrógeno, DBAD (101 mg, 0.44 mmol) se añade en una porción y la reacción se deja reaccionar durante 5 horas. La mezcla se desgasifica mediante la aplicación de vacío y después se introduce nitrógeno. $Pd(PPh_3)_4$ (39 mg, 0.034 mmol) se añade y la mezcla se desgasifica una vez más. Se añade morfolina (294 µl, 3.4 mmol) y la mezcla se agita bajo nitrógeno por 3h. La mezcla se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El compuesto del

titulo se obtiene como un sólido blanco después de la purificación por MDAP (64 mg, 42%).

LC/EM: m/z 457 $[MH]^+$, temperatura ambiente 3.4 minutos.

^{1}H RMN (DMSO-d_6) δ 0.85 (t, 3H, J= 7 Hz), 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



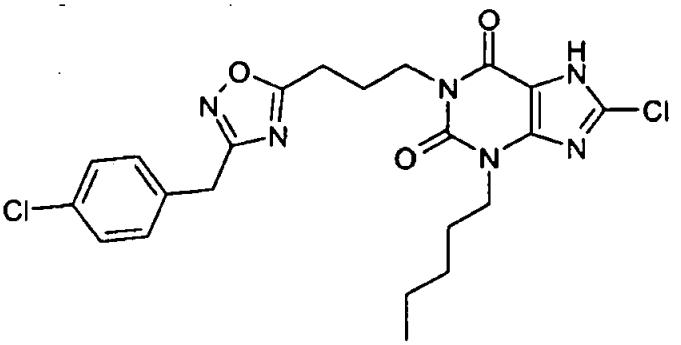
Una mezcla de γ-butirolactona (223 μl, 2.9 mmol), oxima de benzamidina (480 mg, 3.2 mmol), 21% de solución de NaOEt en EtOH (1.3 ml) y EtOH (3 ml) se calienta en microondas a 140°C durante 10 minutos. La mezcla se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El producto del titulo se purifica sobre sílice usando el sistema Companion™ para proporcionar un aceite amarillo pálido (143 mg, 23%).

LC/EM: m/z 219 $[MH]^+$, temperatura ambiente 2.4 minutos.

EJEMPLO 69

8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

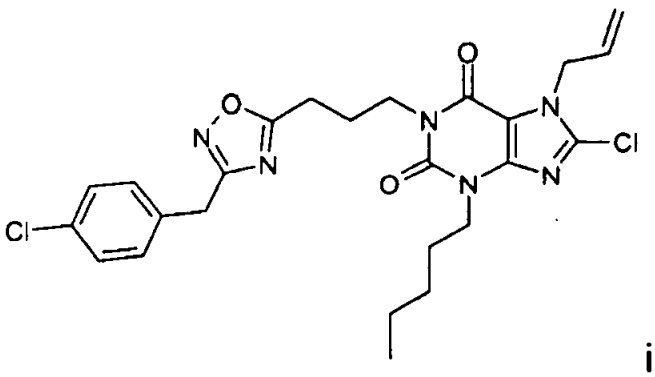
a) 8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



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-1H-purina-2,6-diona (0.18 g, 0.34 mmol) en DMF (5 ml) se desgasifica por evaluación secuencial del matraz y admisión de nitrógeno (x3) y morfolina (0.5 ml, 5.8 mmol), y $Pd(PPh_3)_4$ (80 mg, 0.68 mmol) se añade. La solución se agita durante 72 horas después se concentra y los residuos se cargan en un SPE de animopropilo (10 g) con MeOH. La elusión con MeOH seguida por AcOH/MeOH al 5% proporciona el compuesto del titulo como un sólido amarillo pálido, que se lava con éter para producir un sólido blanco (0.053 g, 32%).

LC/EM: m/z 491 $[MH]^+$, temperatura ambiente 3.69 minutos.

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-1H-purina-2,6-diona



i)

i) Una mezcla γ-butirolactona (8 ml, 104 mmol)), oxima de 4-clorobenzamidina (3.0 g, 16.25 mmol), solución al 30% de NaOMe en MeOH (5ml) y MeOH (80 ml) se calienta a reflujo durante 30 horas, se enfría y se concentra. Los residuos se purifica por cromatografía instantánea sobre sílice fluyendo con DCM/EtOH/0.88 amoniaco ac. (200:8:1) para proveer un aceite amarillo (13 g). Este material se disuelve en DCM (150 ml) y se lava con hidróxido de sodio 2M (100 ml) y los orgánicos se separan, se secan y se concentran para producir 3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}-1-propanol como un aceite viscoso (3.95 g, 95%) que se usan en la siguiente etapa.

ii) A una solución 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (0.10 g, 0.34 mmol), 3-{3-[(4-clorofenilmetil)metil]-1,2,4-oxadiazol-5-il}-1-propanol (0.086 g, 0.34 mmol) y trifenilfosfina (0.186 g, 0.69 mmol) en THF (5 ml) se añade dibencilazodicarboxilato (0.204 g, 0.68 mmol) y la solución se agita durante 18 horas. La solución después se concentra y a

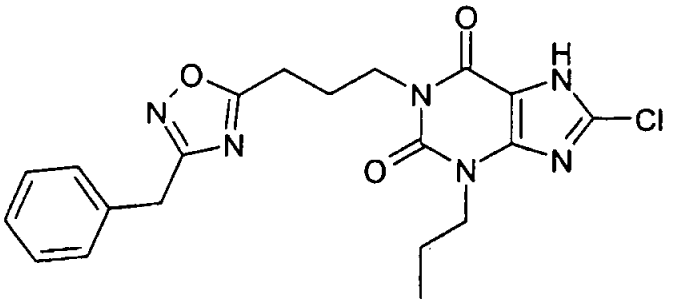
los residuos se les realiza la cromatografía sobre sílice (20 g, SPE) eluyendo con DCM inicialmente después mezclas de DCM/Et_2O para producir el compuesto del titulo contaminado con productos secundarios de dibencilazodicarboxilato (0.18 g). El material se usa crudo en la etapa de desprotección.

LC/EM: m/z 531 $[MH]^+$, temperatura ambiente 3.83 minutos.

EJEMPLO 70

8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3-propil-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3-propil-3,7-dihidro-1H-purina-2,6-diona



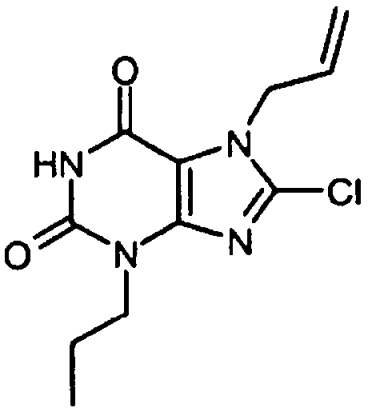
Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona (200 mg, 0.74 mmol) en THF (4 ml) se trata con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (195 mg, 0.89 mmol) y PPh_3 (254 mg, 0.96 mmol). Se añade DBAD (223 mg, 0.96 mmol) en una porción y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 18

horas. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. El producto crudo se purifica por una columna SPE de sílice usando un gradiente ciclohexano/EtOAc 0-70%. Las fracciones de producto se combinan, se concentran y se purifican adicionalmente por una columna SPE de sílice usando un gradiente ciclohexano/EtOAc 0-60%. Las fracciones de producto se combinan y se concentran después se disuelven en THF anhidro (4 ml). La solución se desgasifica mediante alto vacío después $Pd(PPh_3)_4$ (86 mg, 0.074 mmol) y morfolina (644 µl, 7.4 mmol) se añade y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 1 día. La mezcla se divide entre EtOAc y HCl (ac.). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra por alto vacío. El producto crudo se purifica por un SPE aminopropilo usando MeOH para cargar el compuesto en la columna y se lava a través de las impurezas después un gradiente AcOH/MeOH 2-4% para eluir el producto. Las fracciones de producto se combinan y se concentran por alto vacío para dejar el compuesto del titulo como un sólido blanco (74 mg, 23%).

LC/EM: m/z 429 $[MH]^+$, temperatura ambiente 3.14 minutos.

^1H RMN; (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 traslapado, 4H), 7.27 (m, 5H) 14.46 (s, 1 H).

b) 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona

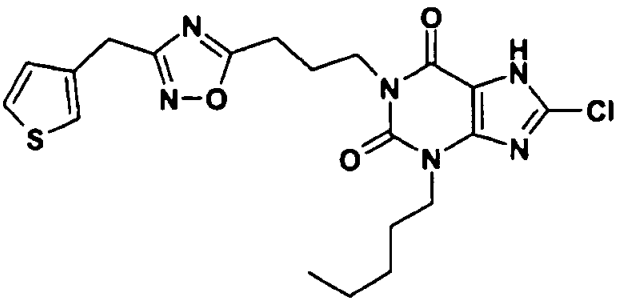


Una mezcla de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (1.5 g, 6.6 mmol), 1-yodopropano (1.2 g, 6.9 mmol) y carbonato de sodio (0.9 g, 8.5 mmol) en DMF (40 ml) se calienta a 50°C durante 18 horas. La mezcla de reacción se concentra *in vacuo* y el residuo se trata con agua (60 ml) y se extrae con EtOAc (3x 80 ml). Los extractos orgánicos combinados se secan ($MgSO_4$) se filtra y se evaporan. El residuo se tritura con éter/ciclohexano, el sólido se filtra y se seca para producir el compuesto del titulo (0.82 g, 46%).

EJEMPLO 71

8-cloro-3-pentil-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona

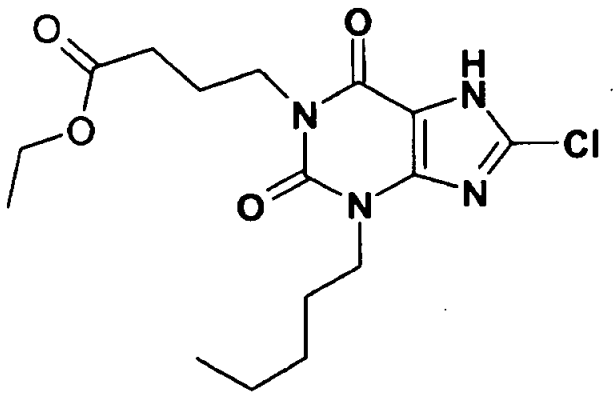
a) 8-cloro-3-pentil-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



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 mmol), N-hidroxi-2-(3-tienil)etanimidamida (36 mg, 0.23 mmol), solución al 21% de NaOEt en EtOH(78 μl, 0.21 mmol) y EtOH (1.5 ml) se calienta en microondas a 140°C durante 10 minutos. Después del enfriamiento la reacción se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa y la capa acuosa se extrae nuevamente con EtOAc. Los extractos combinados se concentran y se purifican por MDAP. El compuesto del titulo se seca por congelamiento a partir de 1,4-dioxano para proporcionar un sólido blanco (27 mg, 31%).

LC/EM: m/z 463 $[MH]^+$, temperatura ambiente 3.4 minutos.

b) 4-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo



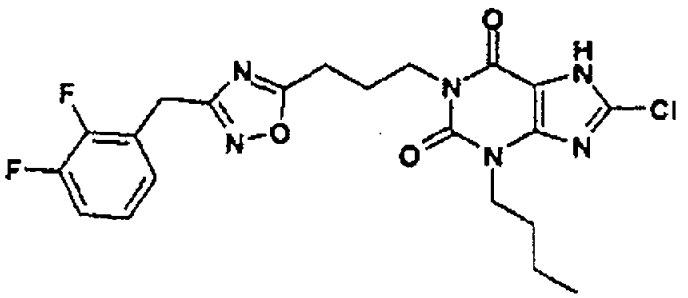
Una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (3.0 g, 10.1 mmol) en DMF anhidro (35 ml) se trata con Cs_2CO_3 (3.6 g, 11.1 mmol) y 4-bromobutirato de etilo (1.6 ml, 11.1 mmol). La mezcla se agita a temperatura ambiente durante 18 horas después se desgasifica bajo vacío suave, después se induce el nitrógeno. Esto se repite dos veces. Se añade $Pd(PPh_3)_4$ (1.17 g, 1.0 mmol) y la mezcla se desgasifica una vez más. Se añade morfolina (8.8 ml, 101 mmol) y se deja agitar durante 3 horas a temperatura ambiente. La mezcla se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra, proporcionando un sólido amarillo (5.16 g). El residuo se toma en MeOH y se divide en dos porciones iguales, y después cada uno pasa debajo de SPE de aminopropilo (20 g), se eluye con MeOH seguido por AcOH/MeOH al 5%. Las fracciones de producto se combinan y se concentran proporcionando el compuesto del titulo como un sólido blanco puro (3.01g, 80%).

LC/EM: m/z 371 $[MH]^+$, temperatura ambiente 3.2 minutos.

EJEMPLO 72

3-butil-8-cloro-1-{3-[3-(2,3-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 3-butil-8-cloro-1-{3-[3-(2,3-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



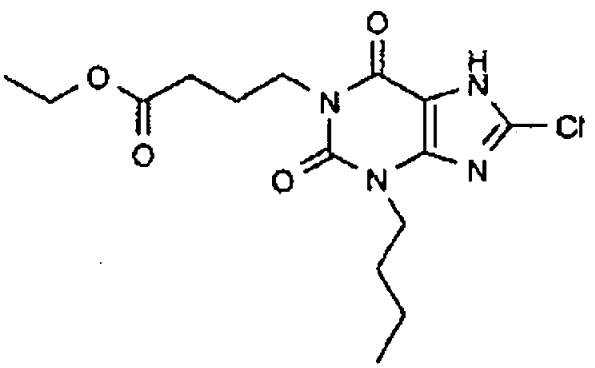
Se disuelve 2,3-difluorofenilacetonitrilo (23 mg, 0.15 mmol) se disuelve en EtOH (1 ml). Se añade clorhidrato de hidroxilamina (14 mg, 0.20 mmol), seguido por agua (0.5 ml) y carbonato de potasio (41 mg, 0.3 mmol). La mezcla se calienta a reflujo toda la noche y después se enfría y se divide entre EtOAc y salmuera. La fase orgánica se evapora y la amidoxima cruda así obtenida se disuelve en EtOH (1 ml). 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (43 mg, 0.12 mmol) y 21% en peso de etóxido de sodio etanólico (0.067 ml, 0.18 mmol) se añade y la mezcla se calienta en el reactor de microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOAc y HCl 2M, la fase orgánica se evapora y el producto se

purifica por MDAP para proveer el compuesto del titulo como un sólido (13 mg).

LC/EM: m/z 479 $[MH]^+$, temperatura ambiente 3.52 minutos.

^1H RMN (MeOH-d_6) 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-1H-purin-1-il)butanoato de etilo



A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (6.0 g, 21.24 mmol) en DMF seco (100 ml) se añade Cs_2CO_3 (7.62 g, 23.36 mmol) seguido por 4-bromobutirato de etilo (4.556 g, 23.36 mmol). La mezcla se calienta a 55°C durante 18 horas y se deja enfriar después se desgasifica por evacuación y re-admisión repetidamente de nitrógeno. Se añade morfolina (14.9 g, 171 mmol) seguida por tetraquis(trifenilfosfina)paladio (0) (4.0 g, 3.46 mmol) y la mezcla se agita durante 4 horas. Se añade EtOAc (300 ml) y HCl 2M (150 ml) y agua (100 ml) y la fase orgánica se separa, se lava con

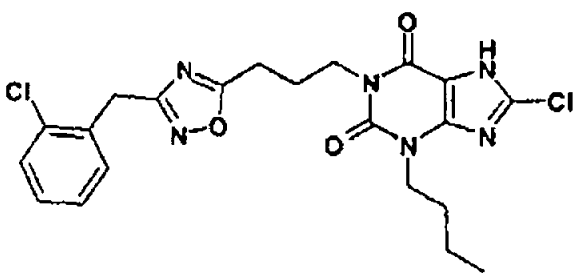
salmuera (3 x 100 ml) y se filtra. El filtrado se seca (Na_2SO_4) y se evapora. El producto crudo (10 g) se purifica por SPE de aminopropilo (3 x 20 g), se carga en THF/MeOH (1:1), se lava con THF/MeOH (1:1) y MeOH puro y se eluye el producto con DCm/MeOH (1:1) que contiene 5% de AcOH añadido para producir el compuesto del titulo (5.08 g).

LC/EM: m/z 357 $[MH]^+$, temperatura ambiente 3.06 minutos.

^1H 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).

EJEMPLO 73

3-butil-8-cloro-1-{3-[3-(2-clorobencil)-1,2,4-oxadiazol-5-il]propil9-3,7-dihidro-1H-purina-2,6-diona



4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (53 mg, 0.15 mmol) y (1Z)-2-(2-clorofenil)-N-hidroxietanimidamida (30 mg, 0.18 mmol; entrada 1, cuadro 7) se calienta en EtOH (0.75 ml) con etóxido de sodio etanólico al 21% (0.083 ml, 0.22 mmol) a 140°C durante 10 minutos. La mezcla después se divide entre EtOAc y HCl 2M y se evapora la fase orgánica. El producto se purifica por MDAP para

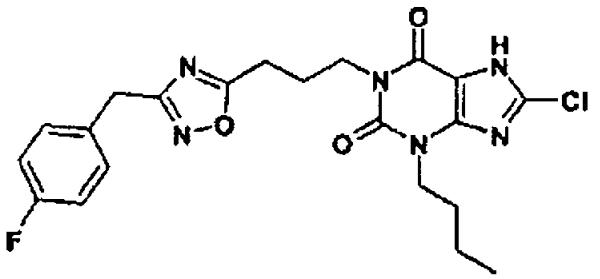
producir el compuesto del titulo como un sólido (34.8 mg).

LC/EM: m/z 477 $[MH]^+$, temperatura ambiente 3.59 minutos.

^1H 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 74

3-butil-8-cloro-1-{3-[3-(4-fluorobencil)-1,2,4-oxadizol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



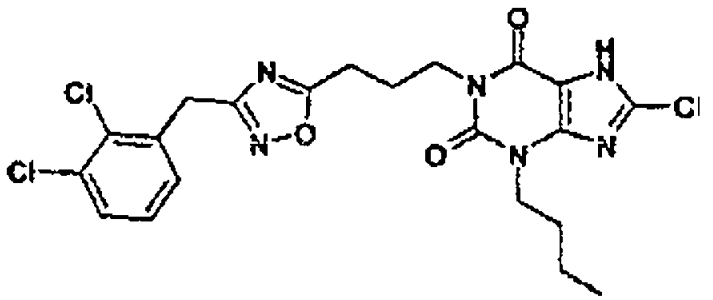
Iniciando a partir de (1Z)-2-(4-fluorofenil)-N-hidroxietanimidamida (28 mg, 0.18 mmol; entrada 2, cuadro 7) se obtiene similarmente el compuesto del titulo como un sólido (10.0 mg).

LC/EM: m/z 461 $[MH]^+$, temperatura ambiente 3.49 minutos.

290

EJEMPLO 75

3-butil-8-cloro-1-{3-[3-(2,3-diclorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



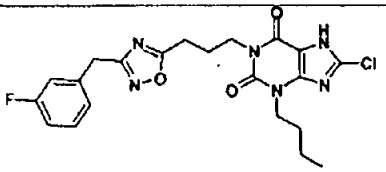
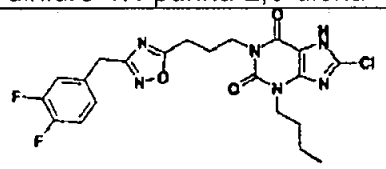
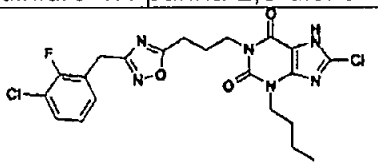
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (53 mg, 0.15 mmol) y (1Z)-2-(2,3-diclorofenil)-N-hidroxietanimidamida (36 mg, 0.165 mmol; entrada 3, cuadro 7) y etóxido de sodio etanólico (0.083 ml, 0.22 mmol) se calientan juntos en EtOH (0.75 ml) en el reactor de microondas a 140°C durante 10 minutos. La mezcla después se divide entre EtOAc y HCl 2M, la fase orgánica se separa, se evapora y el producto se purifica por MDAP para proporcionar el compuesto del titulo como un sólido (42.1 mg).

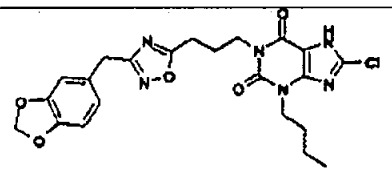
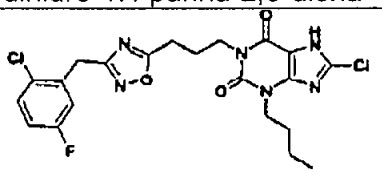
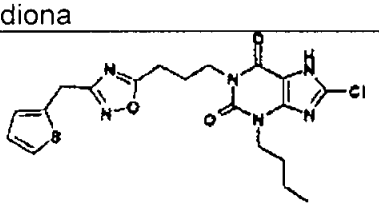
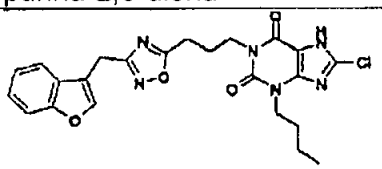
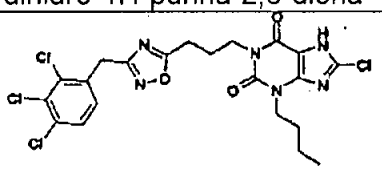
LC/EM m/z 511, 513, 515 (isótopos) $[MH]^+$, temperatura ambiente 3.66 minutos.

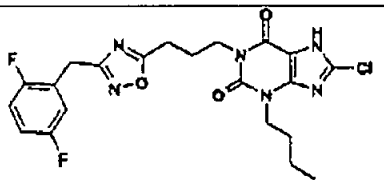
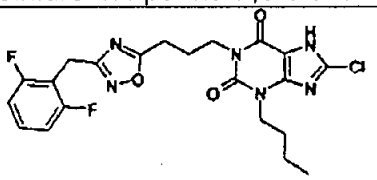
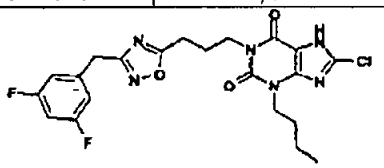
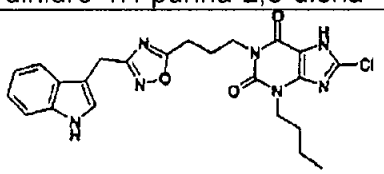
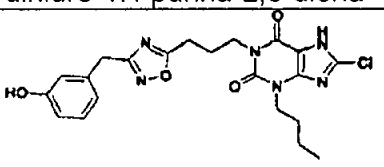
Los siguientes compuestos (cuadro 4) se preparan usando un método análogo al del ejemplo 75, usando amidoxima apropiada, (con las excepciones de que para el ejemplo 87 (cuadro 4) durante la preparación el pH se ajusta a 5 antes de la extracción con EtOAc; y en el caso del ejemplo 88 (cuadro 4) el producto crudo se agita durante 18 horas con EtOH (1 ml) y

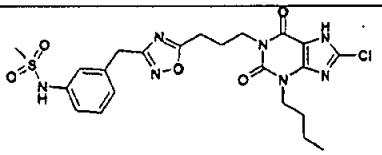
NaOH 2M (0.5 ml) y el ejemplo 89 (cuadro 4) se agita durante 18 horas con EtOH (0.75 ml) y NaOH 2M (0.5 ml) antes de repetir la preparación y purificación por MDAP).

CUADRO 4

Ejemplo	Estructura	Amidoxima (véase cuadro 7)	Peso de amidoxima mg	Rend. mg	LC/EM
76	 3-butil-8-cloro-1-{3-[3-(3-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	4	28	32.4	m/z 461 $[MH]^+$ RT 3.41 min
77	 3-butil-8-cloro-1-{3-[3-(3,4-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	5	31	28.3	m/z 479 $[MH]^+$ RT 3.46 min
78	 3-butil-8-cloro-1-{3-[3-(3-cloro-2-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	6	33	32.3	m/z 495 $[MH]^+$ RT 3.55 min

79	 1-{3-[3-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	10	32	30.5	m/z 487 $[MH]^+$ RT 3.27 min
80	 3-butil-8-cloro-1-[3-{3-[(2-cloro-5-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil]-3,7-dihidro-1H-purina-2,6-diona	19	33	26.2	m/z 495 $[MH]^+$ RT 3.47 min
81	 3-butil-8-cloro-1-{3-[3-(2-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	21	26	33.4	m/z 449 $[MH]^+$ RT 3.23 min
82	 1-{3-[3-(1-benzofuran-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	22	31	27.3	m/z $[MH]^+$ 483 RT 3.47 min
83	 3-butil-8-cloro-1-(3-{3-[(2,3,4-triclorofenil)metil]-1,2,4-oxadiazol-5-il}-propil)-3,7-dihidro-1H-purina-2,6-diona	15	42	29.8	m/z 545 $[MH]^+$ RT 3.79 min

84	 3-butil-8-cloro-1-(3-{3-[(2,5-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	16	31	34.8	m/z 479 $[MH]^+$ RT 3.35 min
85	 3-butil-8-cloro-1-(3-{3-[(2,6-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17	31	38.2	m/z 479 $[MH]^+$ RT 3.31 min
86	 3-butil-8-cloro-1-(3-{3-[(3,5-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	18	31	35.4	m/z 479 $[MH]^+$ RT 3.39 min
87	 3-butil-8-cloro-1-{3-[3-(1H-indol-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	20	31	16.1	m/z 482 $[MH]^+$ RT 3.31 min
88	 3-butil-8-cloro-1-(3-{3-[(3-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	7	28	10	m/z 459 $[MH]^+$ RT 3.07 min

89	 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]metanosulfonamida	25	40	28.4	m/z 536 $[MH]^+$ RT 3.03 min

Detalles de RMN para ejemplos seleccionados del cuadro 4

EJEMPLO 76

3-butil-8-cloro-1-{3-[3-(3-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-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, 1 H).

EJEMPLO 77

3-butil-8-cloro-1-{3-[3-(3,4-difluorobencil)-1,2,4-oxadiazol-5-il]propil}3,7-dihidro-1H-purina-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 79

1-{3-[3-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1H-purina-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 87

3-butil-8-cloro-1-{3-[3-(1H-indol-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-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, 1 H).

EJEMPLO 88

3-butil-8-cloro-1-{3-[3-[(3-hidroxifenil)metil]-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-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, 1 H), 9.40 (s,1 H).

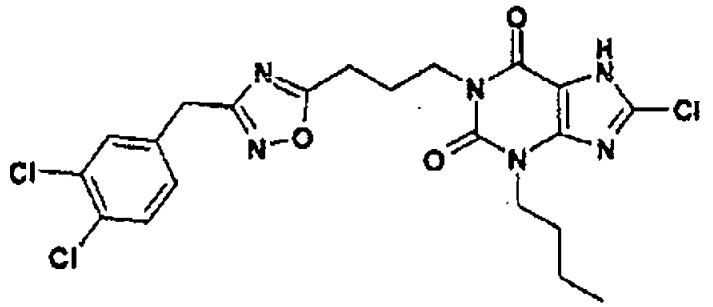
EJEMPLO 89

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]metanosulfonamida

^{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, 1 H), 7.06-7.13 (m, 2H), 7.26 (t, 1 H, J = 8Hz), 9.75 (s, 1 H), 14.45 (br s, 1H).

EJEMPLO 90

3-butil-8-cloro-1-(3-{3-[(3,4-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona



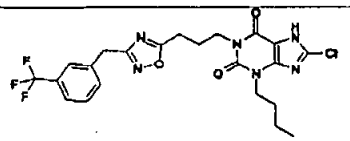
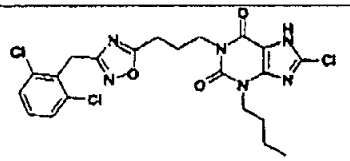
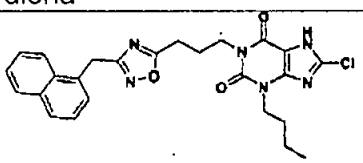
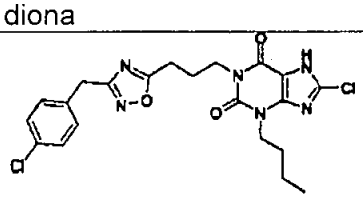
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (71 mg, 0.2 mmol), (1Z)-2-(3,4-diclorofenil)-N-

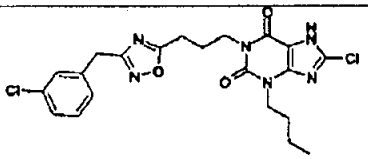
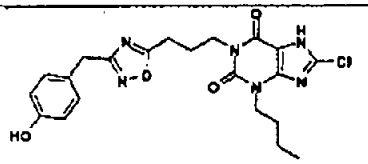
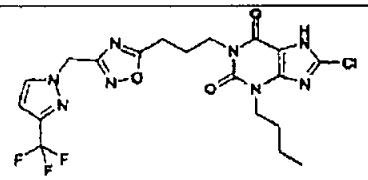
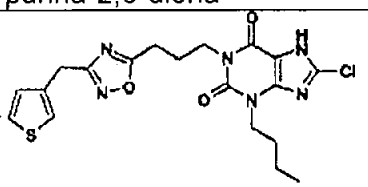
hidroxietanimidamida (48 mg, 0.22 mmol) y 21% en peso de etóxido de sodio etanoico (0.111 ml, 0.3 mmol) se calientan juntos en EtOH (1 ml) en reactor de microondas a 140°C durante 10 minutos. La mezcla después se divide entre EtOAc y HCl 2M, la fase orgánica se separa y se evapora, y el producto crudo se purifica por MDAP para proporcionar el compuesto del titulo como un sólido (48.8 mg).

LC/EM: m/z 511, 513 $[MH]^+$, temperatura ambiente 3.65 minutos.

Los siguientes compuestos (cuadro 5) se preparan usando un método análogo al del ejemplo 90, usando amidoxima apropiada (con la excepción de que para el ejemplo 91, se añaden 0.185 ml (0.5 mmol) de etóxido de sodio al 21% a fin de permitir que las amidoximas sean las sales de clorhidrato).

CUADRO 5

Ej.	Estructura	amidoxima	Peso de amido-xima mg	Rend. Mg	LC/EM
91	 3-butil-8-cloro-1-[3-(3-{[3-(trifluorometil)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	Clorhidrato de (1Z)-N-hidroxi-2-[3-(trifluorometil) fenil]-etanimidamida	56	46.5	m/z 511 $[MH]^+$ RT 3.63 min.
92	 3-butil-8-cloro-1-{3-[3-[(2,6-diclrofenil)metil]1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	(1Z)-2-(2,6-diclorofenil)-N-hidroxietanimi-damida	48	53.8	m/z 511 $[MH]^+$ RT 3.64 min.
93	 3-butil-8-cloro-1-{3-[3-(1-naftalenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	(1Z)-N-hidroxi-2-{1-naftalenil}-etanimidamida	44	48.6	m/z 493 $[MH]^+$ RT 3.67 min.
94	 3-butil-8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	(1Z)-2-(4-clorofenil)-N-hidroxietanimi-damida	41	35.6	m/z 4776 $[MH]^+$ RT 3.60 min.

95	 3-butil-8-cloro-1-(3-{3-[(3-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	(1Z)-2-(3-clorofenil)-N-hidroxietanimidamida	41	39.4	m/z 477 $[MH]^+$ RT 3.64 min.
96	 3-butil-8-cloro-1-(3-{3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	(1Z)-N-hidroxi-2-(4-hidroxifenil)etinimidamida	36	53.5	m/z 459 $[MH]^+$ RT 3.08 min.
97	 3-butil-8-cloro-1-[3-(3-{[3-(trifluorometil)-1H-pirazol-1-il]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	(1Z)-N-hidroxi-2-[3-(trifluorometil)-1H-pirazol-1-il]etanimidamida	46	58.1	m/z 501 $[MH]^+$ RT 3.33 min.
98	 3-butil-8-cloro-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	(1Z)-N-hidroxi-2-(3-tienil)etanimidamida	34	32.6	m/z 449 $[MH]^+$ RT 3.31 min.

Detalles de RMN para ejemplos seleccionados del cuadro 5

300

EJEMPLO 91

^{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 94

3-butil-8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona

^{1}H RMN (DMSO-d_6) δ 0.89 (t, 3H, J = 7Hz)1 1.23-1.37 (m, 2H), 1.55-1.67 (m, 2H)1 1.97-2.09 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz)1 4.00 (s, 2H), 7.27-7.40 (m, 4H).

EJEMPLO 96

3-butil-8-cloro-1-(3-[3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1H-purina-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, 1 H).

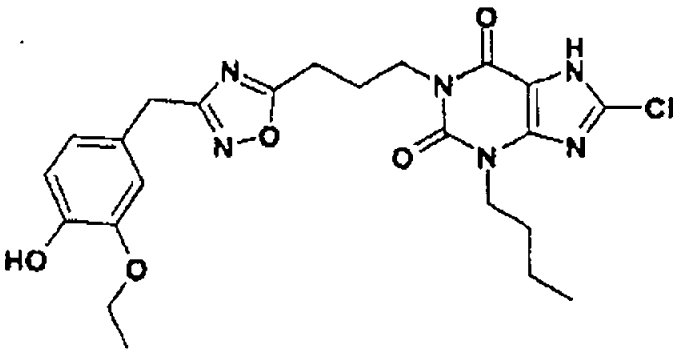
EJEMPLO 97

3-butil-8-cloro-1-[3-(3-{[3-(trifluorometil)-1H-pirazol-1-il]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-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, 1 H), 8.10 (s, 1H).

EJEMPLO 99

3-butil-8-cloro-1-[3-(3-{[3-(etiloxi)-4-hidroxifenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona



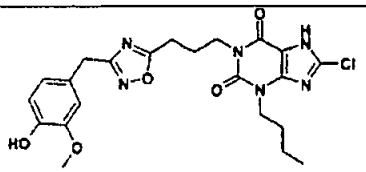
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (53 mg, 0.15 mmol), y (1Z)-2-[3-(etiloxi)-4-hidroxifenil]-N-hidroxietanimidamida (35 mg, 0.165 mmol; entrada 11, cuadro 7) se mezcla en EtOH (0.75 ml). Etóxido de sodio etanólico (21% en peso, 0.083 ml, 0.22 mmol) se añade y la mezcla se calienta en el microondas a 140°C durante 10 minutos. Unos 0.055 ml adicionales (0.15 mmol) de solución de NaOEt después se añade y la mezcla se calienta durante un periodo de 10 minutos

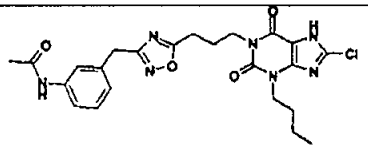
adicionales a 140°C. La mezcla se divide entre EtOAc y HCl 2M y la fase orgánica se evapora y se purifica por MDAP para proporcionar el compuesto del titulo como un sólido (29.6 mg).

LC/EM: m/z 503 $[MH]^+$, temperatura ambiente durante 3.15 minutos.

Los siguientes compuestos (cuadro 6) se preparan usando un método análogo al del ejemplo 99, usando amidoxima apropiada (con la excepción de que para el ejemplo 100 (cuadro 6), el producto crudo después se trata con agitación con EtOH (1 ml) y NaOH 2M (0.5 ml) toda la noche a fin de hidrolisar el éster de inicio residual, antes de tratar HCl repetido y la purificación por MDAP).

CUADRO 6

Ej.	Estructura	amidoxima	Peso de amido-xima mg	Rend. Mg	LC/EM
100	 3-butil-8-cloro-1-[3-(3-[(4-hidroxi-3-(metiloxifenil)metil)-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1H-purina-2,6-diona	12	32	19.3	m/z 489 $[MH]^+$ RT 2.98 min

Ej.	Estructura	amidoxima	Peso de amido-xima mg	Rend. Mg	LC/EM
101	 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	23.6	m/z 500 $[MH]^+$ RT 2.94 min

Detalles RMN para ejemplos seleccionados del cuadro 6

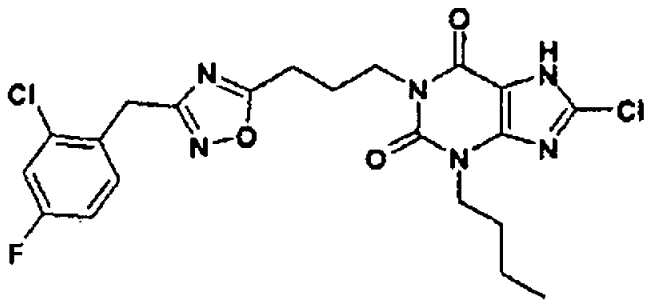
EJEMPLO 101

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

^{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, 1 H).

EJEMPLO 102

3-butil-8-cloro-1-(3-{3-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona



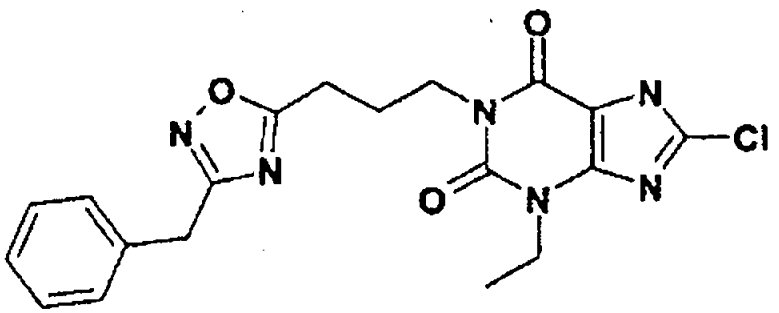
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidroi-1H-purin-1-il)butanoato de etilo (100 mg, 0.28 mmol) y (1Z)-2-(2-cloro-4-fluorofenil)-N-hidroxietanimidamida (62.4 mg, 0.308 mmol) y 21% en peso de etóxido de sodio etanólico (0.157 ml, 0.42 mmol) se calientan juntos en un reactor de microondas en EtOH (1.5 ml) a 140°C durante 10 minutos. La mezcla se trata mediante la división entre EtOAc y HCl 2M. La fase orgánica se evapora y se purifica por MDAP para producir el compuesto del titulo como un sólido (73 mg).

LC/EM: m/z 495 $[MH]^+$, temperatura ambiente 3.55 minutos.

EJEMPLO 103

8-cloro-3-etil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-3-etil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



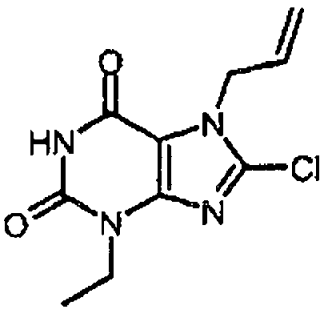
Una solución de 8-cloro-3-etil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (150 mg, 0.59 mmol) en THF anhidro (4 ml) se trata con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (154 mg, 0.71 mmol) y trifenilfosfina (200 mg, 0.76 mmol). Se añade DBAD (162 mg, 0.71 mmol) en una porción y la mezcla se deja agitar a temperatura ambiente, bajo nitrógeno por 18 horas. La mezcla se desgasifica por alto vacío después $Pd(PPh_3)_4$, (68 mg, 0.059 mmol) y morfolina (515 µl, 5.9 mmol) se añade. La mezcla se deja agitar a temperatura ambiente, bajo nitrógeno, durante 3 horas. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra por alto vacío. El material crudo se purifica por un SPE aminopropilo usando MeOH para cargar el compuesto dentro de la columna y se lava a través de las impurezas, después con

AcOH/MeOH al 2% para eluir el compuesto. Las fracciones activas de UV se combinan y se concentran por alto vacío. El producto se purifica adicionalmente por MDAP. Las fracciones de producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (61 mg, 25%).

LC/EM: m/z 415 $[MH]^+$, temperatura ambiente 3.01 minutos.

^{1}H RMN; (DMSO-d_6) δ 1.19 (t, 3H, J = 7Hz)1 2.93 (m, 2H), 2.91 (t, 2H1 J = 7.5Hz), 3.96 (m, 6H), 7.27 (m, 5H) 14.46 (s, 1 H).

b) 8-cloro-3-etil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona



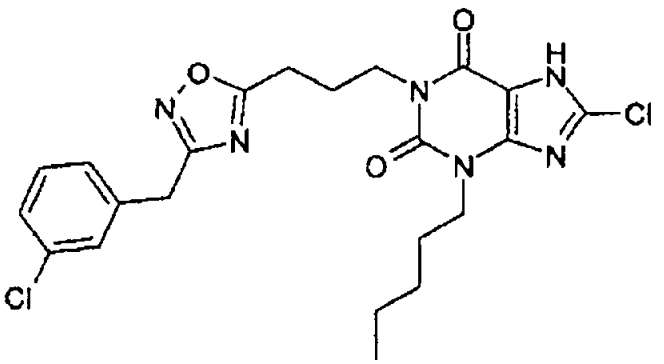
Una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (10 g, 0.044 mol) en DMF anhidro (100 ml) se trata con yodoetano (5.4 ml, 0.058 mol) y Na_2CO_3 (4.9 g, 0.046 mol). La mezcla de reacción se deja agitar a temperatura ambiente bajo nitrógeno durante 2 días. Se añade yodoetano (0.35 ml, 0.0044 mol) y la mezcla se deja agitar a temperatura ambiente durante 1 día. La mezcla se divide entre EtOAc y HCl 2M. La capa orgánica se separa, se lava consecutivamente con solución de sulfito de sodio saturado y salmuera, se seca ($MgSO_4$) y se concentra. El sólido crudo se lava

con Et_2O para proporcionar el compuesto del titulo como un sólido blanco (8.37 g, 75%).

LC/EM: m/z 255 $[MH]^+$, temperatura ambiente 2.35 minutos.

EJEMPLO 104

8-cloro-1-(3-{3-[(3-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (70 mg, 0.19 mmol) se disuelve en EtOH. La solución se trata con una solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmol) y (1Z)-2-(3-clorofenil)-N-hidroxietanimidamida (38 mg, 0.21 mmol). La reacción se calienta en el microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOH y HCl 2M (ac). La capa orgánica se decanta y se concentra. El producto crudo se purifica en MDAP. Las fracciones de producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (46 mg, 49%).

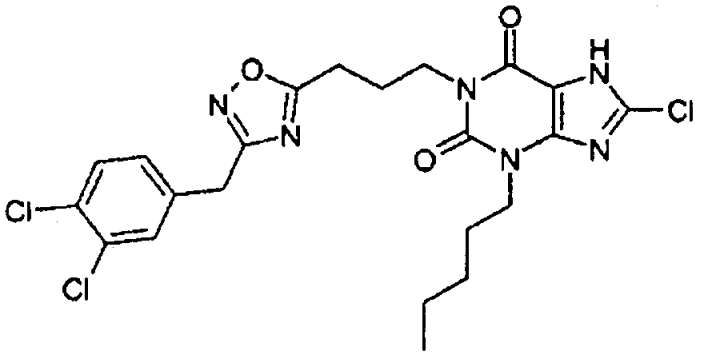
LC/EM: m/z 491 $[MH]^+$, temperatura ambiente 3.64 minutos.

^1H 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, 1 H, J = 7Hz), 7.34 (m, 3H).

EJEMPLO 105

8-cloro-1-(3-{3-[(3,4-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

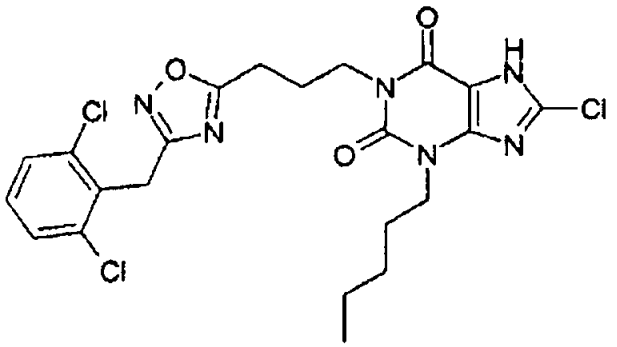


5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (70 mg, 0.19 mmol) se disuelve en EtOH. La solución se trata con una solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmol) y (1Z)-2-(3,4-diclorofenil)-N-hidroxietanimidamida (46 mg, 0.21 mmol). La reacción se calienta en el microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOH y HCl 2M (ac). La capa orgánica se decanta y se concentra. El producto crudo se purifica en MDAP. Las fracciones del producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (66 mg, 66%).

LC/EM: m/z 527 $[MH]^+$, temperatura ambiente 3.80 minutos.

EJEMPLO 106

8-cloro-1-(3-{3-[(2,6-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

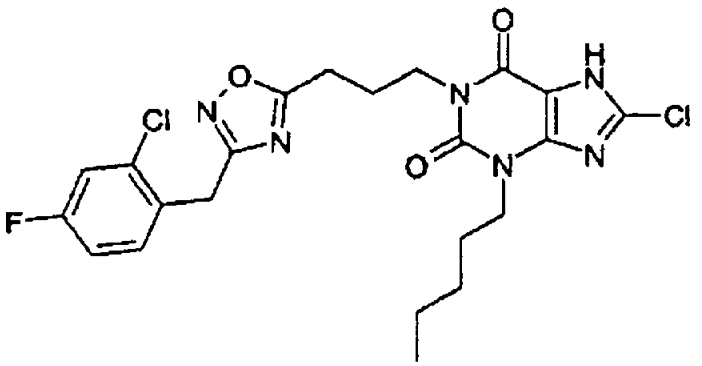


5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (70 mg, 0.19 mmol) se disuelve en EtOH. La solución se trata con una solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmol) y (1Z)-2-(2,6-diclorofenil)-N-hidroxietanimidamida (46 mg, 0.21 mmol). La reacción se calienta en el microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOH y HCl 2M (ac). La capa orgánica se decanta y se concentra mediante soplado de nitrógeno. El producto crudo se purifica en MDAP. Las fracciones del producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (80 mg, 80%).

LC/EM: m/z 526 $[MH]^+$, temperatura ambiente 3.6 minutos.

EJEMPLO 107

8-cloro-1-(3-{3-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

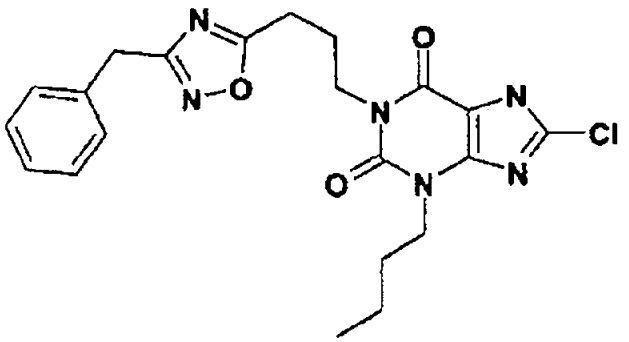


5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (70 mg, 0.19 mmol) se disuelve en EtOH. La solución se trata con una solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmol) y (1Z)-2-(2-cloro-4-fluorofenil)-N-hidroxietanimidamida (46 mg, 0.21 mmol). La reacción se calienta en el microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOH y HCl 2M (ac). La capa orgánica se decanta y se concentra. El producto crudo se purifica en MDAP. Las fracciones del producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (65 mg, 67%).

LC/EM: m/z 509 $[MH]^+$, temperatura ambiente 3.63 minutos.

EJEMPLO 108

3-butil-8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona



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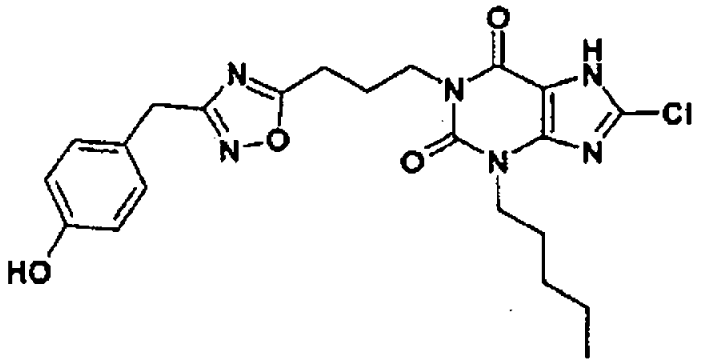
Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (205 mg, 0.73 mmol) en THF anhidro (4 ml) se trata con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (190 mg, 0.87 mmol) y PPh_3 (247 mg, 0.94 mmol). Se añade una porción de DBAD (217 mg, 0.94 mmol) y la mezcla se agita a temperatura ambiente bajo nitrógeno durante 18 horas. La mezcla se desgasifica por alto vacío después se añade $Pd(PPh_3)_4$ (4 mg, 0.073 mmol) y morfolina (636 µl, 7.3 mmol). La mezcla se agita a temperatura ambiente bajo nitrógeno durante 3 horas. La mezcla se divide entre EtOAc y HCl 2M (ac) y la capa orgánica se separa, se lava con salmuera, se secan ($MgSO_4$) y se concentra. El material crudo se purifica mediante una columna de aminopropilo usando MeOH para cargar el compuesto dentro de la columna y se lava a través de las impurezas, después con gradiente AcOH/MeOH 2-4% para remover el compuesto a partir de la columna. Purificación adicional se efectúa por MDAP para proporcionar el compuesto del titulo como un sólido blanco (75 mg, 23%).

LC/EM: m/z 443 $[MH]^+$, temperatura ambiente 3.37 minutos.

^{1}H RMN (DMSO-d_6) δ 0.89 (t, 3H, J = 7.5 Hz)1 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 109

8-cloro-1-(3-{3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



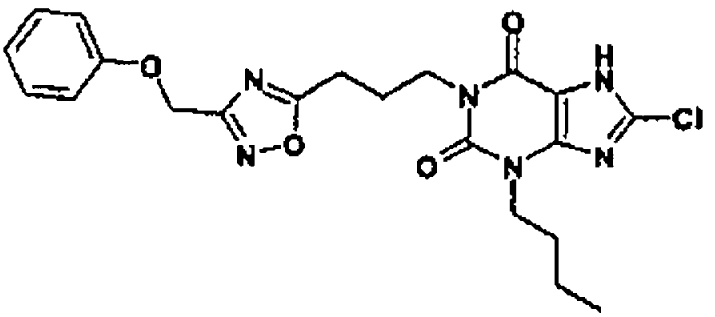
5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (29 mg, 0.078 mmol) y (1Z)-N-hidroxi-2-(4-hidroxifenil)etanimidamida (14 mg, 0.084 mmol) se calienta en EtOH (1 ml) con etóxido de sodio etanólico al 21% (0.043 ml, 0.117 mmol) bajo irradiación de microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOAc y HCl 2M y se evapora la fase orgánica. Este material se agita con EtOH (1 ml) y NaOH 2M (0.5 ml) durante 18 horas, antes de ser tratado nuevamente mediante la división entre EtOAc y HCl 2M. la purificación mediante MDAP produce el compuesto del titulo (6.5 mg).

LC/EM: m/z 473 $[MH]^+$, temperatura ambiente 3.34 minutos.

^{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 110

3-butil-8-cloro-1-(3-{3-[(feniloxi)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona



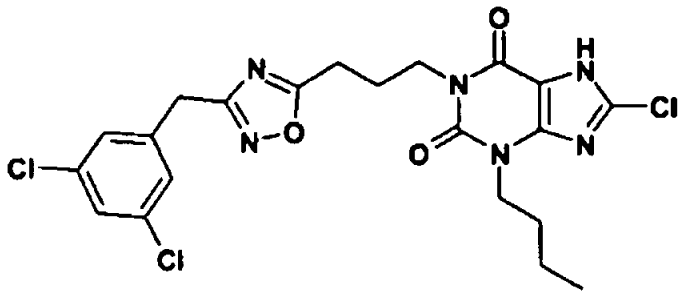
A 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (26 mg, 0.073 mmol) y clorhidrato de (1Z)-N-hidroxi-2-(feniloxi)etanimidamida (16 mg, 0.079 mmol) en EtOH (1 ml) se añade solución de etóxido de sodio etanólico al 21% en peso (0.068 ml, 0.183 mmol) y la mezcla se calienta bajo irradiación de microondas a 140°C durante 10 minutos. La mezcla se divide entre EtOAc y HCl 2M, la fase orgánica se seca (Na_2SO_4) se evapora y se purifica por MDAP para proporcionar el compuesto del titulo como una goma que se solidifica en la trituración con éter (5.9 mg).

LC/EM: m/z 459 $[MH]^+$, temperatura ambiente 3.39 minutos.

^{1}H RMN (DMSO-d_6) δ 0.90 (t, 3H1 J = 8Hz), 1.22-1.36 (m, 2H), 1.57-1.68 (m, 2H), 2.02-2.14 (m, 2H), 3.00 (t, 2H1 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 111

3-butil-8-cloro-1-(3-{3-[(3,5-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona

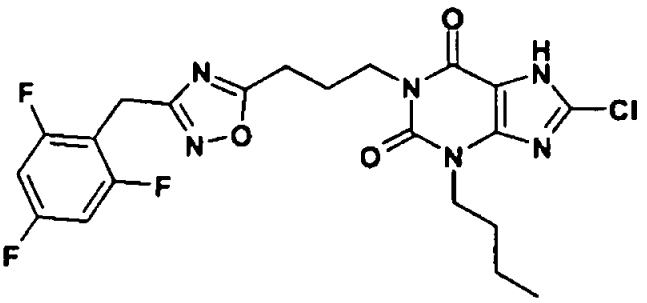


A 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (185 mg, 0.52 mmol) y (1Z)-2-(3,5-diclorofenil)-N-hidroxietanimidamida (126 mg, 0.58 mmol; entrada 23, cuadro 7) en EtOH seco (2 ml) se añade solución de etóxido de sodio etanólico al 21% de rendimiento (0.29 ml, 0.78 mmol) y la mezcla se calienta por microondas a 140°C durante 10 minutos. La reacción se trata mediante la división entre EtOAc y HCl 2M y se evapora la fase orgánica. La purificación por MDAP produce el compuesto del titulo como un sólido (135 mg).

LC/EM: m/z 511 $[MH]^+$, temperatura ambiente 3.71 minutos.

EJEMPLO 112

3-butil-8-cloro-1-(3-{3-[(2,4,6-trifluorofenil)metilo]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona



Se prepara similarmente iniciando a partir de (1Z)-N-hidroxi-2-(2,4,6-trifluorofenil)etanimidamida (119 mg, 0.58 mmol; entrada 24, cuadro 7) en un rendimiento de 135 mg.

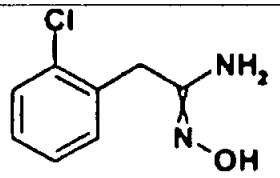
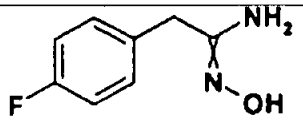
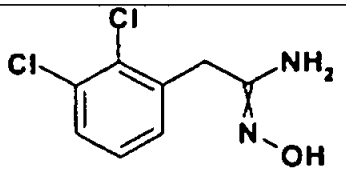
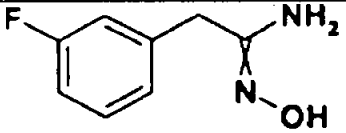
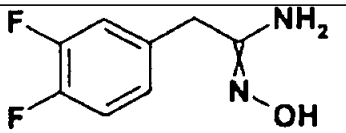
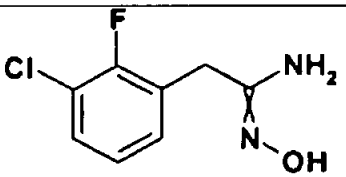
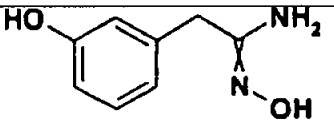
LC/EM: m/z 497 $[MH]^+$, temperatura ambiente 3.39 minutos.

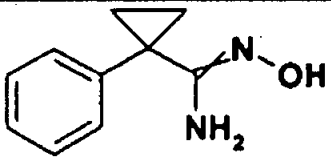
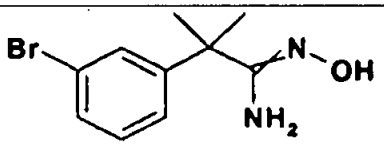
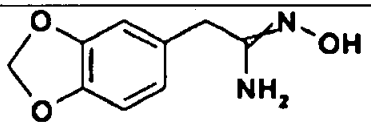
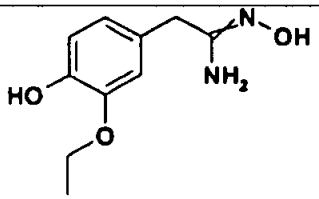
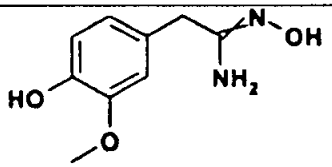
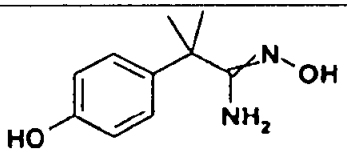
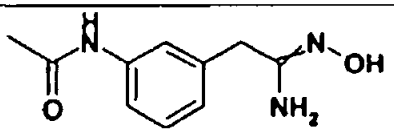
^{1}H RMN (DMSO-d_6) δ 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, J = 8Hz), 3.91 (t, 2H, J = 8 Hz), 3.94 - 4.02 (m, 4H), 7.18-7.28 (m, 2H).

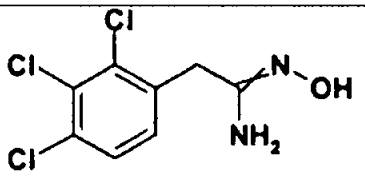
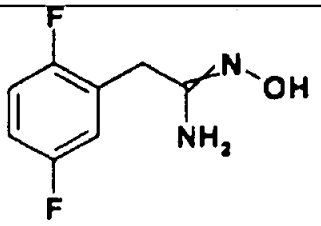
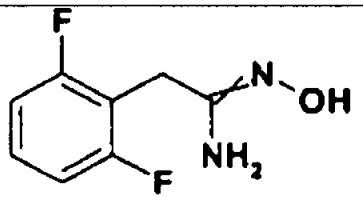
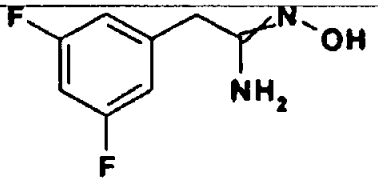
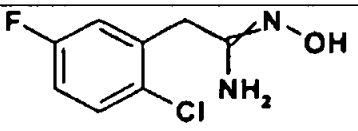
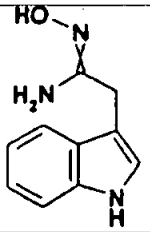
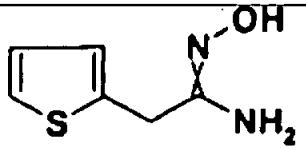
Amidoximas

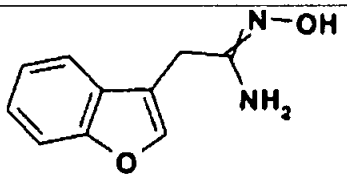
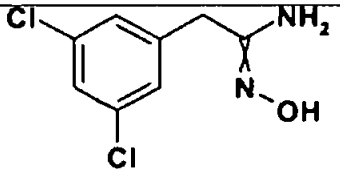
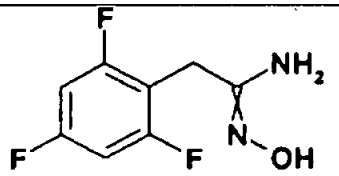
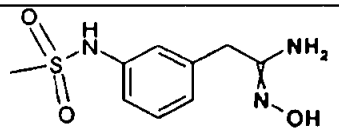
Estas son disponibles mediante los métodos detallados posteriormente y se ejemplifican por análogos en el cuadro 7.

CUADRO 7

Ej.	Estructura	Nombre	Método	Rend. mg	LC/EM
1		(1Z)-2-(2-clorofenil)-N-hidroxietanimidamida	G	38	m/z 185 $[MH]^+$ RT 1.04 min
2		(1Z)-2-(4-fluorofenil)-N-hidroxietanimidamida	G	42	m/z 169 $[MH]^+$ RT 0.72 min
3		(1Z)-2-(2,3-diclorofenil)-N-hidroxietanimidamida	B	64	m/z 219 $[MH]^+$ RT 1.83 min
4		(1Z)-2-(3-fluorofenil)-N-hidroxietanimidamida	A	78	m/z 169 $[MH]^+$ RT 0.62 min
5		(1Z)-2-(3,4-difluorofenil)-N-hidroxietanimidamida	A	88	m/z 187 $[MH]^+$ RT 0.74 min
6		(1Z)-2-(3-cloro-2-fluorofenil)-N-hidroxietanimidamida	A	92	m/z 203 $[MH]^+$ RT 1.40 min
7		(1Z)-N-hidroxi-2-(3-hidroxifenil)etanimidamida	A	67	m/z 167 $[MH]^+$ RT 0.46 min

8		N-hidroxi-1-fenilciclopropanocarboximidamida	C	75	m/z 177 $[MH]^+$ RT 1.06 min
9		(1Z)-2-(3-bromofenil)-N-hidroxi-2-metilpropanamida	D	74	m/z 257 $[MH]^+$ RT 1.06 min
10		(1Z)-2-(1,3-benzodioxol-5-il)-N-hidroxietanimidamida	C	98	m/z 195 $[MH]^+$ RT 0.73 min
11		(1Z)-2-[3-(etiloxi)-4-hidroxifenil]-N-hidroxietanimidamida	C	109	m/z 211 $[MH]^+$ RT 0.76 min
12		(1Z)-N-hidroxi-2-[4-hidroxi-3-(metiloxi)fenil]etanimidamida	C	98	m/z 197 $[MH]^+$ RT 0.50 min
13		(1Z)-N-hidroxi-2-(4-hidroxifenil)-2-metilpronimidamida	D	66	m/z 195 $[MH]^+$ RT 0.85 min
14		N-{3-[(2Z)-2-(hidroxiamino)-2-iminoetil]fenil}acetamida	C	91	m/z 208 $[MH]^+$ RT 0.73 min

15		(1Z)-N-hidroxi-2-(2,3,4-triclorofenil)etanimida-mida	C	124	m/z 253 $[MH]^+$ RT 2.29 min
16		(1Z)-2-(3,5-difluorofenil)-N-hidroxietanimidamida	C	89	m/z 187 $[MH]^+$ RT 0.66 min
17		(1Z)-2-(2,6-difluorofenil)-N-hidroxietanimidamida	C	86	m/z 187 $[MH]^+$ RT 0.62 min
18		(1Z)-2-(333,5-difluorofenil)-N-hidroxietanimidamida	C	96	m/z 187 $[MH]^+$ RT 0.80 min
19		(1Z)-2-(2-cloro-5-fluorofenil)-N-hidroxietanimidamida	C	97	m/z 203 $[MH]^+$ RT 0.90 min
20		(1Z)-N-hidroxi-2-(1H-indol-3-il)etanimidamida	C	95	m/z 190 $[MH]^+$ RT 0.90 min
21		(1Z)-N-hidroxi-2-(2-tienil)etanimidamida	C	74	m/z 157 $[MH]^+$ RT 0.38 min

22		(1Z)-2-(1-benzofuran-3-il)-N-hidroxietanimidamida	C	87	m/z 191 $[MH]^+$ RT 1.46 min
23		(1Z)-2-(3,5-diclorofenil)-N-hidroxietanimidamida	E	165	m/z 219 $[MH]^+$ RT 2.03 min
24		(1Z)-N-hidroxi-2-(2,4,6-trifluorofenil)etanimida-mida	F	297	m/z 205 $[MH]^+$ RT 0.66 min
25		(1Z)-N-hidroxi-2-{3-[(metilsulfonil)amino]fenil}-etanimidamida	C	125	m/z 244 $[MH]^+$ RT 0.63 min

Se debe notar que  como se usa aquí representa un enlace doble de geometría no definida.

Método A

El nitrilo correspondiente (0.5 mmol) se agita en EtOH (1.5 ml) con solución de hidroxilamina acuosa al 50% (0.08 ml, 1.3 mmol) y se calienta a 65°C durante 4.5 horas. Después del enfriamiento de la mezcla de reacción cruda se carga en un cartucho SPE SCX (2 g) y se lava con MeOH, después el producto de amidoxima se eluye con amoniaco 2M en MeOH.

320

Método B

Es similar al método A excepto que el producto se cristaliza a partir de la mezcla de reacción cruda y se aísla mediante filtración en lugar de SCX.

Método C

Es similar al método A excepto que el producto se purifica en un cartucho SCX de 5 g.

Método D

Es similar al método C excepto que el periodo de calentamiento es 18h.

Método E

Es similar al método C excepto que la escala es 0.753 mmol de nitrilo.

Método F

Es similar al método A excepto que la escala es 1.5 mmol de nitrilo y la purificación es en un cartucho SCX de 10 g.

Método G

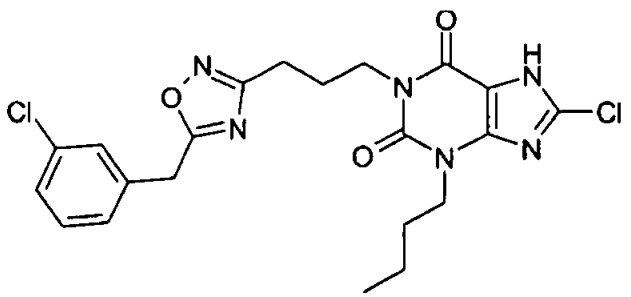
Es similar al método A excepto que el tiempo de calentamiento

es 7.5 h y la escala es 0.25 mmol de nitrilo.

EJEMPLO 113

3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-1,2,4-oxadiazol-3-il}-propil)-3,7-dihidro-1H-purina-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-purina-2,6-diona

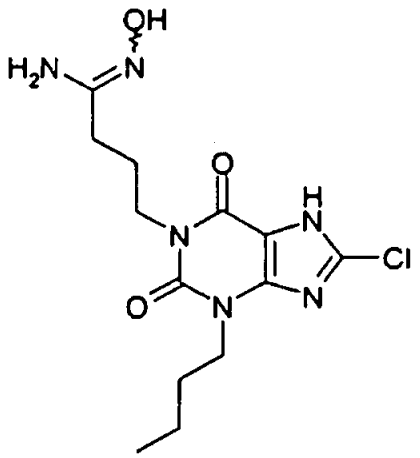


Ácido (3-clorofenil)acético (0.1 mmol), clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (21 mg, 0.11 mmol) y 1H-1m2m3-benzotriazol-1-ol (15 mg, 0.11 mmol) se agitan en 1-metil-2-pirrolidinona (1 ml). A esto se añade (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida (34 mg, 0.1 mmol) y la mezcla se agita a temperatura ambiente durante 17 horas y después 80°C durante 24 horas. La mezcla de reacción se purifica, sin modificación adicional, mediante HPLC preparativa (auto prep.) para proporcionar el compuesto del titulo (13 mg, 27%).

LC/EM. m/z 477, 479 $[MH]^+$, temperatura ambiente 3.5 minutos.

^{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, 2H1 J = 7.5Hz), 4.05-4.24 (m, 6H), 7.16-7.30 (m, 4H).

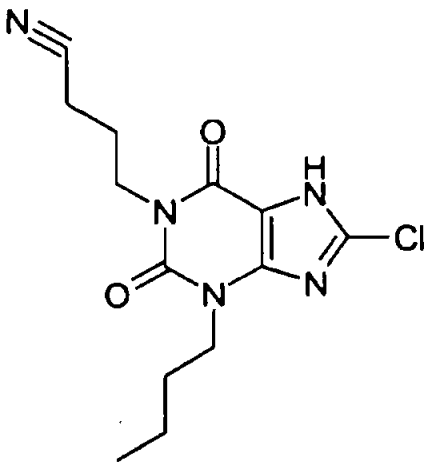
b) (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida



Se agita 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanonitrilo (1 g, 0.0032 mol) en EtOH (3.5 ml) y agua (1.8 ml). Se añade clorhidrato de hidroxilamina (344 mg, 0.0049 mol) y carbonato de potasio (652 mg, 0.0049 mol) se añade y la mezcla se calienta a 80°C durante 3 días. Después del enfriamiento la mezcla de reacción cruda se evapora. El producto crudo se disuelve en agua, se neutraliza a pH 7 con HCl, y se carga en un cartucho Oasis™ (2 g). Este se eluye con agua para remover las sales y después con MeOH, para proporcionar el compuesto del titulo (957 mg, 86%).

LC/EM: m/z 343, 345 $[MH]^+$, temperatura ambiente 2.04 minutos.

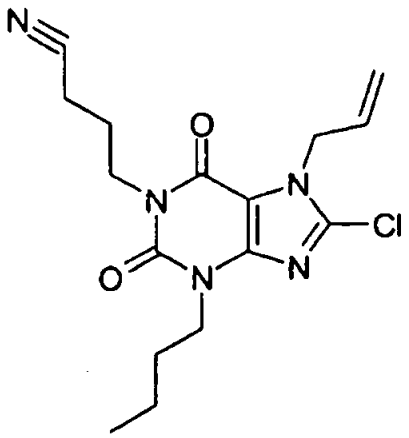
c) 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetahidro-1H-purin-1-il)butanonitrilo



4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butanonitrilo (2.1 g, 6 mmol) se agita en una mezcla de DCM desgasificado con nitrógeno (20 ml) y AcOH (2 ml). Se añade tetraquis(trifenilfosfina)paladio (675 mg, 0.6 mmol) y fenil silano (7.4 ml, 60 mmol) y la mezcla se agita a temperatura ambiente durante 2d. Este después se evapora y el residuo triturado con una mezcla de dietileter:ciclohexano (1:1) para producir el compuesto del titulo (1.47 g, 60%) como un sólido blanco.

LC/EM: m/z 310 $[MH]^+$, temperatura ambiente 2.66 minutos.

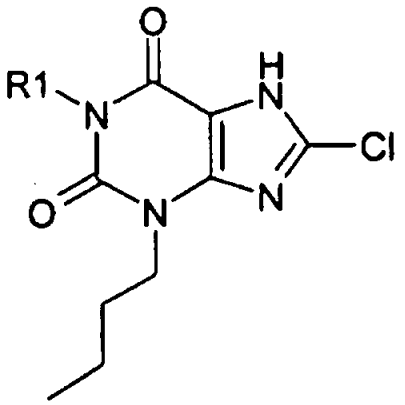
d) 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butanonitrilo



3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (2.0 g, 0.0072 mol) en MeCN seco (20 ml) se añade Ca_2CO_3 (4.68 g, 0.0144 mol) seguido por bromobutironitrilo (1.38 g, 0.0094 mol). La mezcla se calienta a 80°C durante 18 horas y se deja enfriar. La mezcla de reacción se evapora y el producto crudo se divide entre EtOAc y HCl (2N). La fase orgánica se separa y se lava con salmuera, se seca ($MgSO_4$) y se evapora para proporcionar el producto crudo. Esta se purifica por SPE de sílice (50 g), eluyendo con ciclohexano:etilacetato (2:1 a 1:1) para producir el compuesto del titulo como un aceite claro (2.1 g, 85%).

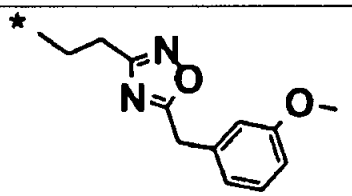
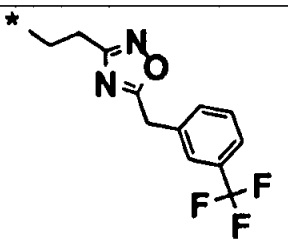
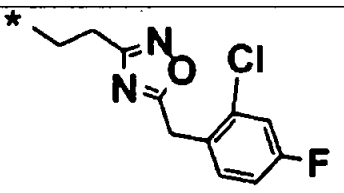
LC/EM: m/z 350 $[MH]^+$, temperatura ambiente 3.10 minutos.

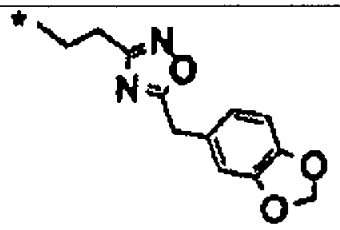
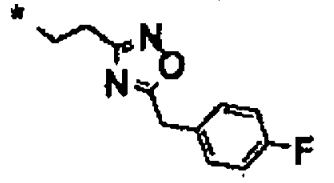
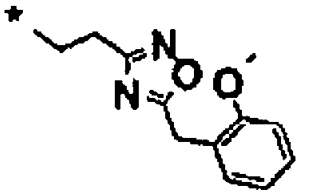
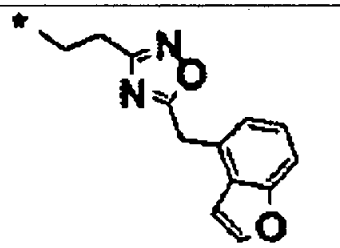
Los siguientes compuestos (cuadro 8) se preparan usando un método análogo al del ejemplo 113, a partir de los ácidos correspondientes y (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida.



Donde * se usa en los ejemplos aquí indican el punto de unión del grupo R al núcleo xantina.

CUADRO 8

Ej.		Compuesto R1 =	% de rend.	LC/EM
114	3-butil-8-cloro-1-[3-(5-{[3-(metiloxi)fenil]-metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purina-2,6-diona		22	m/z 473 $[MH]^+$ RT 3.3 min.
115	3-butil-8-cloro-1-[3-(5-{[3-(trifluorometil)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purina-2,6-diona		23	m/z 511 $[MH]^+$ RT 3.5 min.
116	3-butil-8-cloro-1-(3-{5-{(2-cloro-4-fluorofenil)metil}-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona		28	m/z 495 $[MH]^+$ RT 3.5 min.

Ej.		Compuesto R1 =	% de rend.	LC/EM
117	1-{3-[5-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-3-il]propil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona		27	m/z 473 $[MH]^+$ t.a. 3.3 min.
118	3-butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona		28	m/z 511 $[MH]^+$ t.a. 3.5 min.
119	3-butil-8-cloro-1-(3-{5-[(2-metiloxi)fenil]metil}-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona		21	m/z 495 $[MH]^+$ t.a. 3.5 min.
120	1-{3-[5-(1-benzofuran-4-ilmetil)-1,2,4-oxadiazol-3-il]propil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona		24	m/z 483 $[MH]^+$ t.a. 3.4 min.

Detalles de RMN para los ejemplos seleccionados del cuadro 8

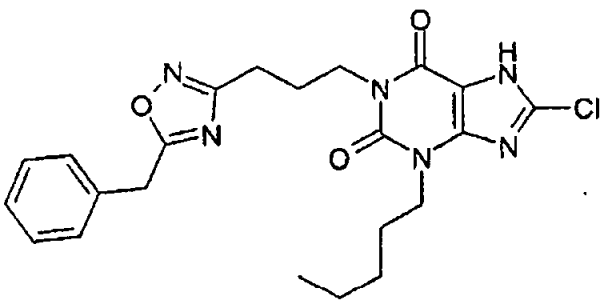
EJEMPLO 115

^1H RMN ($CDCl_3$) δ 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 121

8-cloro-3-pentil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-3-pentil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona

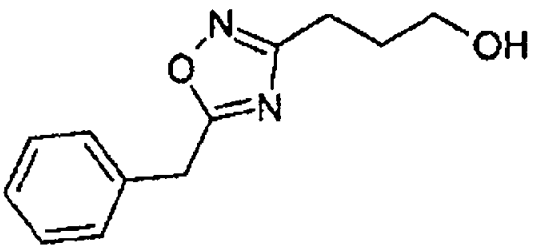


A una solución agitada de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (0.20, 0.67 mmol) en THF (5 ml) se añade 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (0.162 g, 0.74 mmol), DBAD (0.186 g, 0.81 mmol) y trifenilfosfina (0.212 g, 0.81 mmol) y la solución se agita durante 18 horas. A la solución se añade $Pd(PPh_3)_4$ (75 mg, 0.067 mmol) y morfolina (600 µl, 6.7 mmol) se añade y se agita a temperatura ambiente bao nitrógeno durante 3 horas adicionales. Se añaden 75 mg de $Pd(PPh_3)_4$ y la mezcla se deja agitar por otras 3 horas. La mezcla se divide entre EtOAc y HCl 2M (ac). El material crudo se purifica mediante un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y se lava a través de las impurezas, después con AcOH/MeOH 2-4% para eluir el compuesto. Las fracciones de producto se combinan y se concentran después se purifican

adicionalmente por MDAP. Las fracciones de producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (51 mg, 20%).

LC/EM: m/z 457 $[MH]^+$, temperatura ambiente 3.54 min.

b) 3-[5-(fenilmetil)-1,2,4-oxadizol-3-il]-1-propanol



Una mezcla de (1E)-4,4-bis(etiloxi)-N-hidroxibutanimidamida (3.2 g, 16.8 mmol), fenilacetato de etilo (2.3 ml, 14.4 mmol) y etóxido de sodio (solución al 21% en EtOH, 6.4 ml) se calienta en un microondas a 140°C durante 10 minutos. El material se combina con esta a partir de la segunda reacción (usando 1.2 g de (1E)-4,4-bis(etiloxi)-N-hidroxibutanimidamida y se conduce como anteriormente) y se divide entre solución HCl 1M y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca y se concentra para proveer 5-[3,3-bis(etiloxi)propil]-5-(fenilmetil)-1,2,4-oxadiazol que se usa sin purificación adicional en la siguiente etapa.

3-[3,3-bis(etiloxi)propil]-5-(fenilmetil)-1,2,4-oxadiazol crudo (5.63 g, 19.4 mmol) en EtOH (75 ml) se agita con ácido p-toluenosulfónico (0.738 g, 3.9 mmol) durante 1 hora y la mezcla se divide entre EtOAc y agua. Los orgánicos se aísla y se lavan con agua y salmuera, se secan y se concentran

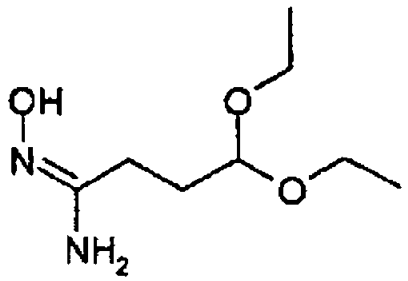
a un aceite rojo. Este material contiene cantidades significantes se acetal, por lo tanto el aceite se disuelve en THF (15 ml) y se trata con solución de HCl 2M durante 2 horas después se divide entre EtOAc y agua. Los orgánicos se aíslan y se lavan con salmuera, se secan y se concentra para producir 3-[5-fenilmetil]-1,2,4-oxadiazol-3-il]propanal como un aceite rojo/café (3.77 g) que se usa crudo en la siguiente etapa.

Una solución de 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propanal crudo (3.76 g, 17.4 mmol) en MeOH (60 ml) se enfría a 0^0C y se añade a manera de porción borohidruro de sodio (0.724 g, 19.1 mmol) alrededor de 30 minutos. El baño de enfriamiento se remueve y la solución se agita por 1 hora adicional después se divide entre HCl 1M y EtOAc. La capa orgánica se separa y la acuosa se extrae con EtOAc. Los extractos orgánicos combinados se lavan con salmuera, se secan y se concentran a un líquido naranja. Este se purifica en un SPE de sílice de 50 g eluyendo con ciclohexano/EtOAc (gradiente 20% a 80% de elusión) para proveer el compuesto del titulo como un aceite amarillo (2.24 g).

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

330

c) (1E)-4,4-bis(etiloxi)-N-hidroxibutanimidamida

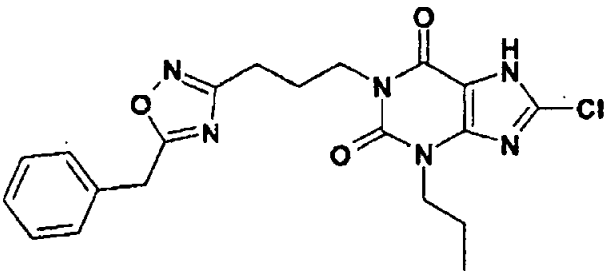


Una mezcla de dietilacetal de 3-cinopropionaldehído (6.12 g, 39 mmol), clorhidrato de hidroxilamina (4.06 g, 58.4 mmol), carbonato de potasio (10.76 g, 77.9 mmol) en agua (20 ml) y EtOH (40 ml) se calienta a reflujo durante 24 horas. La mezcla se deja enfriar y después se divide entre agua y EtOAc. La capa orgánica se separa y la acuosa se extrae con EtOAc. Las fracciones orgánicas combinadas se lavan con salmuera, se secan y se concentran para proveer el compuesto del titulo como un aceite incoloro contaminado con ~20% iniciando con nitrilo (6.03 g, 81%).

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

EJEMPLO 122

8-cloro-1-(3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purina-2,6-diona (200 mg, 0.74 mmol) en THF (4 ml) se trata con 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (195 mg, 0.89 mmol) y PPh_3 (254 mg, 0.96 mmol). Se añade DBAD (223 mg, 0.96 mmol) en una porción y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 18 horas. La mezcla se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra por alto vacío. El producto crudo se purifica en una columna SPE de sílice usando un gradiente de ciclohexano/EtOAc 0-70%. Las fracciones de producto se combinan, se concentran por alto vacío y se purifican en una columna de SPE de sílice usando gradiente de ciclohexano/EtOAc 0-60%. Las fracciones de producto se combinan y se concentran después se disuelven en THF anhidro (4 ml). La solución se desgasifica mediante alto vacío después se añade $Pd(PPh_3)_4$ (61 mg, 0.053 mmol) y morfolina (460 µl, 5.3 mmol) y la mezcla se deja agitar a temperatura ambiente bajo nitrógeno durante 1 día. La mezcla

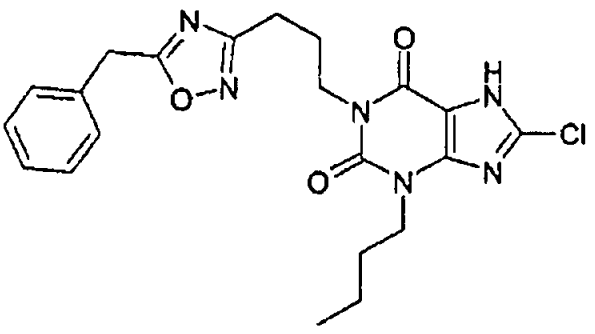
se divide entre EtOAc y HCl 2M (ac). La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra a alto vacío. El producto crudo se purifica mediante un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y se lava a través de las impurezas, después un gradiente de AcOH/MeOH 2-4% para eluir el producto. Las fracciones del producto se combinan y se concentran para dejar el compuesto del titulo como un sólido blanco (36 mg, 11%).

LC/EM: m/z 429 $[MH]^+$, temperatura ambiente 3.14 minutos.

^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 123

3-butil-8-cloro-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona



Una solución de 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (594 mg, 2.7 mmol) en THF (25 ml) se trata con 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (700 mg, 2.48 mmol) y PPh_3 (779 mg,

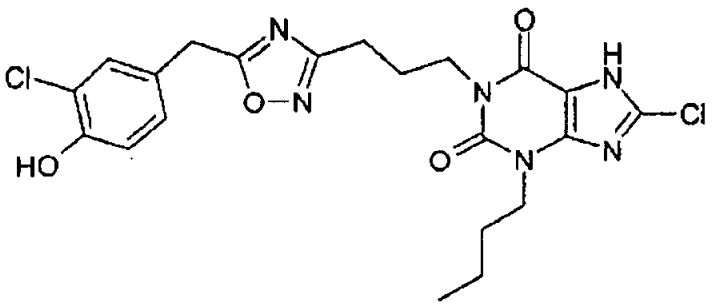
2.97mmol) bajo nitrógeno. Se añade DBAD (684 mg, 2.97 mmol) en una porción y la reacción se deja reaccionar durante 60 horas. La mezcla se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$), y se concentra. Se añade MeOH al residuo y después se pasa debajo de una columna de aminopropilo con el producto eluyendo con AcOH/MeOH 2-4%. Las fracciones de producto se combinan se concentran. El residuo blancuzco se recristaliza a partir de EtOAc:ciclohexano (1:1), proporcionando el compuesto del titulo como un sólido blanco (696 mg, 63%).

LC/EM: m/z 443 $[MH]^+$, temperatura ambiente 3.4 minutos.

^1H 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, 1 H).

EJEMPLO 124

3-butil-8-cloro-1-(3-{5-[(3-cloro-4-hidroxifenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona



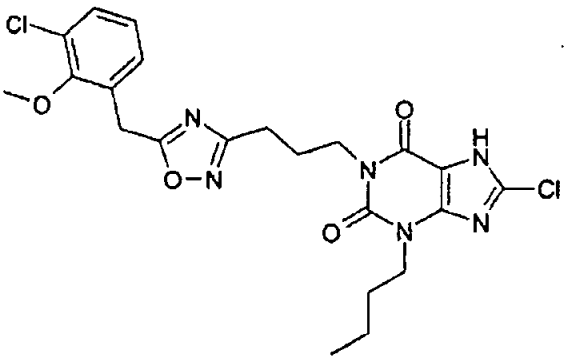
Una solución de ácido 3-cloro-4-hidroxifenilacético (24 mg, 0.13

mmol) en DMSO (1 ml) se trata con CDI (21 mg, 0.13 mmol) y se deja reaccionar durante 30 minutos. Se añade (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida (50 mg, 0.15 mmol) se añade y la mezcla se calienta en el microondas a 120°C durante 15 minutos. La solución se purifica directamente por MDAP para obtener el compuesto del titulo como un sólido blanco (12 mg, 17%).

LC/EM: m/z 493 $[MH]^+$, temperatura ambiente 3.2 minutos.

EJEMPLO 125

3-butil-8-cloro-1-[3-(5-{[3-cloro-2-(metiloxi)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purina-2,6-diona



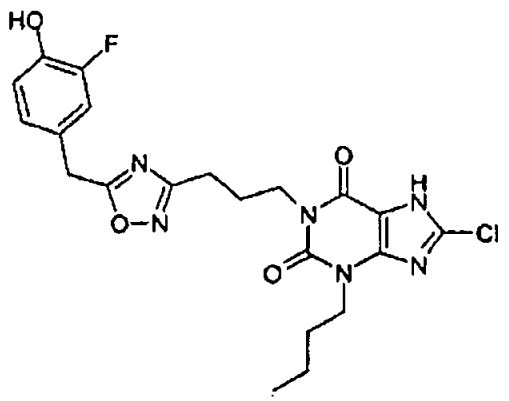
Una mezcla de ácido [3-cloro-2-(metiloxi)fenil]acético (32 mg, 0.16 mmol) en DMF (1.5 ml) se trata con CDI (26 mg, 0.16 mmol) y se deja reaccionar durante 45 minutos. Se añade (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida (60 mg, 0.18 mmol) y la mezcla de reacción se calienta en el microondas a 140°C durante 15 minutos. Después del enfriamiento, la reacción se divide entre HCl 2M (ac) y

EtOAc. La capa orgánica se separa después se concentra y se purifica por el MDAP. El compuesto del titulo se obtiene como un sólido blanco (25 mg, 28%).

LC/EM: m/z $[MH]^+$, temperatura ambiente 3.5 minutos.

EJEMPLO 126

3-butil-8-cloro-1-(3-{5-[(3-fluoro-4-hidroxifenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona



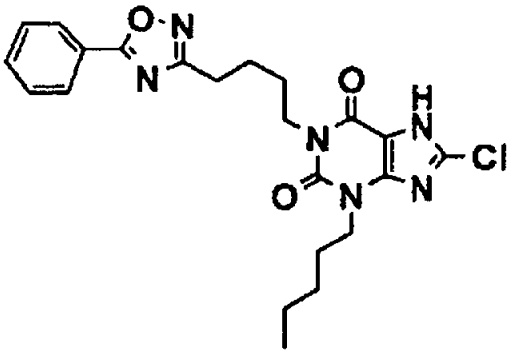
Una mezcla de ácido (3-fluoro-4-hidroxifenil)acético (27 mg, 0.16 mmol) en DMF (1.5 ml) se trata con CDI (26 mg, 0.16 mmol) y se deja reaccionar durante 45 minutos. Se añade (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida (60 mg, 0.18 mmol) se añade y la mezcla se calienta en el microondas a 140°C durante 15 minutos. Después del enfriamiento, la reacción se divide entre HCl 2M (ac) y EtOAc. La capa orgánica se separa después se concentra y se purifica por MDAP. El compuesto del titulo se obtiene como un sólido blanco (10 mg, 12%).

LC/EM: m/z 477 $[MH]^+$, temperatura ambiente 3.2 minutos.

EJEMPLO 127

8-cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona

a) Preparación de 8-cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona



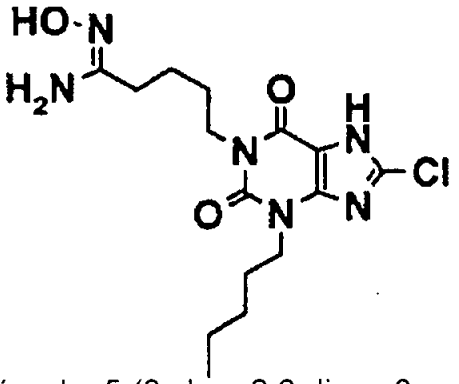
Se trata ácido benzoico (18 mg, 0.15 mmol) con una solución de hidrato de 1H-1,2,3-benzotriazol-1-ol (25 mg, 0.19 mmol) en DMSO (0.3 ml). A esta se añade una solución/suspensión de clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (29 mg, 0.15 mmol) en DMSO (0.3 ml) seguido por una solución de 5.(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida 855 mg, 0.15 mmol) en DMSO (0.3 ml). La mezcla se calienta a 40°C durante 1 hora, después a 80°C durante 5 horas y después se enfría. La mezcla se somete a purificación por MDAP. Las fracciones que contienen el producto se soplan a sequedad mediante una corriente de nitrógeno para producir el compuesto del titulo como un sólido

blanco (17.2 mg, 25%).

LC/EM: m/z 457 $[MH]^+$, temperatura ambiente 3.67 minutos.

^1H RMN ($CDCl_3$) 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, 1 H), 8.08, (d, 2H1 J = 7.3Hz).

b) 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanamidamida

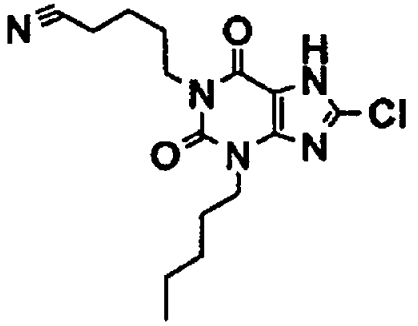


Una solución de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanonitrilo (3.0 g, 8.9 mmol) en EtOH (30 ml) se trata con agua (15 ml), carbonato de potasio (1.48 g, 10.7 mmol) y clorhidrato de hidroxilamina (0.74 g, 10.7 mmol) y después se calienta a 70°C toda la noche. un carbonato de potasio adicional (1.5 g, 10.9 mmol) y clorhidrato de hidroxilamina (1.0 g, 14.5 mmol) se añade cuidadosamente a la mezcla que después se calienta a 90°C durante 24 horas. La mezcla se enfría y se concentra *in vacuo* para remover más del EtOH. La mezcla residual se trata con agua (30 ml) y se acidifica a pH 7 por la adición cautelosa de ácido clorhídrico acuoso 2M. El sólido precipitado se filtra, se lava con agua,

después con dietiléter y se seca completamente para producir el compuesto del titulo como un sólido blanco (2.80 g, 85%).

LC/EM: m/z 371 $[MH]^+$, temperatura ambiente 2.27 minutos.

c) 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanonitrilo



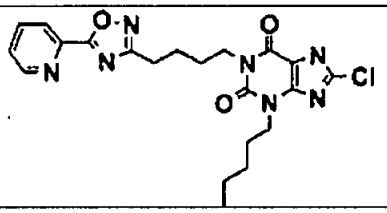
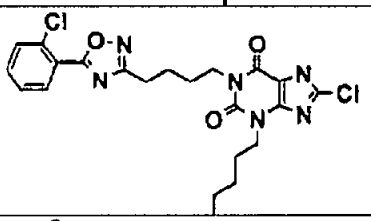
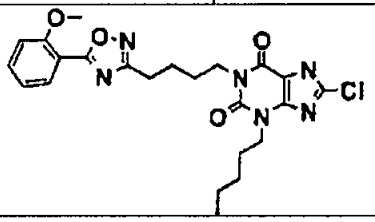
Una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (4.0 g, 13.5 mmol) en DMF (100 ml) se trata con carbonato de cesio (4.83 g, 14.8 mmol) y 5-bromopentanonitrilo (1.73 ml, 14.8 mmol). La mezcla se calienta a 50°C en una atmósfera de nitrógeno durante 19 horas y después se enfría. La mezcla después se desgasifica por la aplicación sucesiva repetida de un vacío y después presión de nitrógeno. La mezcla después se trata con tetraquis(trifenilfosfina)paladio (0) (1.1 g, 0.94 mmol) y morfolina (11.8 ml, 136 mmol). La mezcla se agita en una atmósfera de nitrógeno durante 3 horas y después se divide entre EtOAc y ácido clorhídrico acuoso 2M. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra para revelar un residuo amarillo aceitoso. Este se disuelve en MeOH, se divide igualmente en cuatro porciones y cada porción

se aplica a un SPE de aminopropilo de 20 g que después se lava a través de MeOH. El producto deseado se eluye del cartucho con una solución al 5% v/v de AcOH en MeOH. Las fracciones que contienen el producto se combinan y se concentran para producir el compuesto del titulo como un sólido amarillo pálido (4.03 g, 85%).

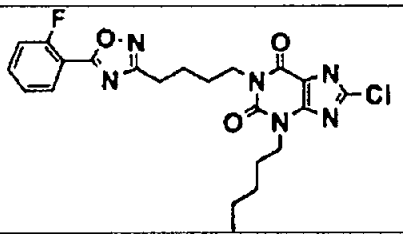
LC/EM: m/z 338 $[MH]^+$, temperatura ambiente 3.05 minutos.

Los siguientes compuestos se preparan usando un método análogo al del ejemplo 127 (8-cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona) a partir de los ácidos correspondientes.

CUADRO 9

Ej.	Estructura	Nombre	Rend.	LC/EM
128		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 $[MH]^+$ RT 3.21 min
139		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 $[MH]^+$ RT 3.77 min
130		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 $[MH]^+$ RT 3.54 min

340

Ej.	Estructura	Nombre	Rend.	LC/EM
131		8-cloro-1-{4-[5-(2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	16.6 mg (23%9	m/z 458 $[MH]^+$ RT 3.21 min

Además,

EJEMPLO 128

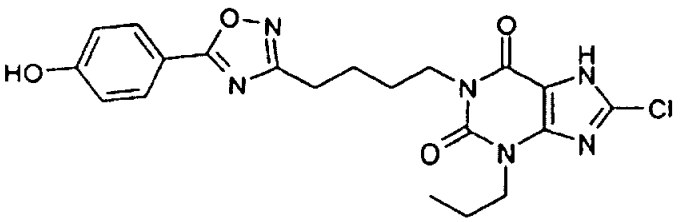
8-cloro-3-pentil-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

Tiene los siguientes datos de espectros

^{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 = 7.1 Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1 H)1 7.92 (m, 1 H), 8.18 (m, 1 H), 8.83 (m, 1 H), 13.40 (br s, 1 H).

EJEMPLO 132

8-cloro-1-{4-[5-(4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1H-purina-2,6-diona

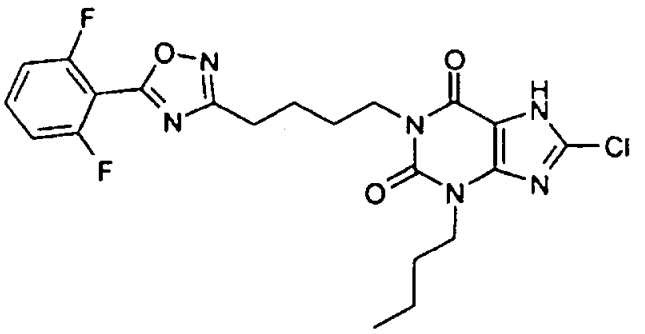


Ácido 4-Hidroxibenzoico (18 mg, 0.13 mmol) y CDI (24 mg, 0.15 mmol) se agitan en DEMO anhidro (0.9ml) a temperatura ambiente durante 1 hora. (1Z)-5-(8-Cloro-2,6-dioxo-3-propil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.15 mmol; preparada de una manera similar a (1Z)-5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida como se describe en el ejemplo 128(b)) se añade y la mezcla se agita a 90°C durante 2 horas. La mezcla de reacción se purifica por MDAP. La fracción de producto se combina y se concentra bajo alto vacío para proporcionar el compuesto del titulo como un sólido blanco (7 mg, 11%).

LC/EM: m/z 443 $[MH]^+$, RT 3.28min.

EJEMPLO 133

3-Butyl-8-cloro-1-{4-[5-(2,6-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

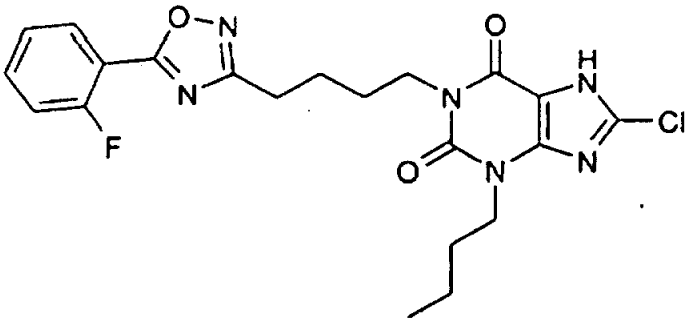


Ácido 2,6-difluorobenzoico (40 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica por MDAP. La fracción de producto se combina y se concentra para proporcionar el compuesto del titulo como un sólido blanco (18 mg, 15%).

LC/EM: m/z 479 $[MH]^+$, RT 3.40 min.

EJEMPLO 134

3-Butil-8-cloro-1-{4-[5-(2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

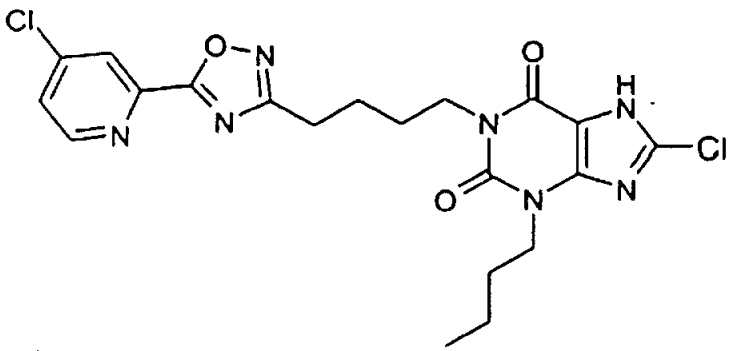


Ácido 2-fluorobenzoico (36 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica por MDAP. La fracción de producto se combina y se concentra para proporcionar el compuesto del titulo como un sólido blanco (33 mg, 29%).

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

EJEMPLO 135

3-Butil-8-cloro-1-{4-[5-(4-cloro-2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona



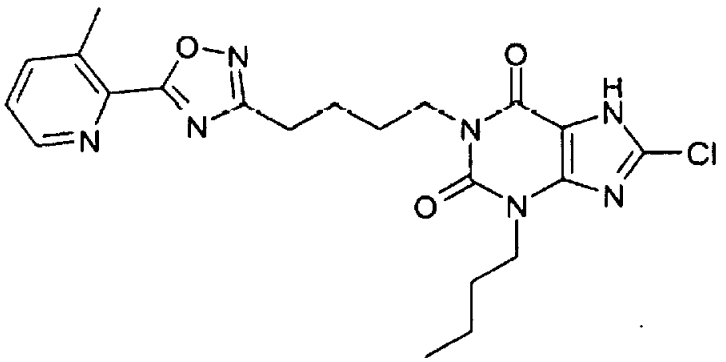
Ácido 4-cloro-2-piridinocarboxílico (40 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica por MDAP. La fracción de producto se combina y se concentra para proporcionar el compuesto del titulo como un sólido blanco (13 mg, 11%).

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

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

EJEMPLO 136

3-Butil-8-cloro-1-{4-[5-(3-metil-2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona



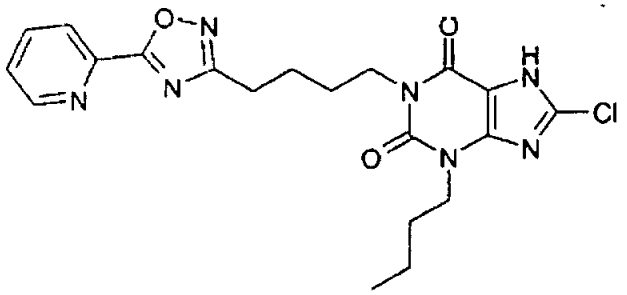
Ácido 3-metil-2-piridinocarboxílico (35 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica por MDAP. La fracción de producto se combina y se concentra para proporcionar el compuesto del titulo como un sólido blanco (14 mg, 12%).

LC/EM: m/z 458 $[MH]^+$, RT 3.13 min.

EJEMPLO 137

3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

Método A

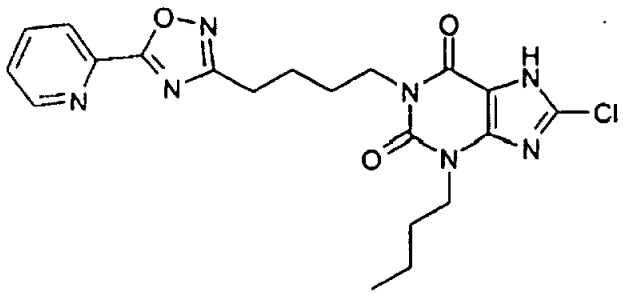


Ácido 2-piridinocarboxílico (31 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.5 ml) a temperatura ambiente durante 1 hora. Una solución de (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) en DEMO (0.4 ml) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica directamente por MDAP. Las fracciones de producto se combinan y se concentran para proporcionar el compuesto del titulo como un sólido blanco (14 mg, 12%).

LC/EM: m/z 444 $[MH]^+$, RT 3.01 min.

^{1}H RMN (DEMO-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 1 H1 J = 5 & 7Hz), 8.07 (m, 1 H), 8.19 (d, 1 H, J = 8Hz), 8.81 (d, 1 H, J = 5Hz), 14.5 (br. s, 1 H).

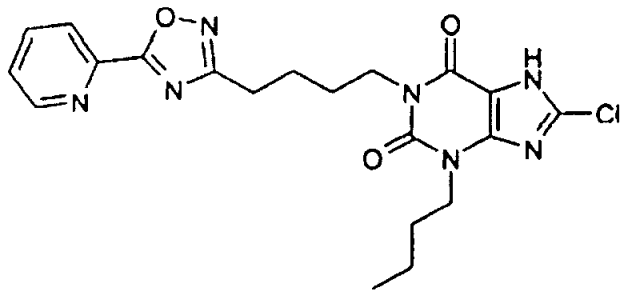
Método B



Ácido 2-piridinocarboxílico (675 mg, 5.3 mmol) y CDI (909 mg, 5.6 mmol) se agitan en DEMO anhidro (30 ml) a temperatura ambiente bajo nitrógeno durante 90 minutos. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (2.0 g, 5.6 mmol) y DMF (10 ml) se añade y la mezcla se agita a 100°C durante 20 horas. La mezcla de reacción se enfría a temperatura ambiente y después se divide entre NH_4Cl (acuoso) y EtOAc. La capa orgánica se separa, y la solución acuosa se extrae con EtOAc. Los extractos combinados se lavan con salmuera, se seca con $MgSO_4$ y se concentra proporcionando un líquido color naranja. Esto se purifica usando el sistema Companion™ proporcionando dos sólidos blancos idénticos (649mg; 240mg).

LC/EM: m/z 444 $[MH]^+$, RT 3.04min.

Método C



Un matraz de fondo redondo de 12 litros se equipa con un agitador mecánico superior, una sonda de temperatura con un controlador de temperatura J-KEM, un condensador y un adaptador de entrada de nitrógeno. El matraz se carga con ácido picolínico (0.180 kg, 1.46 mol), MIBK (4.0 L), 1,1'-carbonildiimidazol (0.23 kg, 1.42 mol,) y más MIBK (0.66 l). La mezcla se agita y se calienta a 50°C por aproximadamente 1 hora, y la temperatura se dispara a 56°C. Los sólidos se disuelven durante el calentamiento ascendente a 50°C y se genera dióxido de carbono. Después de 1 hora a 50°C, (1Z)-5-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (0.467 kg, 1.31 mol) se añade a la reacción. La mezcla entonces se calienta a 90°C durante 1 hora. El análisis de HPLC de la reacción después del calentamiento a 90°C durante 5.5 horas indica que la reacción se completa. El calentamiento se interrumpe, y solución de ácido clorhídrico 1.0 N (2.33 l) se añade. La temperatura desciende a 61°C. Después de agitación durante la noche, el producto precipita y se filtra. La torta de filtro se lava con agua (1 x 2.23 l, 1 x 2.43 l) y heptanos (1.40 l). La torta de filtro se seca en un horno de vacío a 50°C durante 22 horas para

proveer 396 g de producto (68%) análisis HPLC 97.7% (AUC) t_R = 18.6 min.

Los métodos A, B y C del ejemplo 137 produce 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina forma 2.

Método D

Formación de 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona Forma 1

El recipiente de reacción se carga con 3-Butil-8-cloro-1-{4-[5-(2-pyridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona (1 peso), acetona (20 vol) y agua (0.6 vol). La mezcla se agita y se calienta a 50-60°C y se agita por un mínimo de 1 hora. Una solución se forma la cual se clarifica a esta temperatura por medio de filtración a través de un filtro de 1 micra en un segundo recipiente de reacción. La solución se enfría por aproximadamente 3 horas a 33-38°C se siembra a esta temperatura con 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona (Forma 1, 0.01 peso). La suspensión rebajada se agita a esta temperatura por un mínimo de 1 hora y entonces se enfría a 20-25°C y se mantiene a esta temperatura por un mínimo de 12 horas. La suspensión formada de este modo se enfría 13-17°C y se mantiene a esta temperatura durante un mínimo de 1 hora. La suspensión entonces se muestrea* y el sólido se colecta por filtración en el laboratorio. El sólido se seca y se analiza por medio de 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 se descarga una vez que el análisis muestra que los niveles de solvente sean aceptables (acetona, agua)

Rendimiento esperado (75-80% p/p).

Si la forma de la muestra tomada en * muestra ser diferente de la forma 1 pura, entonces ** el lote se calienta nuevamente a 35-45°C y se agita a esta temperatura durante un mínimo de 1 hora. La suspensión rebajada entonces se enfría a 20-25°C y se mantiene a esta temperatura durante un mínimo de 12 horas. La suspensión formada de esta forma entonces se enfría a 13-17°C y se mantiene a esta temperatura durante un mínimo de 1 hora. La suspensión entonces se muestrea, y el sólido se colecta por filtración en el laboratorio. El sólido se seca y se analiza por medio de xrpd/DSC para verificar la forma. Si la forma es como la requerida (forma 1) el lote se filtra, se lava y se seca como se describió previamente. Si la forma no es forma 1 pura, entonces el ciclo de** se repite hasta obtener un resultado satisfactorio.

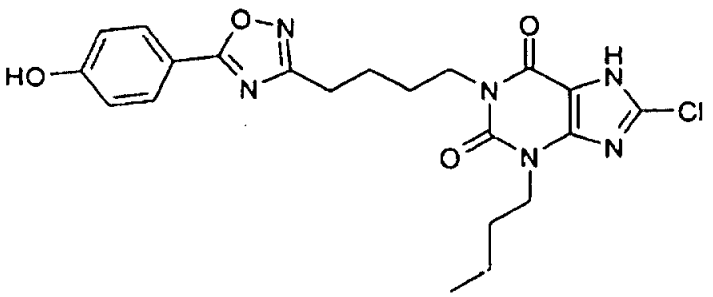
Difracción de polvo en rayos X (XRPD)

Los datos de difracción de polvo en rayos X (XRPD) se muestran en las figuras 1-3. Los datos se adquieren en un difractómetro de polvo PANalytical X'Pert Pro, modelo PW3040/60, número de serie DY1850 usando un detector X'Celerator. Las condiciones de adquisición son: radiación: Cu Kα, tensión del generador: 40 kV, corriente del generador: 45 mA, ángulo de inicio:

2.0°2θ, ángulo final: 40°2θ, tamaño de etapa: 0.0167°2θ, tiempo por etapa: 31.75 segundos. Las muestras se preparan al montar algunos miligramos de muestra en placas de disco de Si (fondo cero), resultando en una capa fina de polvo.

EJEMPLO 138

3-Butil-8-cloro-1-{4-[5-(4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

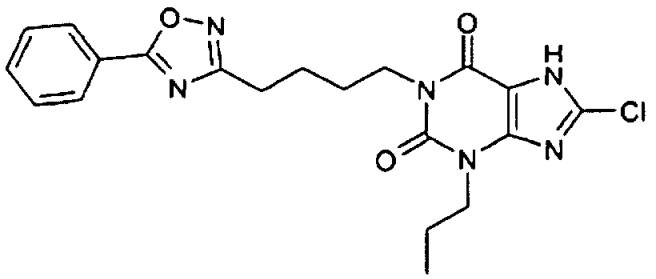


Ácido 4-hidroxibenzoico (35 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla de reacción se purifica por MDAP para proporcionar el compuesto del titulo como un sólido blanco (5 mg, 4%).

LC/EM: m/z 459 $[MH]^+$, RT 3.24 min.

EJEMPLO 139

8-Cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3-propil-3,7-dihidro-1H-purina-2,6-diona



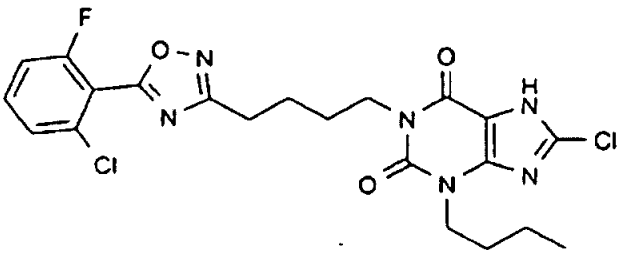
Ácido benzoico (9 mg, 0.074 mmol) y CDI (13 mg, 0.081 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (28 mg, 0.081 mmol) se añade y la mezcla se agita a 80°C durante 4 horas. La mezcla se purifica por MDAP para proporcionar el compuesto del titulo como un sólido blanco (0.6 mg, 2%).

LC/EM: m/z 429 $[MH]^+$, RT 3.21 min.

^{1}H RMN (MeOH-d_4) δ: 0.93 (t, 3H1 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).

EJEMPLO 140

3-Butil-8-Cloro-1{4-[5-(2-cloro-6-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

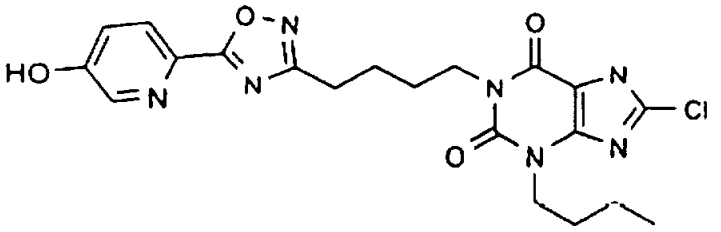


Ácido 2-cloro-6-fluorobenzoico (44 mg, 0.25 mmol) y CDI (45 mg, 0.28 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla se purifica por MDAP. La fracción de producto se combina y se concentra para proporcionar el compuesto del titulo como un sólido blanco (6.4 mg, 5%).

LC/EM: m/z 495 $[MH]^+$, RT 3.58 min.

EJEMPLO 141

3-Butil-8-cloro-1-{4-[5-(5-hidroxi-2-piridinil)-1,2,4-oxadiazol-3-il]butyl}-3,7-dihidro-1H-purina-2,6-diona

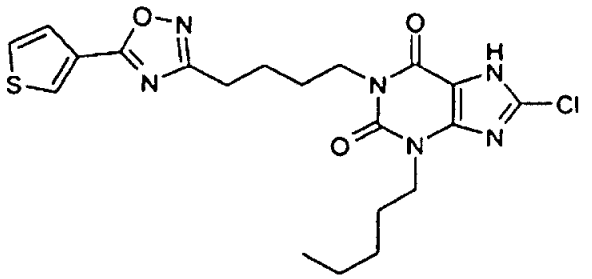


Ácido 5-hidroxi-2-piridinacarboxílico (24 mg, 0.17 mmol) y CDI (31 mg, 0.19 mmol) se agitan en DEMO anhidro (0.9 ml) a temperatura ambiente durante 1 hora. (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (68 mg, 0.19 mmol) se añade y la mezcla se agita a 90°C durante 16 horas. La mezcla se purifica por MDAP y las fracciones de producto se concentran para proporcionar el compuesto del titulo como un sólido blanco (19 mg, 24%).

LC/EM: m/z 459 $[MH]^+$, RT 3.03 min.

EJEMPLO 142

8-Cloro-3-pentil-1-{4-[5-(3-tienil)-1,2,4-oxadiazol-3- il]butil}-3,7-dihidro-1H-purina-2,6-diona

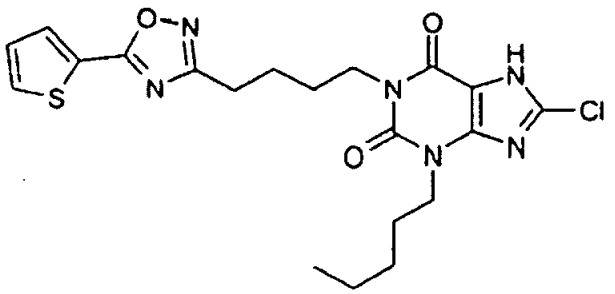


A una solución de (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.13 mmol) en EtOH (1 ml) se trata con una solución al 21% de NaOEt en EtOH (55 µl, 0.21 mmol) y 3-tiofenocarboxilato de etilo (18 µl, 0.13 mmol). La mezcla se calienta en el microondas a 150°C durante 10 minutos. Después del enfriamiento, la reacción se divide entre HCL 2M (acuoso) y EtOAc. La capa orgánica se separa y la fase acuosa se extrae nuevamente con EtOAc. Los extractos combinados se concentran y purifican por medio de MDAP. El compuesto del titulo se obtiene como un sólido blancuzco (20 mg, 32%).

LC/EM: m/z 463 $[MH]^+$, RT 3.6 min.

EJEMPLO 143

8-Cloro-3-pentil-1-{4-[5-(2-tienil)-1,2,4-oxadiazol-3-yl]butil}-3,7-dihidro-1H-purina-2,6-diona

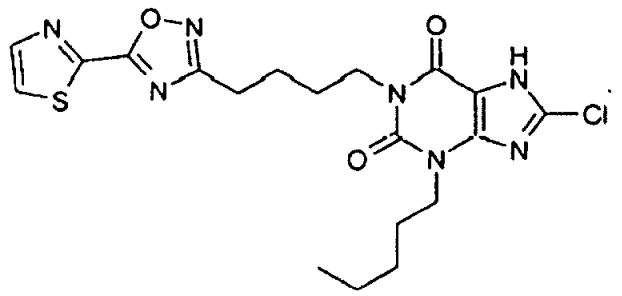


Ácido 2-tiofenocarboxílico (14 mg, 0.11 mmol) se disuelve en NMP (0.9 ml) y se trata con CDI (18 mg, 0.11 mmol). Después de 1 hora, (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.13 mmol) se añade y la mezcla se calienta en el microondas a 150°C durante 15 minutos. La solución se purifica directamente por medio de MDAP para obtener el compuesto del titulo el cual se congela en seco entonces de 1,4-dioxano para proporcionar el compuesto del titulo como un sólido blanco (19 mg, 31%).

LC/EM: m/z 463 $[MH]^+$, RT 3.5min.

EJEMPLO 144

8-Cloro-3-pentil-1-{4-[5-(1,3-tiazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona



A una solución de (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.13 mmol) en EtOH (1 ml) se trata con una solución al 21% de NaOEt en EtOH (50 µl, 0.13 mmol) y 1,3-tiazol-2-carboxilato de etilo (18 mg, 0.11 mmol). La mezcla se calienta en el microondas a 170°C durante 10 minutos. Después del enfriamiento, la reacción se divide entre HCl 2M (acuoso) y EtOAc. La capa orgánica se separa y entonces se concentra y purifica por medio de MDAP. El compuesto del título se obtiene como un sólido blanco (13 mg, 21%).

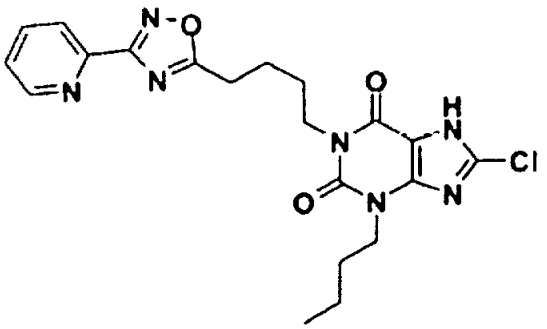
LC/EM: m/z 464 $[MH]^+$, RT 3.3 min.

^{1}H RMN (DEMO-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, 1 H, J = 3Hz), 8.27 (d, 1 H, J = 3Hz),14.4 (br s, 1H).

EJEMPLO 145

3-butil-8-cloro-1{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-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-purina-2,6-diona

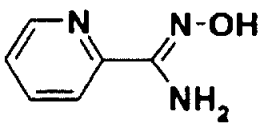


A una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato (120 mg, 0.32 mmol) y de N-hidroxi-2-piridinacarboximidamida (50 mg, 0.36 mmol) en EtOH (2 ml) se añade una solución 21% (p/v) de etóxido de sodio en EtOH (0.225 ml, 0.62 mmol) y entonces se calienta en un frasco sellado en un horno de microondas a 140°C durante 10 minutos. La mezcla enfriada se evapora a sequedad y el residuo se divide entre cloroformo (5 ml) y cloruro de amonio acuoso saturado (5 ml). La fase orgánica se evapora a sequedad y el producto crudo se somete a purificación por medio MDAP. Las fracciones que contienen el producto se combinan y se evaporan hasta secarse. El producto se tritura a un sólido en una cantidad pequeña de dietil éter y entonces se seca para dar el compuesto del título como un sólido blanco (44mg, 31%).

LC/EM: m/z 444 $[MH]^+$, RT 3.03min.

^{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, 1 H), 7.64 (m, 1H), 8.10 (m, 1 H), 8.79 (m, 1 H).

b) Preparación de N-hidroxi-2-piridinacarboximidamida



A una mezcla de 2-piridinacarbonitrilo (3 g, 29 mmol) y carbonato de potasio (4.1 g, 30 mmol) en EtOH (30 ml) se añade agua (15 ml) y, cuidadosamente, clorhidrato de hidroxilamina (2.9 g, 42 mmol) y entonces se calienta a reflujo durante 6 horas, se enfría y evapora hasta secarse. El residuo se trata con agua (100 ml) y el producto sólido suspendido se filtra, se lava con agua y se seca para producir el compuesto del titulo como un sólido blanco (2.28g, 57%).

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

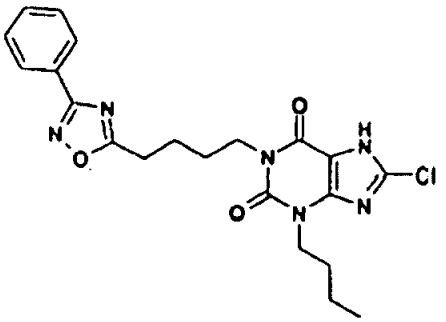
360

EJEMPLO 146

3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-yl)butil-3,7-dihidro-1H-purina-2,6-diona

Método A

a) 3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1H-purina-2,6-diona



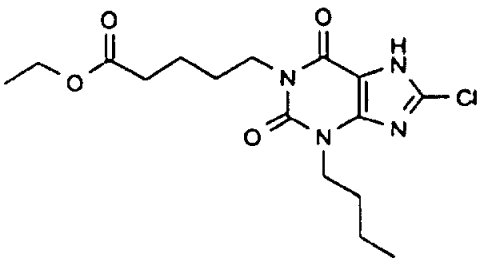
5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (74 mg, 0.2 mmol) y benzamidoxima (30 mg, 0.22 mmol) se suspenden en EtOH seco (1 ml) y etóxido de sodio etanólico (21% en peso, 0.111 ml, 0.3 mmol) se añade. La mezcla se calienta suavemente hasta que los sólidos se disuelvan y entonces se calientan en el reactor de microondas a 140°C durante 10 minutos. La mezcla entonces se divide entre EtOAc y 2M HCl y la fase orgánica se seca (Na_2SO_4) y se evapora. MDAP produce el compuesto del título puro (40.7 mg).

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

^1H RMN (DEMO-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)1 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-1H-purin-1-il)pentanoato de etilo

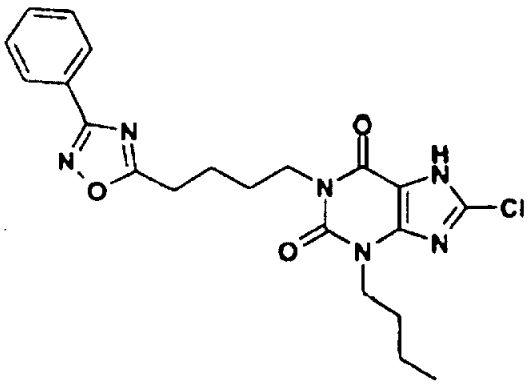


A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (1.5 g, 5.31 mmol) en DMF seco (25 ml) se añade Cs_2CO_3 (1.905 g, 5.84 mmol), seguido por 5-bromovalerato de etilo (1.46 g, 6.99 mmol). La mezcla se calienta a 55°C durante 18 horas entonces se deja enfriar. Se desgasifica por evacuación repetidamente y la readmisión de nitrógeno, entonces morfolina (3.70 ml, 42.5 mmol) y tetrakis(trifenilfosfina)paladio(0) (1.0 g, 0.865 mmol) se añade y la mezcla se agita durante 5 horas. EtOAc (75 ml), 2M HCl (40 ml) y agua (20 ml) se añaden y la fase orgánica se separa, se lava con salmuera (3 x 25 ml), se filtra para remover parte de sólido amarillo insoluble , se seca (Na_2SO_4) y se evapora. El residuo (2.5 g) se purifica por medio de SPE aminopropilo (20 g), se carga en THF-MeOH (1:1), se lava con MeOH y se eluye el producto con DCM-MeOH (1:1) que contiene 5% AcOH añadido para producir el compuesto del título (1.53g).

LC/EM: m/z 371 MH+, RT 3.18min.

Método B

a) 3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihydro-1H-purina-2,6-diona



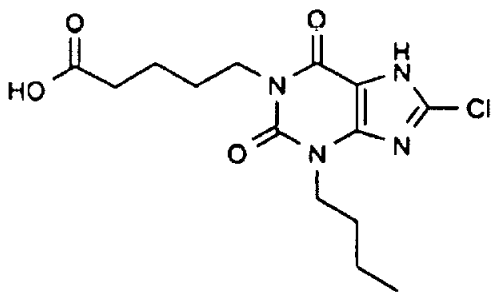
CDI (0.98 g, 6.1 mmol) se añade a una solución de ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico (1.89 g, 5.5 mmol) en DMF (15 ml) y se agita bajo nitrógeno durante 1.5 horas. Benzamidoxima (0.91 g, 6.1 mmol) se añade y la mezcla se agita a 110°C durante la noche. La mezcla de reacción se divide entre EtOAc y 2M HCl. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se evapora. El producto crudo se cristaliza de metanol y entonces se purifica adicionalmente usando el sistema Companion™ y una elusión en gradiente de ciclohexano a EtOAc. Las fracciones que contienen el producto se combinan y se evaporan para dar el compuesto del titulo como un sólido blanco (850mg).

LC/EM: m/z 443 [MH]<+>, RT 3.52min.

^{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)1 7.98-8.02 (m, 2H).

b) ácido oxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico

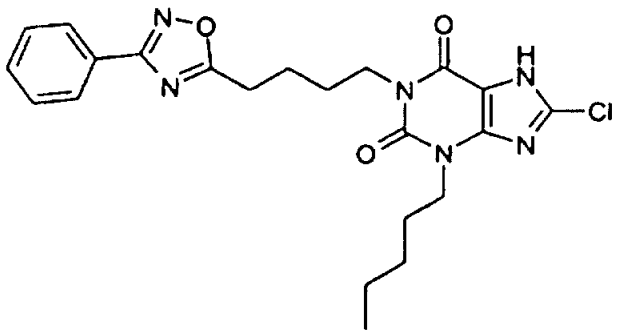


Una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-yl)pentanoato de etilo (2.8 g, 7.55 mmol), LiOH (542 mg, 22.7 mmol), agua (2.5 ml) y metanol (50 ml) se agita a temperatura ambiente durante 60 horas. La mezcla se divide entre agua y EtOAc y el pH de la fase acuosa ajustada a pH 4-5. La capa orgánica se separa, se lava con salmuera, se seca ($MgSO_4$) y se evapora para proveer el compuesto del título como un sólido blanco (2.18 g).

LC/EM: m/z 343 [MH]<+>, RT 2.69min.

EJEMPLO 147

8-Cloro-3-pentil-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1H-purina-2,6-diona



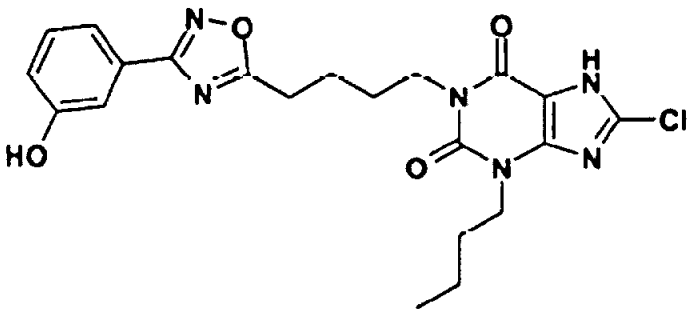
Una mezcla de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de metilo (50 mg, 0.13 mmol), benzamidina oxima (20 mg, 0.15 mmol) y una solución 21% de NaOEt en EtOH (76 μl, 0.20 mmol) en EtOH (1.5 ml) se calienta en el microondas a 140°C durante 10 minutos. Después del enfriamiento la mezcla de reacción se divide entre 2M HCl (acuoso) y EtOAc. La capa orgánica se separa, se seca ($MgSO_4$) y se concentra. La purificación por MDAP proporciona el compuesto del título como un sólido blanco (25mg, 41%).

LC/EM: m/z 457 [MH]+, RT 3.7min.

^{1}H RMN (DEMO-d_6) δ: 0.82 (t, 3H, J = 7 Hz)1 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)1 7.97 (m, 2H), 14.5 (br s, 1 H).

EJEMPLO 148

3-Butil-8-cloro-1-{4-[3-(3-hidroxifenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona

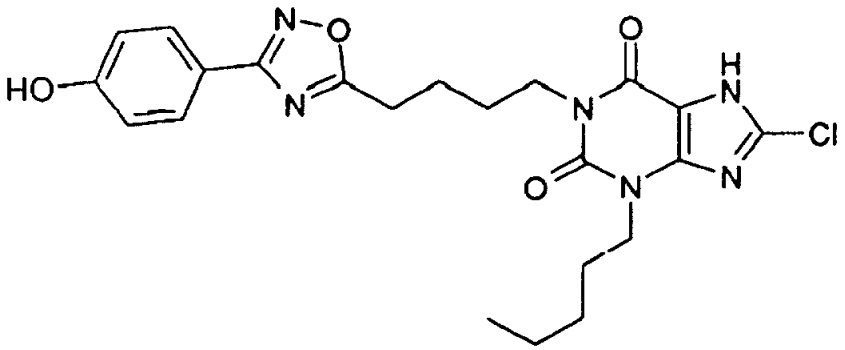


Una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (50 mg, 0.13 mmol), N,3-dihidroxibenzenocarboximidamida (25 mg, 0.16 mmol), solución 21% de NaOEt en EtOH (55 µl, 0.15 mmol) y EtOH (1.5 ml) se calienta en el microondas a 180°C durante 10 minutos. Otra alícuota de solución 21% de NaOEt en EtOH (55 µl, 0.21 mmol) se añade y la mezcla se calienta en el microondas a 175°C por 30 minutos. Después del enfriamiento la reacción se divide entre 2M HCl (acuoso) y EtOAc. La capa orgánica se separa, se concentra y se purifica por MDAP. El compuesto del titulo se obtiene como un sólido blancuzco (20 mg, 32%).

LC/EM: m/z 459 [MH]+, RT 3.3min.

EJEMPLO 149

8-Cloro-1-{4-[3-(4-hydroxifenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

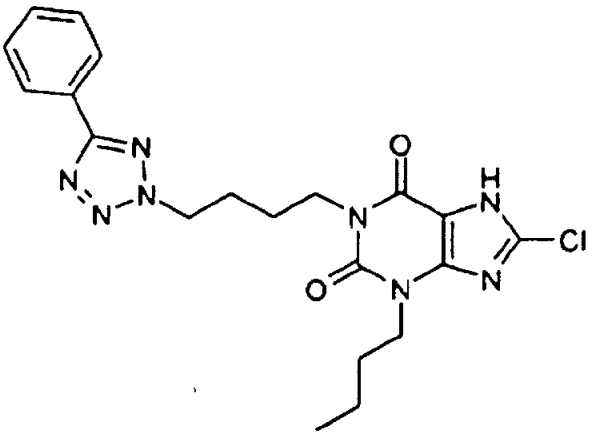


Una solución de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico (50 mg, 0.14 mmol) en DMF (2 ml) se trata con CDI (23 mg, 0.14 mmol) y se agita a temperatura ambiente durante 30 minutos. N,4-dihidroxibencenocarboximidamida (26 mg, 0.17 mmol) se añade y la mezcla se calienta en el microondas a 120°C durante 15 minutos. Después del enfriamiento la reacción se divide entre 2M HCl (acuoso) y EtOAc. La capa orgánica se separa, se concentra y se purifica por MDAP. El compuesto del título se obtiene como un sólido blancuzco (17 mg, 26%).

LC/EM: m/z 473 $[MH]^+$, RT 3.5min.

EJEMPLO 150

3-Butil-8-cloro-1-[4-(5-fenil-2H-tetrazol-2-il)butil]-3,7-dihidro-1H-purina-2,6-diona



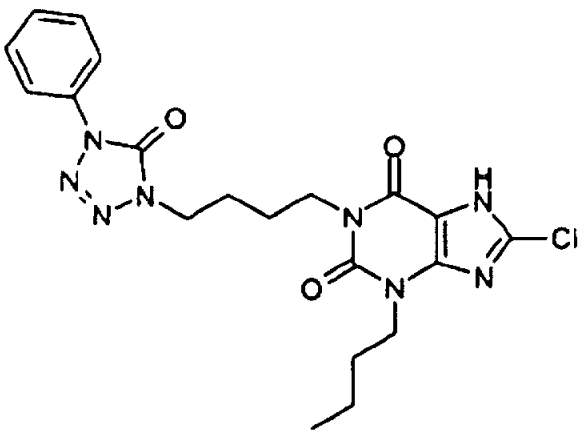
Una mezcla de metanosulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butilo (50 mg, 0.12 mmol), Cs_2CO_3 (45 mg, 0.14 mmol) y DMF (3 ml) se trata con 5-fenil-1H-tetrazol (20 mg, 0.14 mmol) y se agita durante 60 horas a 50°C. Después del enfriamiento, la mezcla se desgasifica al aplicar un vacío y después nitrógeno se introduce. $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) se añade y la mezcla se desgasifica una vez más. Morfolina (150 µl, 1.7 mmol) se añade y la mezcla se agita bajo nitrógeno durante 18 horas, entonces se divide entre 2M HCl (acuoso) y EtOAc. La capa orgánica se separa y la capa acuosa se extrae nuevamente con EtOAc. Los extractos combinados se concentran, proporcionando un residuo. MeOH se añade y entonces se pasa por una columna de NH_2-propilo con el producto fluyendo con AcOH/MeOH 2%. Purificación adicional por MDAP proporcionando el compuesto del título como un sólido blancuzco (15 mg, 29%).

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

^1H RMN (DEMO-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, 1 H).

EJEMPLO 151

3-Butil-8-cloro-1-[4-(5-oxo-4-fenil-4,5-dihidro-1H-tetrazol-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona



Una mezcla de metanosulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butil (50 mg, 0.12 mmol), Cs_2CO_3 (45 mg, 0.14 mmol) y DMF (3 ml) se trata con 1-fenil-1,2-dihidro-5H-tetrazol-5-ona (23 mg, 0.14 mmol) y se agita durante 60 horas a 50°C. después del enfriamiento, la mezcla se desgasifica al aplicar un vacío y después se introduce nitrógeno. $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) se añade y la mezcla se desgasifica una vez. Morfolina (150 µl, 1.7 mmol) se añade y la mezcla se agita bajo nitrógeno durante 18 horas, entonces se divide entre 2M HCl (acuodo) y EtOAc. La capa orgánica se separa y la capa acuosa se

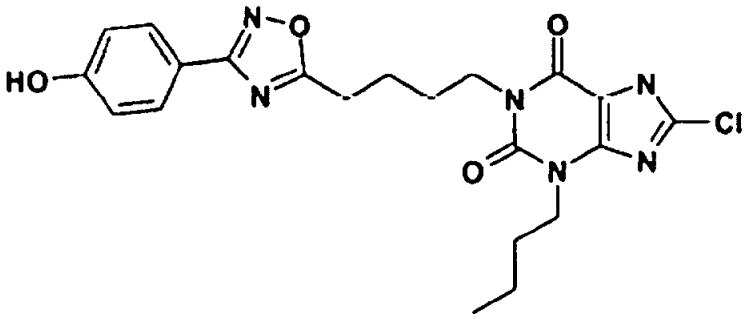
extrae nuevamente con EtOAc. Los extractos combinados se concentran, proporcionando un residuo amarillo. MeOH se añade y entonces se pasa en una columna de aminopropilo con el producto que eluye con AcOH/MeOH 2%. Purificación adicional por MDAP proporcionando el compuesto del título como un sólido blancuzco (27 mg, 51%). NB. ca. 10% material O-alquilado presente.

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

^{1}H RMN (DEMO-d_6) δ: 0.88 (t, 3H, J = 7Hz), 1.28 (m, 2H), 1.62 (m, 4H)1 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, 1 H).

EJEMPLO 152

3-butil-8-cloro-1-{4-[3-(4-hidroxifenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona



A una solución de ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico (100 mg, 0.29 mmol) en DMF (4 ml) se trata con CDI (52 mg, 0.32 mmol). Después de 1 hora, N,4-dihidroxibencenocarboximidamida se añade y la mezcla se calienta a 100°C durante 6 horas. Durante el enfriamiento, la mezcla de reacción se divide

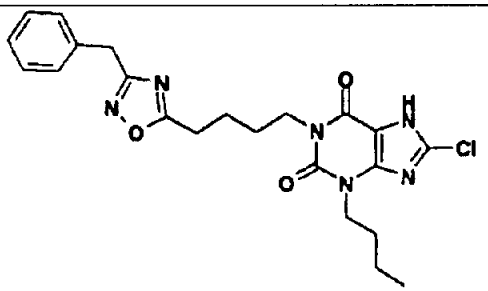
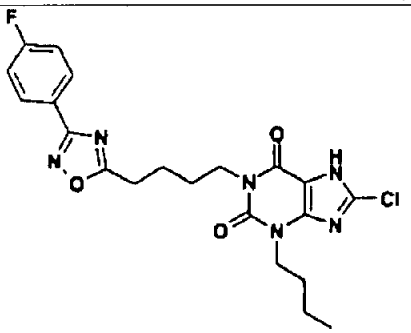
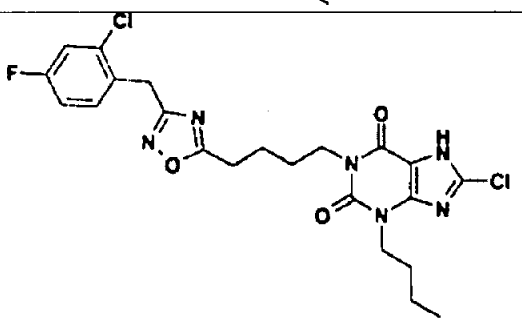
370

entre 2M HCl (acuoso) y EtOAc. La capa orgánica se separa se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. La purificación por MDAP produce el compuesto del titulo como un sólido gis pálido (72 mg).

LC/EM: m/z 459 $[MH]^+$, RT 3.27 min.

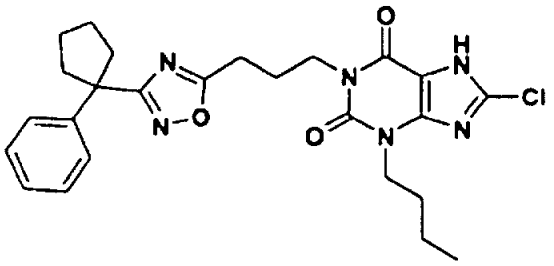
Los siguientes compuestos (cuadro 10) se preparan usando un método análogo a aquel del ejemplo 146, usando la amidoxima apropiada.

CUADRO 10

Ejemplo	Estructura	Rend. (mg)	LC/EM
153		48.4	m/z 457 $[MH]^+$ RT 3.56 min
154		35.8	m/z 457 $[MH]^+$ RT 3.56 min
155		48.2	m/z 457 $[MH]^+$ RT 3.56 min

EJEMPLO COMPARATIVO A

3-Butil-8-cloro-1-{3-[3-(1-fenilciclopentil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona

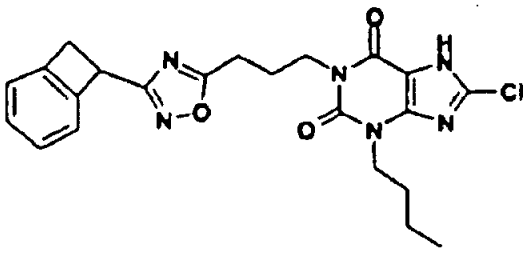


4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato (53 mg, 0.15 mmol), N-hidroxi-1-fenilciclopentanecarboximidamida (34 mg, 0.165 mmol) y métoxido de sodio (20 mg, 0.37 mmol) en MeOH seco (0.75 ml) se calientan a 140°C en el reactor de microondas durante 10 minutos. la mezcla entonces se divide entre acetato de etilo y 2M HCl, la fase orgánica se evapora y el producto se purifica por MDAP para proveer el compuesto del titulo como un sólido (29.1 mg).

LC/EM: m/z 497 [MH]+, RT 3.76min.

EJEMPLO 156

1-[3-(3-biclclo[4.2.0]octa-1.3.5-trien-7-il-1,2,4-oxadiazol-5-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona



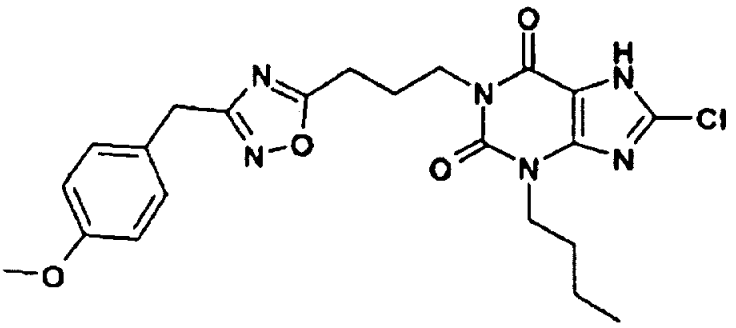
Este compuesto se prepara usando un método análogo a aquel del ejemplo comparativo A, usando la amidoxima apropiada

Rendimiento (mg): 28.8

LC/EM: m/z 455 $[MH]^+$, RT 3.43 min.

EJEMPLO 157

3-Butil-8-cloro-1-[3-(3-{[4-(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona

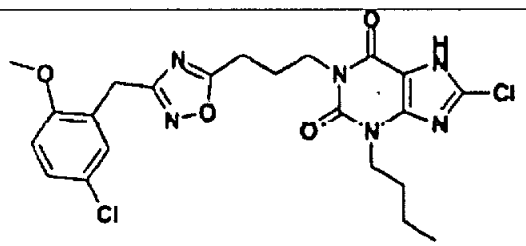


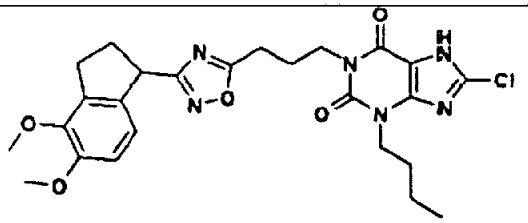
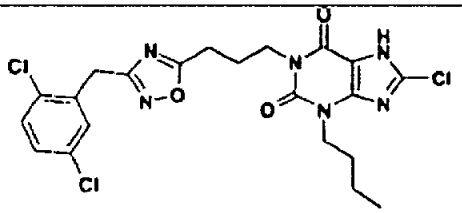
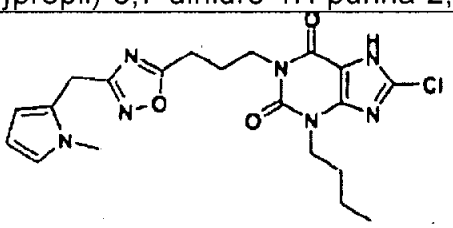
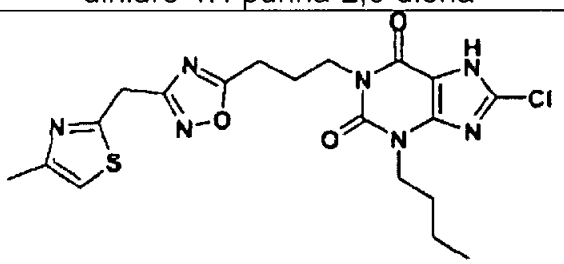
Se prepara usando un método análogo al usado para el ejemplo 93, excepto una etapa de purificación final adicional usando HPLC se emplea. Rendimiento 6.0 mg.

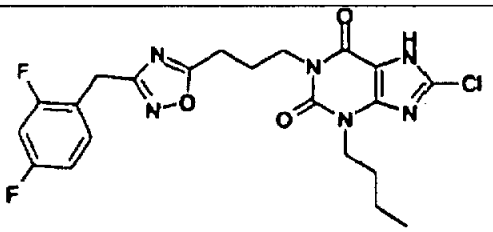
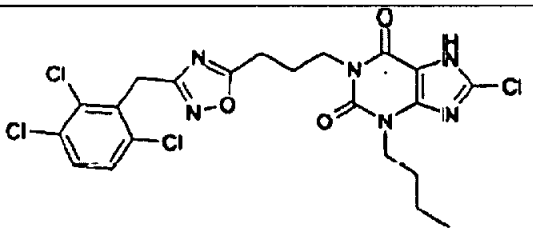
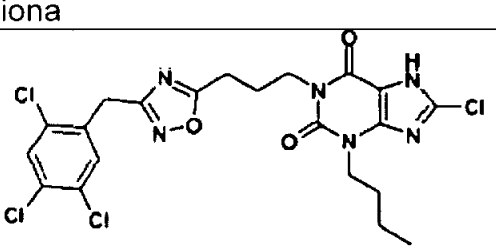
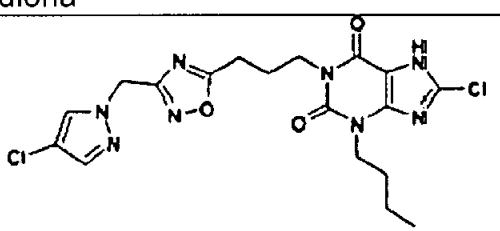
LC/EM: m/z 473 $[MH]^+$, RT 3.27min.

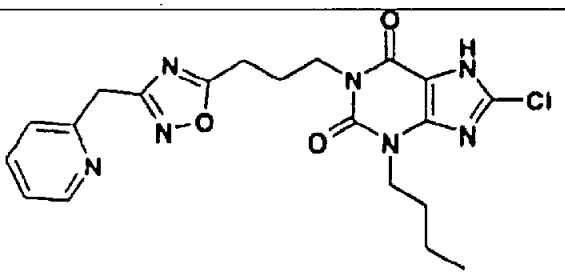
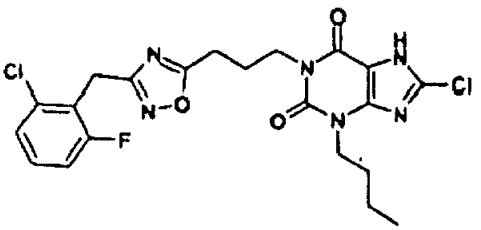
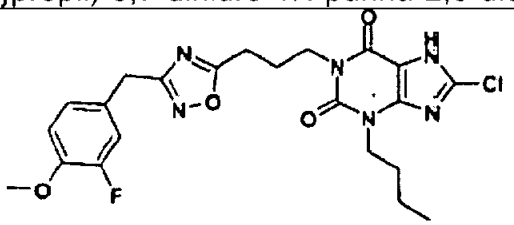
Los siguientes compuestos (cuadro 11) se preparan usando un método análogo al usado para el ejemplo 75, usando la amidoxima apropiada [con la excepción de que para el ejemplo 162 el producto crudo se agita en EtOH (0.75ml) con 2M NaOH (0.5 ml) durante la noche antes de tratamiento con EtOAc/HCl usual y MDAP; el ejemplo 164 se aísla como una impureza de la preparación del ejemplo 165 y se separa de este por HPLC; para los ejemplos 166, y 167 el pH durante el tratamiento acuoso se ajusta a aproximadamente 5 antes de la extracción; adicionalmente el ejemplo 167 se purifica adicionalmente por SPE sílice (2g, DCM-MeOH 40:1 entonces 20:1) después con MDAP].

CUADRO 11

Ejemplo	estructura	Rendimiento (mg)	LC/EM
158	 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 $[MH]^+$ RT 3.58 min

169	 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 $[MH]^+$ RT 3.41 min
160	 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 $[MH]^+$ RT 3.63 min
161	 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 $[MH]^+$ RT 3.15 min
162	 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 $[MH]^+$ RT 2.94 min

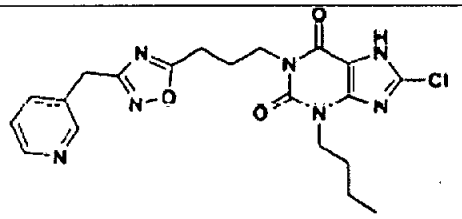
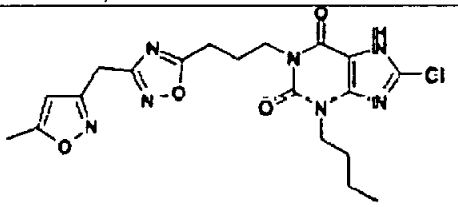
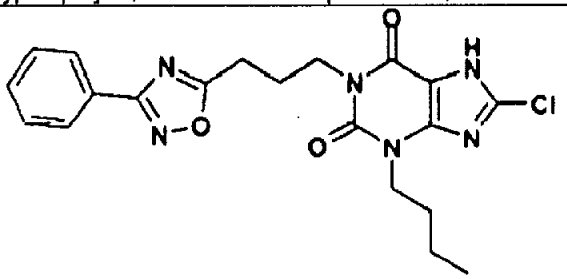
163	 3-butil-8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	33.5	m/z 479 $[MH]^+$ RT 3.35 min
164	 3-butil-8-cloro-1-(3-{3-[(2,3,6-triclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	4.6	m/z 545 $[MH]^+$ RT 3.71 min
165	 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 $[MH]^+$ RT 3.79 min
166	 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 $[MH]^+$ RT 3.24 min

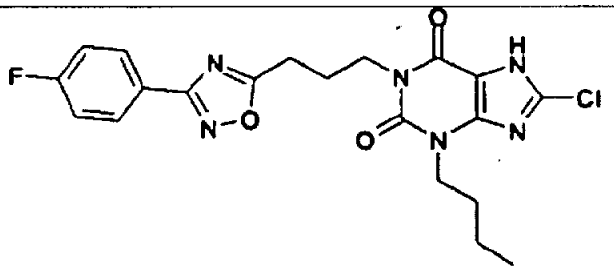
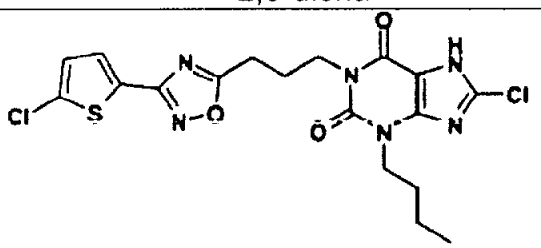
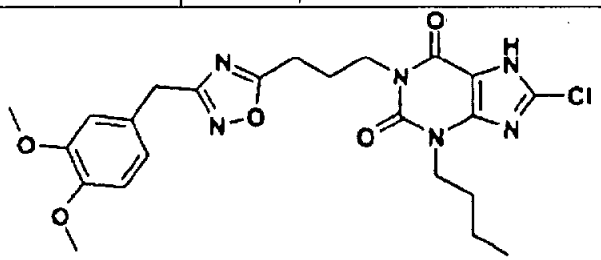
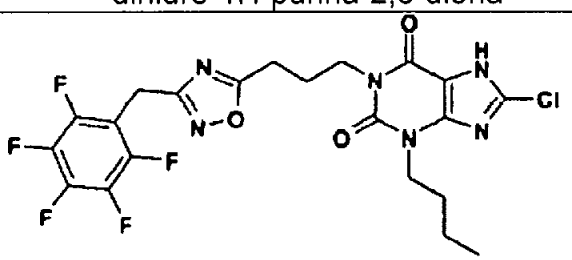
167	 3-butil-8-cloro-1-{3-[3-(2-piridinilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	23.6	m/z 444 $[MH]^+$ RT 2.92 min
168	 3-butil-8-cloro-1-(3-{3-[(2-cloro-6-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	38.8	m/z 495 $[MH]^+$ RT 3.43 min
169	 3-butil-8-cloro-1-[3-(3-{[4-fluoro-4-(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	27	m/z 491 $[MH]^+$ RT 3.31 min

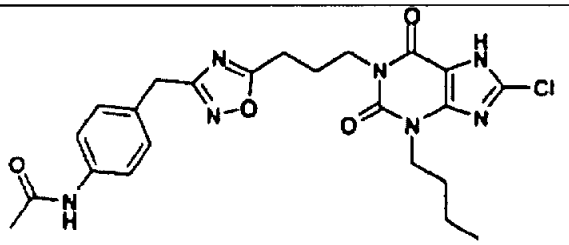
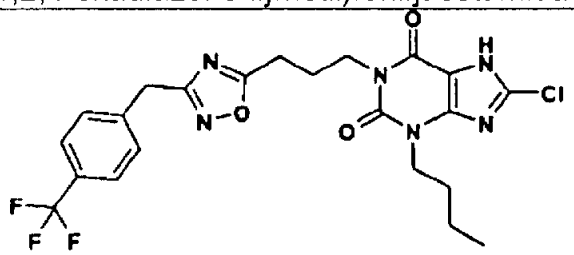
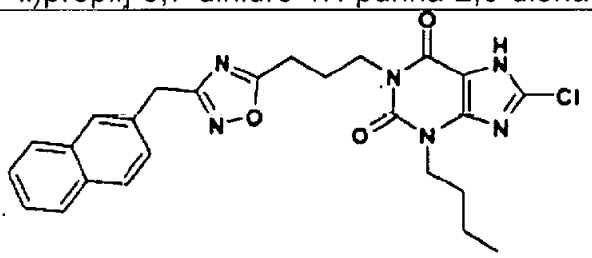
Los siguientes compuestos (cuadro 12) se preparan usando un método análogo al usado para el ejemplo 90, usando la amidoxima apropiada [con la excepción de el ejemplo 170 se conduzca a la mitad de la escala del ejemplo 90 y durante el tratamiento de la fase acuosa se neutraliza antes de la extracción; el ejemplo 171 se conduce a mitad de escala del ejemplo 90 y el producto crudo se agita con 2M NaOH (0.5 ml) en EtOH (1 ml) durante 5

horas antes del tratamiento y MDAP; para el ejemplo 175 se usan 01.85 ml (0.5 mmol) de NaOEt al 21%].

CUADRO 12

Ejemplo	Estructura	Rend. (mg)	LC/EM
170	 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 $[MH]^+$ RT 2.74 min
171	 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 $[MH]^+$ RT 3.13 min
172	 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 $[MH]^+$ RT 3.36 min

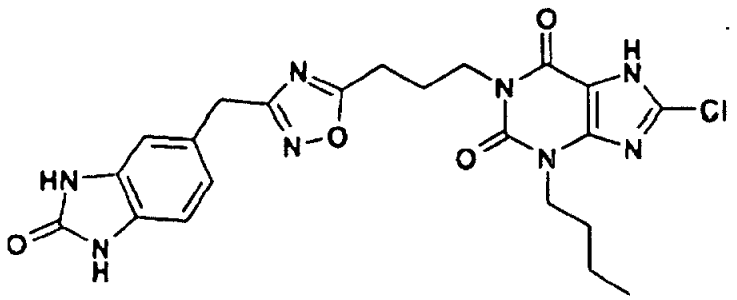
173	 3-butil-8-cloro-1-(3-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	41.1	m/z 447 $[MH]^+$ RT 3.42 min
174	 3-butil-8-cloro-1-(3-[3-(5-cloro-2-tienil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	36.7	m/z 469 $[MH]^+$ RT 3.60 min
175	 1-[3-(3-{[3,4-bis(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	47.0	m/z 503 $[MH]^+$ RT 3.14 min
176	 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 $[MH]^+$ RT 3.62 min

177	 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 $[MH]^+$ RT 3.01 min
178	 3-butil-8-cloro-1-[3-(3-{[4-(trifluorometil)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	37.7	m/z 511 $[MH]^+$ RT 3.65 min
179	 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 $[MH]^+$ RT 3.69 min

380

EJEMPLO 180

3-butil-8-cloro-1-(3-{3-[(2-oxo-2,3-dihidro-1H-bencimidazol-5-il)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona



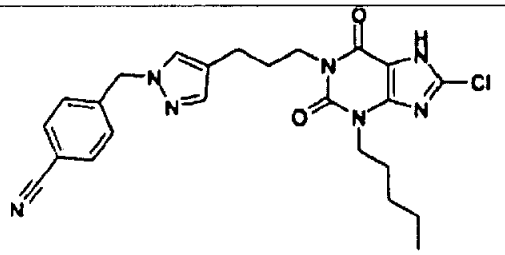
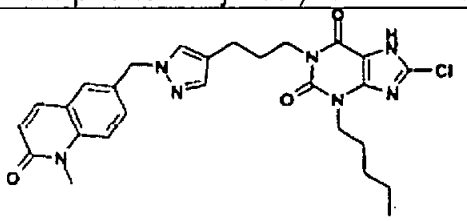
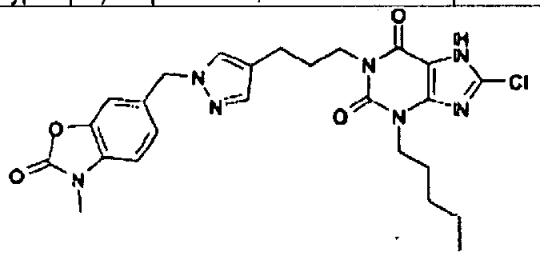
Se sintetiza por un método análogo a aquel del ejemplo 99 con excepción que 2 equivalentes adicionales de etóxido de sodio al 21% (0.11 ml) se usa, el tiempo de calentamiento extra es de 20 minutos y el producto se aísla por medio de filtración seguido por trituración con MeOH caliente. Rendimiento 14.5 mg.

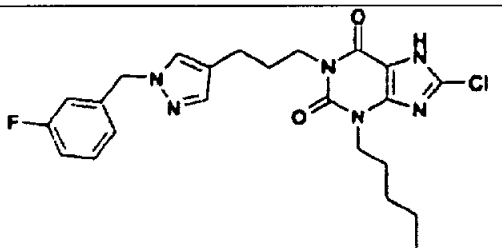
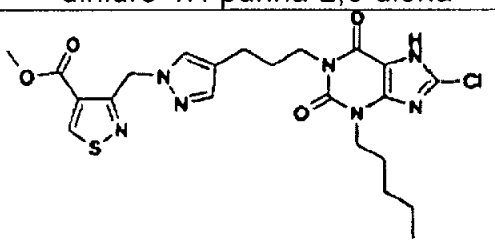
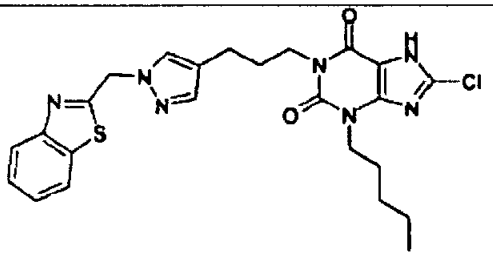
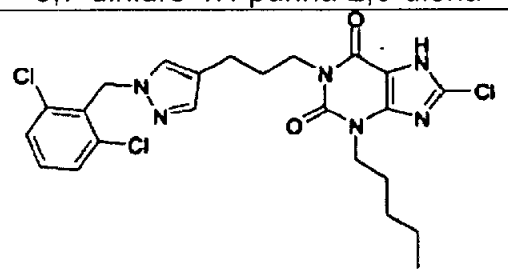
LC/EM; m7z 499 $[MH]^+$, RT 2.78 minutos.

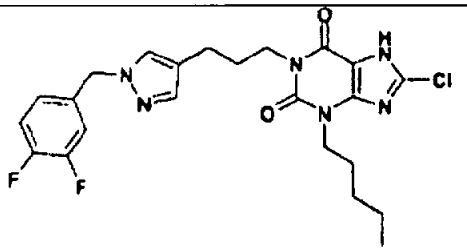
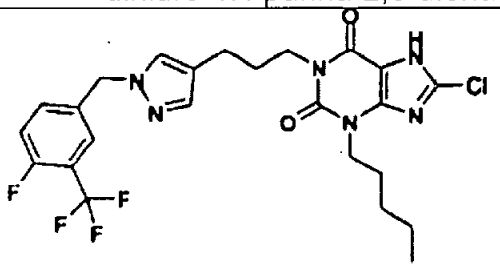
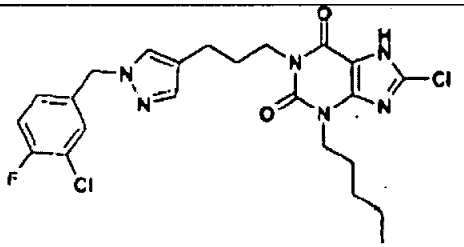
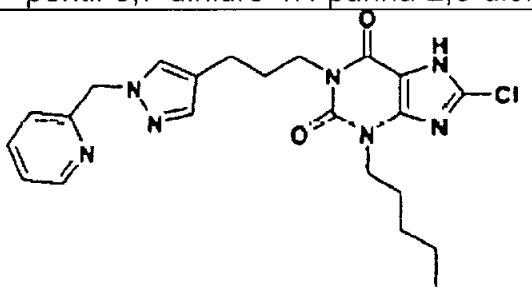
Los siguientes compuestos (cuadro 13) se preparan por medio de un método análogo a aquel del ejemplo 1 [con excepción de que los ejemplos 181-186 se sintetizan todos en una escala iniciando de 50 mg de 8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona; ejemplos 184, 186, 188, 189 y 190 se purifican adicionalmente por MDAP después de aminopopil SPE; el ejemplo 185 se purifica adicionalmente por recristalización de MeOH después de aminopropil SPE; para el ejemplo 191, 128 mg (1.2 mmol) de carbonato de sodio se usa; durante el tratamiento la fase acuosa se ajusta a pH 6 antes de extracción; y el producto se purifica por MDAP entonces por HPLC adicional; para el

ejemplo 184 sólidos que precipitan durante el tratamiento se combinan con los extractos de EtOAc antes de SPE].

CUADRO 13

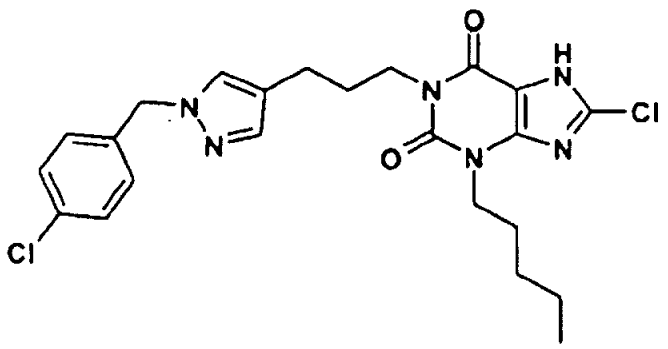
Ejemplo	Estructura	Rend. (mg)	LC/EM
181	 4-({4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il}metil)benzonitrilo	36.0	m/z 480 $[MH]^+$ RT 3.24 min
182	 8-cloro-1-(3-{1-[(1-metil-2-oxo-1,2-dihidro-6-quinolinil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina	7.6	m/z 536 $[MH]^+$ RT 3.03 min
183	 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 $[MH]^+$ RT 3.11 min

184	 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 $[MH]^+$ RT 3.38 min
185	 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 $[MH]^+$ RT 3.12 min
186	 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 $[MH]^+$ RT 3.36 min
187	 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 $MH]^+$ RT 3.77 min

188	 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 $[MH]^+$ RT 3.61 min
189	 8-cloro-1-[3-(1-{[4-fluoro-3-(trifluorometil)fenil)metil}-1H-pirazol-4-il)-propil]-3-pentil-3,7-dihidro-1H-purina-2,6-diona	17.0	m/z 541 $[MH]^+$ RT 3.76 min
190	 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 $[MH]^+$ RT 3.73 min
191	 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 $[MH]^+$ RT 3.13 min

EJEMPLO 192

8-cloro-1-(3-{1-[(4-clorofenil)metil]-1H-pirazol-4-il}-propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



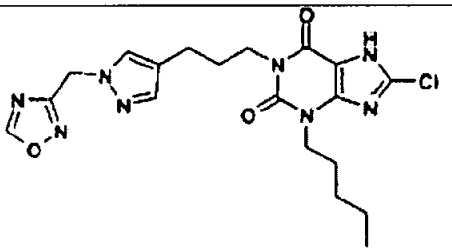
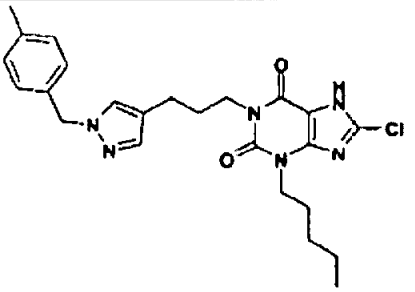
8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona (50 mg, 0.123 mmol) en DMF seco (1.5 ml) se agita con carbonato de sodio (75 mg, 0.708 mmol) y bromuro de 4-clorobencilo (150 mg, 0.73 mmol) a 40°C durante 18 horas. La mezcla se divide entre EtOAc y agua, la fase orgánica se lava con salmuera, se seca y se evapora. El producto se purifica por cromatografía en fase normal en sílice (Companion System, EtOAc- gradiente de ciclohexano) proporcionando un aceite (44 mg). Esto se agita en DMF seco desgasificado (1 ml) con tetrakis(trifenilfosfina)paladio(0) (19 mg) y morfolina (0.072 ml) bajo nitrógeno durante 6 horas. La mezcla se divide entre EtOAc y HCl 2M y la fase orgánica se evaporó y purifica por medio de procedimiento SPE aminopropilo usual. Rendimiento 21.0 mg.

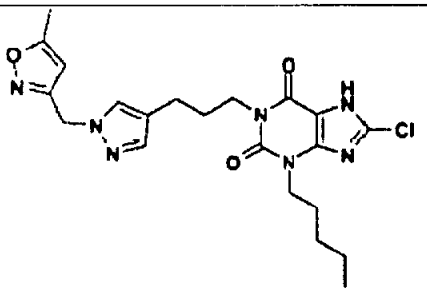
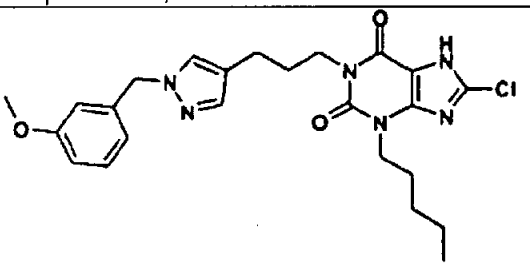
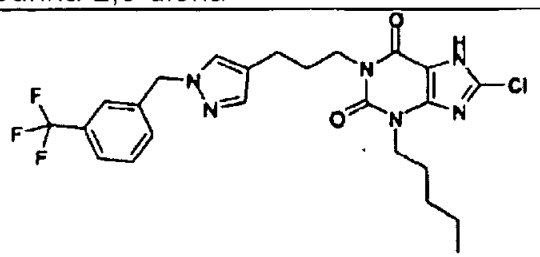
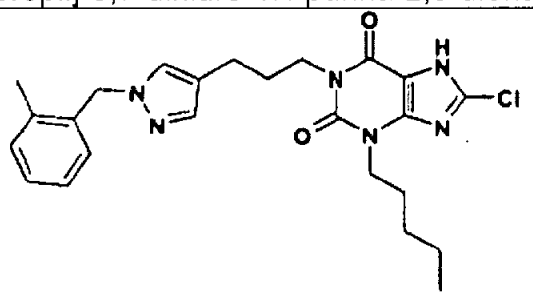
LC/EM: m/z 489 [MH^+], RT 3.59 min.

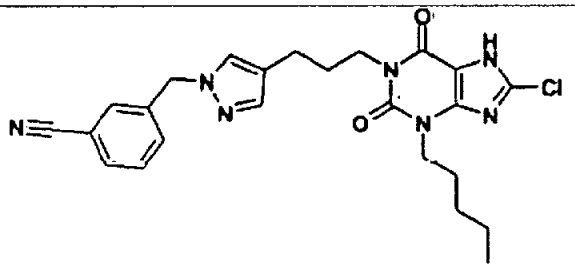
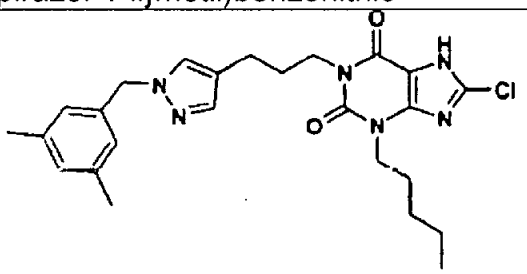
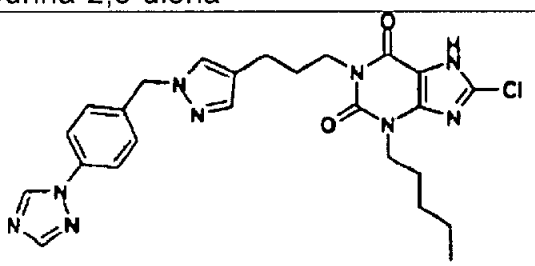
Los siguientes compuestos (cuadro 14) se preparan por medio de un método análogo a aquel del ejemplo 6 [con la excepción de que el

ejemplo 193 una segunda porción de $Pd(PPh_3)_4$ se añade después de 5 horas, la agitación continua durante la noche, y purificación adicional se logra por medio de HPLC; para el ejemplo 195 se requiere purificación adicional por medio de MDAP; el ejemplo 200 requiere purificación adicional por medio de recristalización de MeOH; el ejemplo 201 requiere purificación adicional por medio de trituración con MeOH].

CUADRO 14

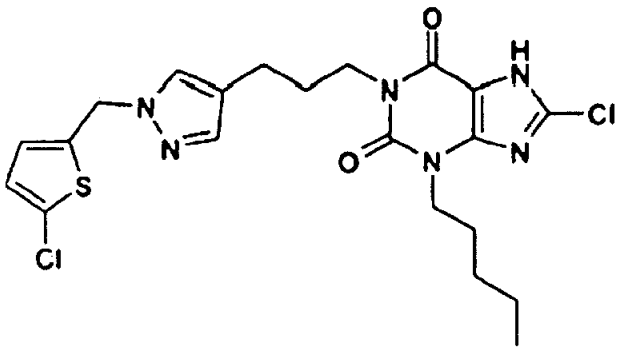
Ejemplo	Estructura	Rend. (mg)	LC/EM
193	 8-cloro-1-{3-[1-(1,2,4-oxadiazol-3-ilmetil)-1H-pirazol-4-il]-propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	7.3	m/z 447 $[MH]^+$ RT 3.06 min
194	 8-cloro-1-(3-{1-[(4-metilfenil)metil]-1H-pirazol-4-il}-propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	23.7	m/z 469 $[MH]^+$ RT 3.49 min

195	 8-cloro-1-(3-{1-[(5-metil-3-isoxazolil)metil]-1H-pirazol-4-il}-propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	29.0	m/z 460 $[MH]^+$ RT 3.10 min
196	 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 $[MH]^+$ RT 3.41 min
197	 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 $[MH]^+$ RT 3.61 min
198	 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 $[MH]^+$ RT 3.54 min

199	 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 $[MH]^+$ RT 3.32 min
200	 8-cloro-1-(3-{1-[(3,5-dimetilfenil)metil]-1H-pirazol-4-il}-propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	36.7	m/z 483 $[MH]^+$ RT 3.66 min
201	 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 $[MH]^+$ RT 3.09 min

EJEMPLO 202

8-cloro-1-(3-{1-[(5-cloro-2-tienil)metil]-1H-pirazol-4-il}-propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona

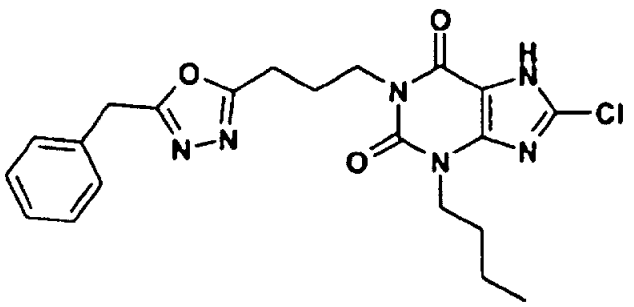


A 8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona (61 mg, 0.15 mmol) en THF seco (1 ml) a -78°C, bajo nitrógeno, se añade t-butóxido de potasio (1 M en THF, 0.15 ml), seguido por 2-cloro-5 (clorometil)tiofeno (25 mg, 0.15 mmol). La agitación continua a -78°C durante 15 minutos, entonces a temperatura ambiente durante 1 hora y finalmente a 60°C durante 18 horas. La solución se desgasifica y morfolina (0.13 ml) y tetrakis(trifenylfosfina)paladio(0) (35 mg) se añaden y se agita de forma continua durante 6 horas. Cantidades adicionales (0.2 ml de morfolina, 50 mg de $Pd(PPh_3)_4$) se añaden y se agitan de manera continua durante la noche. Se trabaja por división entre EtOAc y 2M HCl, la fase orgánica se evapora y se purifica por el procedimiento SPE aminopropilo estándar seguido por MDAP produciendo el compuesto del titulo como un sólido blanco (5.1 mg).

LC/EM: m/z 495 [MH]+, RT 3.68min.

EJEMPLO 203

3-Butil-8-cloro-1-{3-[5-(fenilmetil)-1,3,4-oxadiazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona



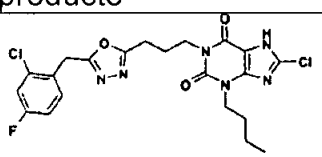
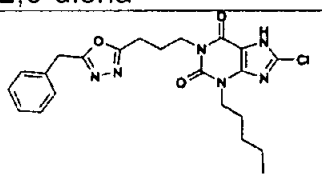
A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (99 mg, 0.35 mmol) en DMF seco (2 ml) se añade carbonato de cesio (137 mg, 0.42 mmol) seguido por una solución en DMF seco (1 ml) de 2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol (99 mg, 0.42 mmol). La mezcla se agita bajo nitrógeno y se calienta a 55°C durante 2.5 horas y después se agita a temperatura ambiente durante la noche. La mezcla se desgasifica por evacuación repetida y admitiendo nitrógeno y después tetrakis(trifenilfosfina)paladio(0) (81 mg, 0.07 mmol) y morfolina (0.305 ml, 3.5 mmol) se añaden y continua la agitación durante 5 horas EtOAc y 2M HCl se añaden y la mezcla se agita durante 20 minutos y después se purifica por SPE aminopropilo (5 g) se lava con THF-MeOH (1:1) y después con MeOH y se eluye el producto ácido con DCM-MeOH (1:1) que contiene 5% AcOH añadido. El producto obtenido de este modo se purifica adicionalmente por MDAP para producir el compuesto del titulo (92mg).

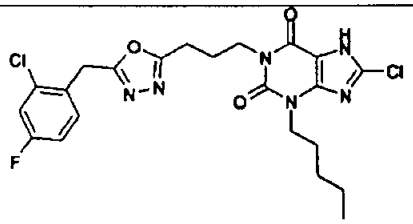
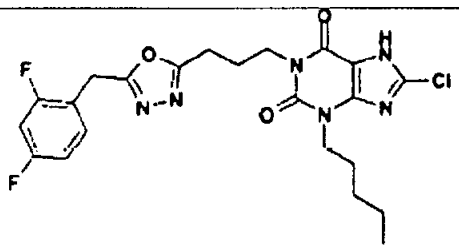
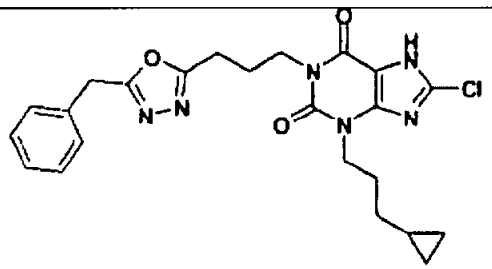
LC/EM: m/z 443 $[MH]^+$, RT 3.18min.

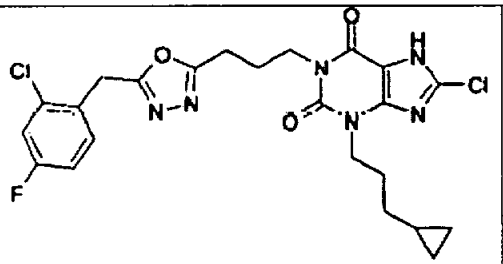
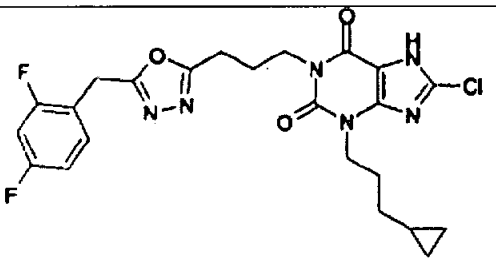
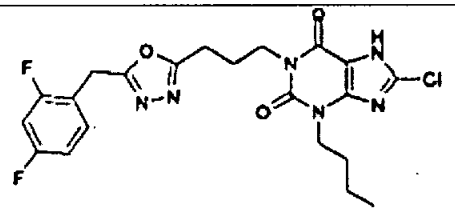
340

Los siguientes compuestos (cuadro 15) se preparan por un método análogo a aquel del ejemplo 203, con excepción de que el ejemplo 211 se purifica adicionalmente por HPLC.

CUADRO 18

Ejemplo	Estructura del producto	Precursor xantina	Agente de alquilación	Rend. (mg)	LC/EM
204	 3-butil-8-cloro-1-(3-{5-[(2-cloro-4-fluorofenil)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 522 $[MH]^+$ RT 3.09 min
205	 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-oxadiazol (99 mg)	98	m/z 457 $[MH]^+$ RT 3.35 min

206	 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 $[MH]^+$ RT 3.52 min
207	 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 $[MH]^+$ RT 3.40 min
208	 8-cloro-3-(3-ciclopropilpropil)-1-(3-[5-(fenilmetil)-1,3,4-oxadiazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-(3-ciclopropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (108 mg)	2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol (99 mg)	95	m/z 469 $[MH]^+$ RT 3.34 min

209	 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 $[MH]^+$ RT 3.51 min
210	 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 $[MH]^+$ RT 3.40 min
211	 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 $[MH]^+$ RT 3.31 min

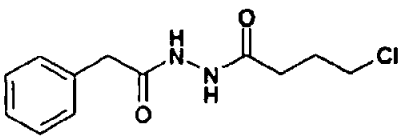
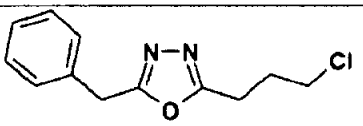
Síntesis de intermedios cloropropilo-1,3,4-oxadiazol del cuadro 15

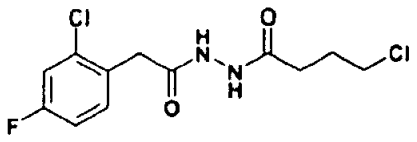
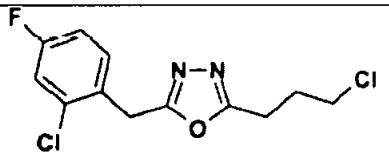
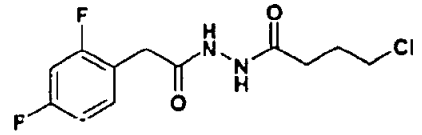
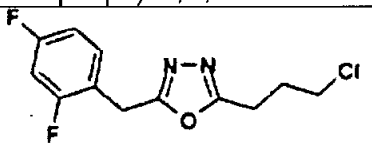
2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol

2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol

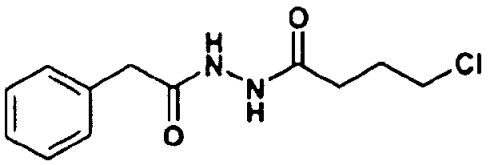
2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol

Hidrazinas de diacilo (500 mg, síntesis posterior) se agita en tolueno seco (4 ml) y oxicloruro fosforoso (4 ml) se añade. Las mezclas se calientan a 90°C durante 2 horas y después se dejan enfriar y los solventes se evaporan. Los residuos se disuelven en tolueno seco, se evaporan y después de dividen entre EtOAc y $NaHCO_3$ acuoso. Las fases orgánicas se lavan con salmuera, se secan sobre Na_2SO_4 y se evaporan para proveer los oxadiazoles requeridos como aceites incoloros. Estos no se purifican adicionallmente pero reaccionan directamente con las xantinas como se mencionó anteriormente.

Hidrazina diacilo	Producto oxadiazol	Rend (mg)	LC/EM
 4-cloro-N'-(fenilacetil)butanohidrazida	 2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol	446	m/z 237 $[MH]^+$ RT 2.94 min

 4-cloro-N'-[(2-cloro-4-fluorofenil)acetil]butanohidrazida	 2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol	405	m/z 289 $[MH]^+$ RT 3.17 min
 4-cloro-N'-[(2,4-difluorofenil)acetil]butanohidrazida	 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol	333	m/z 273 $[MH]^+$ RT 3.03 min

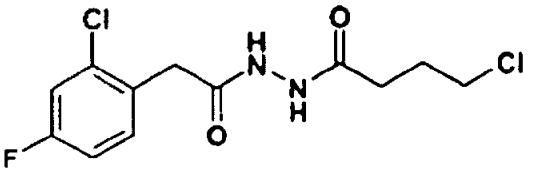
Preparación de 4-cloro-N'-(fenilacetil)butanohidrazida



A cloruro de 4-clorobutirilo (1.12 ml, 10 mmol) en DCM seco (10 ml) se añade, gota agota, durante 40 minutos, una mezcla de hidracida fenil acético (1.5 g, 10 mmol) y DIPEA (1.77 ml, 10.2 mmol) en DCM seco (40 ml) a temperatura ambiente. Un precipitado blanco denso se forma. Después de 20 minutos adicionales, se añade HCl 2M (30 ml) y el compuesto del titulo (sólido blanco) se filtra, se lava con agua y se seca (2.24 g).

LC/EM: m/z 255 $[MH]^+$, RT 2.20 min.

Preparación de 4-cloro-N'-[(2-cloro-4-fluorofenil)acetil]butanohidrazida



(i) Una solución de cloruro de 2-cloro-4-fluorofenilacetilo (l0 mmol) en DCM seco (15 ml) se añade por 20 minutos a una mezcla de carbazato de t-butilo (1.32 g, 10 mmol) y DIPEA (1.77 ml, 10.2 mmol) en DCM seco (20 ml). Después de agitar por 2 horas adicionales, la mezcla se lava con 1 M HCl después con $NaHCO_3$ acuoso. Un sólido blanco precipita en este punto, el cual se filtra, se lava con agua y DCM y después se seca para producir 2-[(2-cloro-4-fluorofenil)acetil]hidrazinacarboxilato de 1,1-dimetiletilo (1.94 g).

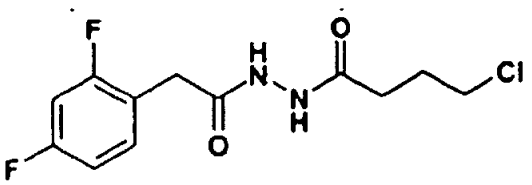
(ii) Este compuesto (1.92 g, 6.34 mmol) se suspende en dioxano (2ml) y 4M HCl en dioxano (5 ml) se añade. Se forma un precipitado blanco denso. Después de 1 hora la mezcla se divide entre EtOAc y $NaHCO_3$ acuoso saturado y la fase orgánica se lava con salmuera, se seca (Na_2SO_4) y se evapora proporcionando 2-(2-cloro-4-fluorofenil)acetohidrazida como un sólido blanco (1.07g).

(iii) Una mezcla de 2-(2-cloro-4-fluorofenil)acetohidrazida (909 mg, 4.5 mmol) y DIPEA (0.817 ml, 4.7 mmol) en DCM seco (65 ml) se añade durante 20 minutos a cloruro de 4-clorobutirilo (0.505 ml, 4.5 mmol) en DCM seco (5 ml). Después de 1.5 horas, 2M HCl se añade y la 4-cloro-N'-[(2-cloro-

4-fluorofenil)acetil]butanohidrazida precipitada se filtra, se lava con agua y se seca (1.24g).

LC/EM: m/z 307 [MH]+, RT 2.61 min.

Preparación de 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol



(i) Una solución de cloruro de 2,4-difluorofenilacetilo (10 mmol) en DCM seco (15 ml) se añade durante 10 minutos, a una mezcla de carbazato de t-butilo (1.32 g, 10 mmol) y DIPEA (1.77 ml, 10.2 mmol) en DCM seco (20 ml). Después de agitar durante 1.5 horas la mezcla se lava con 1 M HCl y después con $NaHCO_3$ acuoso. La fase orgánica se evapora para producir 1,1-dimetiletil2-[(2,4-difluorofenil)acetil]hidrazinecarboxylato como un sólido blanco

(ii) 2-[(2,4-difluorofenil)acetil]hidrazinacarboxilato de 1,1-dimetiletilo (10 mmol) en dioxano (5 ml) se agita con 4M HCl en dioxano (8 ml) durante 1.5 horas. La mezcla se divide entre EtOAc y $NaHCO_3$ acuoso saturado y la fase orgánica se lava con salmuera, se seca (Na_2SO_4) y se evapora. La reacción es incompleta de modo que el residuo se agita nuevamente con 4M HCl en dioxano (10 ml) durante 2.5 horas. El procedimiento anterior proporciona 2-(2,4-difluorofenil)acetohidrazida como un

sólido (570mg).

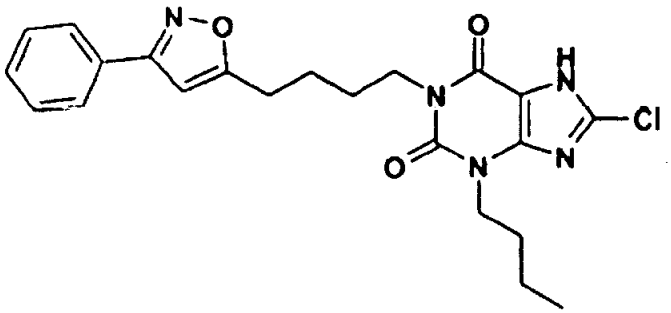
(iii) Una mezcla de 2-(2,4-difluorofenil)acetohidrazida (570 mg, 3.06 mmol) y DIPEA (0.553 ml, 3.2 mmol) en DCM seco (30 ml) se añade a cloruro de 4-clorobutirilo (0.343 ml, 3.06 mmol) en DCM seco (5 ml) durante 15 minutos. Un intermedio precipitado blanco se forma. Después de agitar durante 1 hora, 2M HCl (20 ml) se añade y el sólido 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol se filtra, se lava con agua y se seca (726 mg).

LC/EM: m/z 291 [MH]+, RT 2.45min.

EJEMPLO 212

3-Butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1H-purina-2,6-diona

a) 3-butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1H-purina-2,6-diona

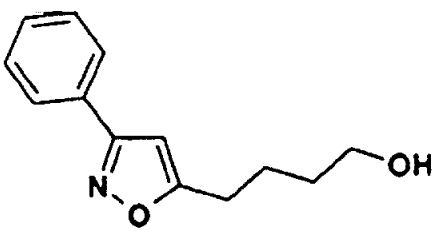


3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (100 mg, 0.354 mmol) y 4-(3-fenil-5-isoxazolil)-1-butanol (77 mg, 0.355 mmol) se disuelven en THF seco (4 ml) bajo nitrógeno. Una solución de

azodicarboxilato de dibencilo (94%, 224 mg, 0.708 mmol) en THF seco (2 ml) se añade. La mezcla se enfría a 0°C y una solución de trifenilfosfina (185 mg, 0.708 mmol) en THF seco (1 ml) se añade. La mezcla se agita durante 20 minutos a 0°C y después a temperatura ambiente durante la noche. La mezcla se desgasifica y entonces se agita con morfolina (0.308 ml) y tetrakis(trifenilfosfina)paladio(0) (82 mg) durante 4.5 horas. 60 mg adicionales de tetrakis(trifenilfosfina)paladio(0) se añade y la agitación continua durante la noche. La reacción se trabaja po división entre EtOAc y 2M HCl, la fase orgánica se evapora y purifica por medio de aminopropilo SPE (5 g) se lava con THF-MeOH (1:1), MeOH y se eluye con DCM-MeOH (1:1) quie contiene 5% AcOH. Purificación adicional por MDAP produce el compuesto del titulo (56 mg).

LC/EM: m/z 442 [MH]+, RT 3.59min.

b) 4-(3-fenil-5-isoxazolil)-1-butanol



A cloruro de N-hidroxibencenocarboximidoilo (622 mg, 4 mmol) en DCM (6 ml) se añade 5-hexin-1-ol (431 mg, 4.4 mmol). La mezcla se enfría a 0°C bajo nitrógeno como trietilamina (0.612 ml, 4.4 mmol) se añade gota a gota durante 10 minutos. se agita por 20 minutos a 0°C y después a

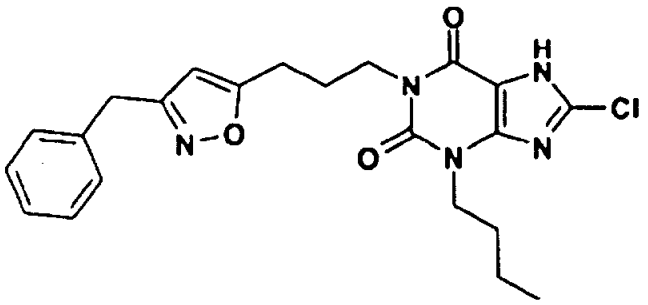
temperatura ambiente durante la noche. La mezcla se lava con agua y la fase orgánica se evapora. El producto se purifica por SPE sílice (20 g) se eluye con EtOAc-ciclohexano (1:2, entonces 3:1) para proveer un sólido ceroso blanco (443 mg).

LC/EM: m/z 218 $[MH]^+$, RT 2.74min.

EJEMPLO 213

3-Butil-8-cloro-1-{3-[3-(fenilmetil)-5-isoxazolil]propil}-3,7-dihidro-1H-purina-2,6-diona

a) 3-Butil-8-cloro-1-{3-[3-(fenilmetil)-5-isoxazolil]propil}-3,7-dihidro-1H-purina-2,6-diona

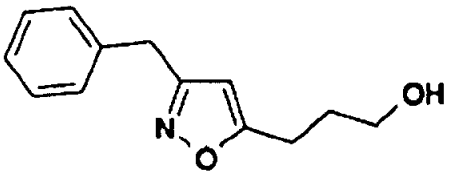


Preparado análogamente a 3-butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1H-purina-2,6-diona (ejemplo 213) usando la mitad de las cantidades molares, iniciando de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (50 mg, 0.177 mmol) y 3-[3-(fenilmetil)-5-isoxazolil]-1-propanol (38.4 mg, 0.177 mmol). Rendimiento 24.2 mg,

LC/EM: m/z 442 [MH]+, RT 3.43min.

400

b) 3-[3-(fenilmetil)-5-isoxazolil]-1-propanol

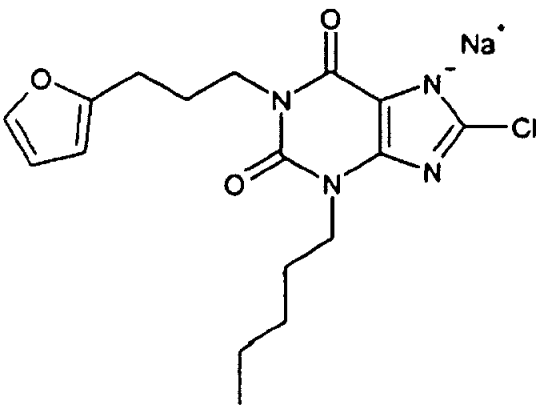


Se sintetiza como con 4-(3-fenil-5-isoxazolil)-1-butanol, usando cloruro de N-hidroxi-2-feniletanimidoilo (253 mg, 1.5 mmol) y 4-pentin-1-ol (139 mg, 1.65 mmol). Rendimiento 61 mg de color amarillo pálido.

LC/EM: m/z 218 [MH]+, RT 2.62min.

EJEMPLO COMPARATIVO B

8-Cloro-1-[3-(2-furanil)propil]-3-pentil-3,7-dihidro-1H-purina-2,6-diona, sal de sodio



Un tubo GreenHouse™ equipado con un agitador se carga con una alícuota de 0.25 ml de una solución 0.54 M de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (0.13 mmol) en THF. A la mezcla se añade 3-(2-furanil)-1-propanol (21 mg, 0.16 mmol, 1.2 eq) en THF (0.25 ml), seguido por una alícuota de 0.25 ml de una solución 0.71 M de bis(1,1-

dimetiletil) (E)-1,2-diazenodicarboxilato (0.18 mmol) en THF y después una alícuota 0.25 ml de una solución 0.71 M de trifenilfosfina (0.18 mmol) en THF. La solución se agita en un GreenHouse™ bajo nitrógeno durante 16 horas. A la mezcla se añade una alícuota 0.25 ml adicional de una solución 1.4 M de bis(1,1-dimetiletil) (E)-1,2-diazenodicarboxylato (0.36 mmol) en THF y después una alícuota adicional de 0.25 ml de una solución 1.4M de trifenilfosfina (0.36 mmol) en THF. La mezcla se agita durante 16 horas bajo una corriente de nitrógeno

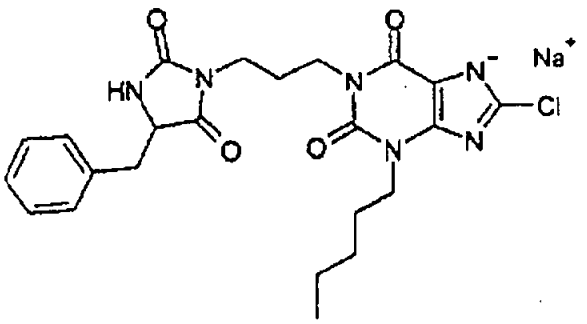
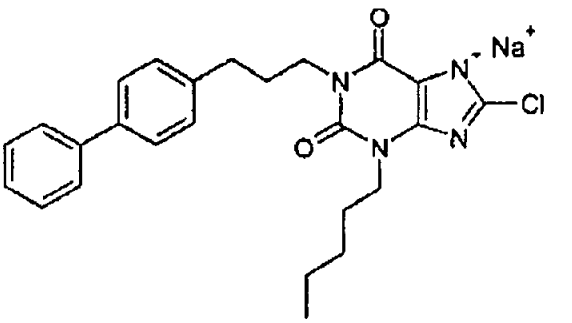
Tetrakis(trifenilfosfina)paladio(0) (16 mg, 0.014 mmol) y morfolina (0.12 ml, 1.35 mmol) se añaden a la mezcla la cual se agita durante 16 horas bajo una corriente de nitrógeno. La mezcla de reacción se concentra bajo nitrógeno y el material crudo se disuelve en solución de NaOH (0.5 ml, 2M). La solución resultante se purifica usando aminopropilo SPE (eluyendo con AcOH en DCM y MeOH). Purificación adicional usando C18 SPE (luyendo con agua, amoníaco y mezcla de MeCN) produce el compuesto del título como una goma clara (22 mg, 45%).

LC/EM: m/z 365 [MH]+, RT 3.48min.

^{1}H RMN (DEMO-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, 1 H, J = 3Hz), 6.32 (dd, 1 H, J = 3 and 2Hz), 7.48 (d, 1 H, J = 2Hz).

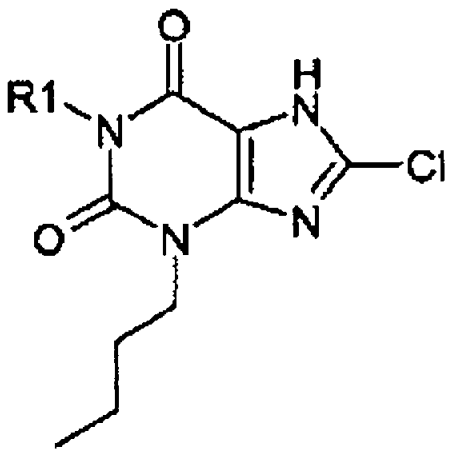
Los siguientes compuestos (cuadro 16) se preparan por un método análogo a aquel para el ejemplo comparativo B.

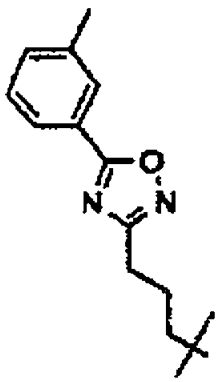
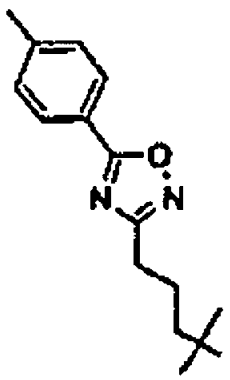
CUADRO 16

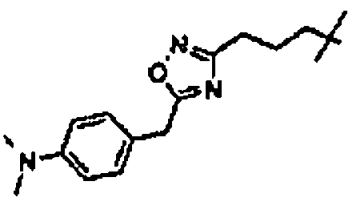
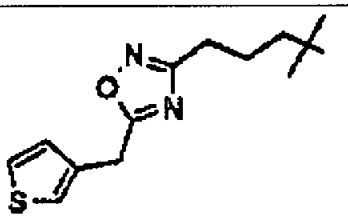
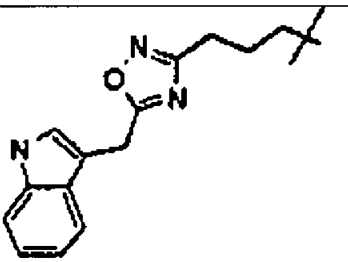
Ejemplo	Estructura	Rend. (mg)	LC/EM
214	 sal sódica de 8-cloro-1-{3-[2,5-dioxo-4-(fenilmetil)-1-imidazolidinil]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	9	m/z 487 $[MH]^+$ RT 3.15 min
215	 sal sódica de 1-[3-(4-bifenil)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purina-2,6-diona	19	m/z 451 $[MH]^+$ RT 4.06 min

Los siguientes compuestos (cuadro 17) se preparan usando un método un método análogo al del ejemplo 113, a partir de ácidos correspondientes y (1Z)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxibutanimidamida.

CUADRO 17



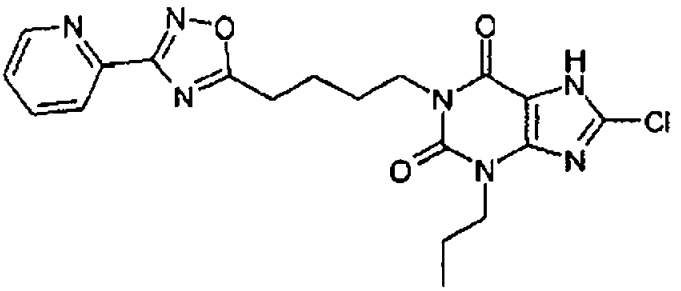
Ej.	Nombre	Compuesto R1=	LC/EM
216	3-butil-8-cloro-1-{3-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona		m/z 443 $[MH]^+$ RT 3.47 min
217	3-butil-8-cloro-1-[3-[5-(4-metilfenil)-1,2,4-oxadiazol-3-il]propil]-3,7-dihidro-1H-purina-2,6-diona		m/z 443 $[MH]^+$ RT 3.34 min

Ej.	Nombre	Compuesto R1=	LC/EM
218	3-butil-8-cloro-1-[3-(5-{[4-(dimetilamino)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purina-2,6-diona		m/z 443 $[MH]^+$ RT 3.47 min
219	3-butil-8-cloro-1-{3-[5-(3-trienilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona		m/z 449 $[MH]^+$ RT 3.24 min
220	3-butil-8-cloro-1-{3-[5-(1H-indol-3-ilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona		m/z 482 $[MH]^+$ RT 3.29 min

EJEMPLO 221

8-cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona

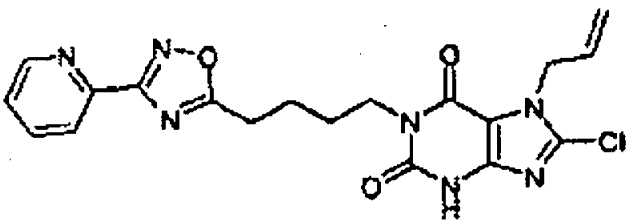


Una solución de 8-cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-

1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona (40 mg, 0.09 mmol) en DMF (3 ml) se trata con carbonato de potasio (15 mg, 0.11 mmol) y 1-yodopropano (19 mg, 0.11 mmol). La mezcla se calienta a 40°C durante 3 horas después a 70°C durante unas 3 horas adicionales. La mezcla se enfría y se desgasifica mediante la aplicación sucesiva de vacío y gas nitrógeno. La mezcla se trata con una solución de tetraquis(trifenilfosfina)paladio (0) (10 mg, 0.009 mmol) y morfolina (0.1 ml, 1.2 mmol) y después se agita toda la noche. La mezcla se evapora y se divide entre cloroformo 82 ml) y agua (2 ml). La fase acuosa se extrae con cloroformo adicional (2 ml) y los orgánicos combinados se evaporan y el residuo se disuelve en metanol (2 ml). La solución se aplica a un SPE de aminopropilo de 1 g y se eluye con metanol y después con ácido acético al 5% en metanol. Las fracciones que contienen el producto se agrupan y evaporan y el producto se purifica adicionalmente por MDAP para revelar 8-cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona (1.4 mg) como un sólido blanco.

LC/EM: m/z 430 $[MH]^+$, temperatura ambiente 2.84 minutos.

b) 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



Una suspensión de N-hidroxi-2-piridinocarboximidamida (1.15 g, 8.4 mmol) y THF anhidro (20 ml) se trata con metóxido de sodio (0.38 g, 7.0 mmol) y la mezcla se agita durante 5 minutos. La mezcla se trata 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 mmol) y se agita durante aproximadamente 5 minutos hasta que todo el material se ha disuelto. La mezcla entonces se sella y se calienta en un microondas a 120°C durante 15 minutos después se enfría y se divide entre acetato de etilo (100 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase acuosa se extrae con acetato de etilo adicional (50 ml) y los orgánicos combinados se secan ($MgSO_4$), se filtran y se evaporan. El producto se purifica mediante cromatografía instantánea usando una elusión de gradiente a partir de acetato de etilo/ciclohexano 1:9 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-1H-purina-2,6-diona (1.49 g) como un sólido blanco.

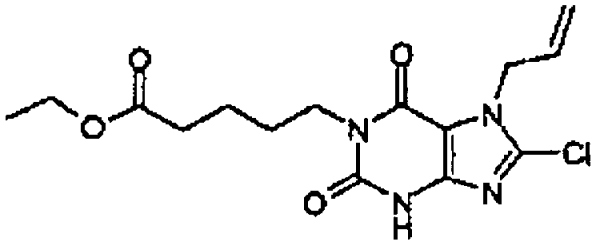
LC/EM: m/z 428 $[MH]^+$, temperatura ambiente 2.70 minutos.

Se prepara de manera similar 8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-7-(2-propen-1-il)-3,7-dihidro-1H-

purina-2,6-diona usando 4-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butanoato de etilo

LC/EM: m/z 463 $[MH]^+$, temperatura ambiente 3.09 minutos.

c) 5-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]pentanoato de etilo



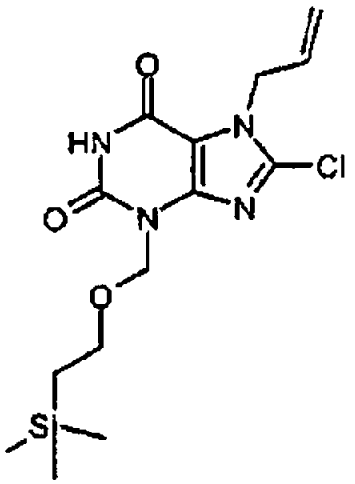
Una solución de 8-cloro-7-(2-propen-1-il)-3-({[2-(trimetilsilil)etil]oxi}metil)-3,7-dihidro-1H-purina-2,6-diona (10 g, 28 mmol) en DMF (10 ml) se trata con carbonato de potasio (4.8 g, 35 mmol) y 5-bromopentanoato de etilo (6.5 g, 31 mmol) y después se calienta a 70°C durante 3 horas, se enfría y se evapora. El residuo se divide entre acetato de etilo (100 ml) y agua (50 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se evapora y el intermedio crudo se disuelve en diclorometano 890 ml), se trata con ácido trifluoroacético (17 ml) y la mezcla se agita a temperatura ambiente toda la noche. Se añade tolueno (50 ml) y la mezcla se evapora a sequedad. El producto se purifica mediante cromatografía instantánea usando una elusión de gradiente 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-1H-purin-1-il]pentanoato de etilo como un sólido blanco.

LC/EM: m/z 355 $[MH]^+$, temperatura ambiente 2.75 minutos.

Se prepara similarmente 4-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butanoato de etilo.

LC/EM: m/z 341 $[MH]^+$, temperatura ambiente 2.61 minutos.

d) 8-cloro-7-(2-propen-1-il)-3-({[2-(trimetilsilil)etil]oxi}metil)-3,7-dihidro-1H-purina-2,6-diona



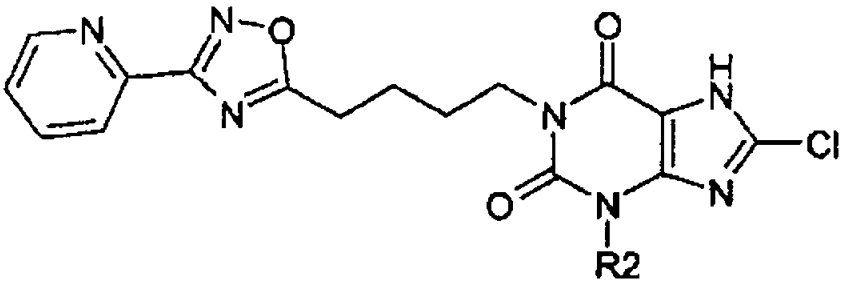
A una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (5 g, 22.1 mmol) en DMF (80 ml) se añade cloruro de 2,2-(trimetilsilil)etoximetilo (4.3 ml, 24.2 mmol) y carbonato de sodio (2.6 g, 24.2 mmol). Después de la agitación a temperatura ambiente toda la noche cloruro de 2-2(trimetilsilil)etoximetilo adicional (4.3 ml, 24.2 mmol) y carbonato de sodio (1.3 g, 12.1 mmol) se añade y la agitación continua durante 2 horas. La mezcla de reacción después se divide entre Lic. Al 5% y acetato de etilo. El extracto orgánico se separa, se lava con salmuera, se seca ($MgSO_4$) y se concentra. La purificación por cromatografía Biotage™ usando un cartucho de

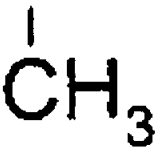
sílice se eluye con acetato de etilo/ciclohexano 1:4-1:2 para producir el compuesto del titulo (3.14 g, 40%).

m/z 374[MNH_4].

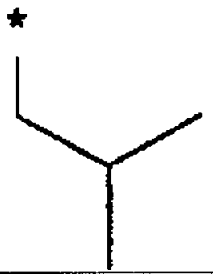
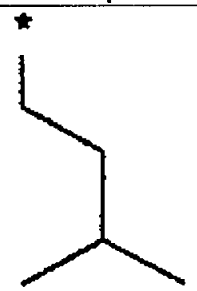
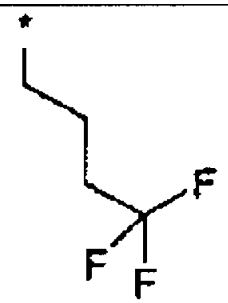
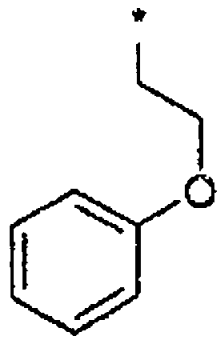
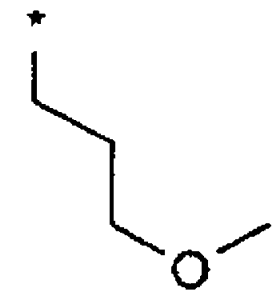
Los siguientes compuestos (cuadro 18) se preparan por un método análogo al del ejemplo 221, a partir de 8-cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona y el agente de alquilación adecuado.

CUADRO 18



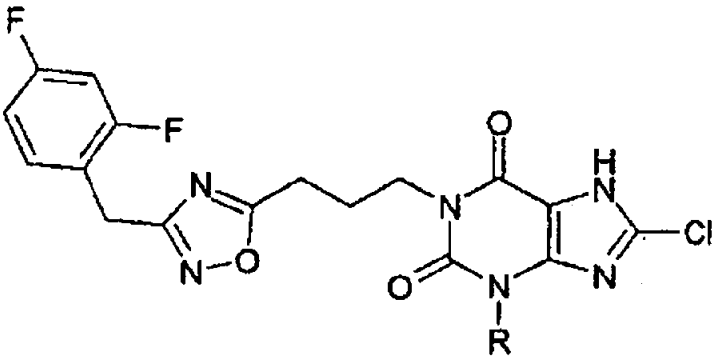
Ej.	R^2=	Nombre	Rend, (mg)	m/z	RT (min)
222		8-cloro-3-metil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	1.7	402	2.53
223		8-cloro-3-etil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	1.4	416	2.66

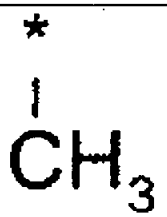
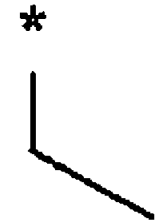
410

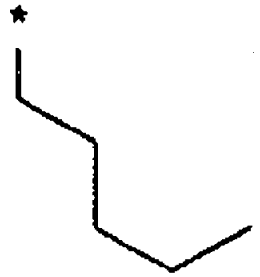
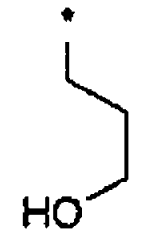
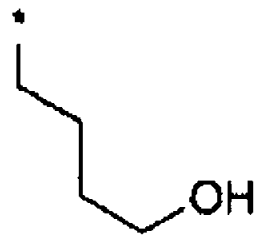
224		8-cloro-3-(2-metilpropil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	2.0	444	2.99
225		8-cloro-3-(3-metilbutil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	1.6	458	3.21
226		8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona	2.1	498	3.07
227		8-cloro-3-[2-(feniloxi)etil]-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	1.7	508	3.11
228		8-cloro-3-[3-(metiloxi)propil]-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	1.0	460	2.65

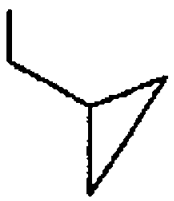
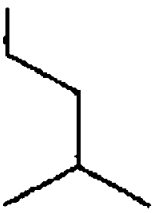
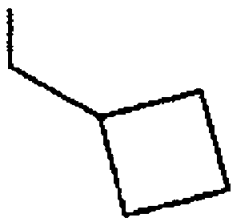
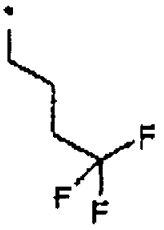
Los siguientes compuestos (cuadro 19) se preparan por el método análogo al del ejemplo 221, a partir de 8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona y el agente de alquilación apropiado.

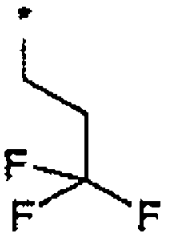
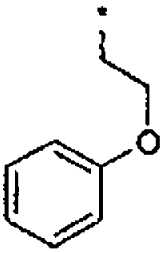
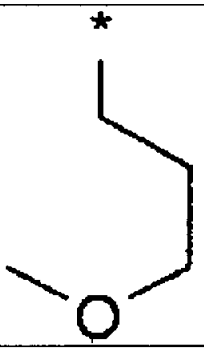
CUADRO 19



Ej.	R=	Nombre	Rend, (mg)	m/z	RT (min)
229		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-metil-3,7-dihidro-1H-purina-2,6-diona	1.7	437	2.92
230		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-etil-3,7-dihidro-1H-purina-2,6-diona	1.4	451	3.06

231		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	2.2	465	3.22
232		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	2.6	493	3.54
233		8-cloro-1-(3-[3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il]propil)-3-(2-hidroxietil)-3,7-dihidro-1H-purina-2,6-diona	2.7	467	2.72
234		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3-hidroxipropil)-3,7-dihidro-1H-purina-2,6-diona	2.0	481	2.77
235		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(4-hidroxibutil)-3,7-dihidro-1H-purina-2,6-diona	1.4	495	2.80

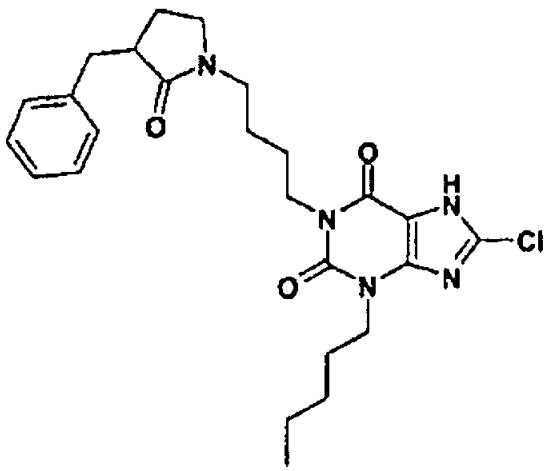
236		8-cloro-3-(ciclopropilmetil)-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	1.8	477	3.30
237		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(2-metilpropil)-3,7-dihidro-1H-purina-2,6-diona	3.5	479	3.36
238		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3-metilbutil)-3,7-dihidro-1H-purina-2,6-diona	3.1	493	3.53
239		8-cloro-3-(ciclobutilmetil)-1-(3-[3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1H-purina-2,6-diona	2.2	491	3.45
240		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-purina-2,6-diona	3.0	533	3.39

241		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-purina-2,6-diona	2.7	519	3.34
242		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(feniloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	1.6	543	3.44
243		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	2.8	495	3.11
244		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	2.6	481	2.98
245		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[3-(metiloxi)propil]-3,7-dihidro-1H-purina-2,6-diona	2.1	495	3.04

EJEMPLO 246

8-cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

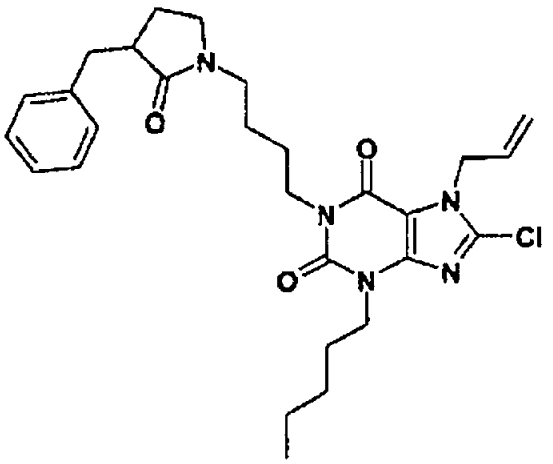
a) 8-cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona



Una solución de 8-cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (0.35 g, 0.67 mmol), $Pd(PPh_3)_4$ (0.082 g, 0.07 mmol) y morfolina (0.6 ml, 6.7 mmol) en THF (10 ml) se desgasifica (evacuación consecutiva seguida por la adición de nitrógeno x 3) después se agita durante 4 horas. La solución después se carga en un SPE de aminopropilo (5 g) y se eluye primero con MeOH después AcOH/MeOH al 5% para proveer el compuesto del titulo que contiene una impureza pequeña. La purificación adicional sobre sílice (SPE de 10 g, elusión de gradiente éter/acetato de etilo 1:0 a 0:1) proporciona el compuesto del titulocomo un aceite claro (0.10 g, 31%).

LC/EM: m/z 486 $[MH]^+$.

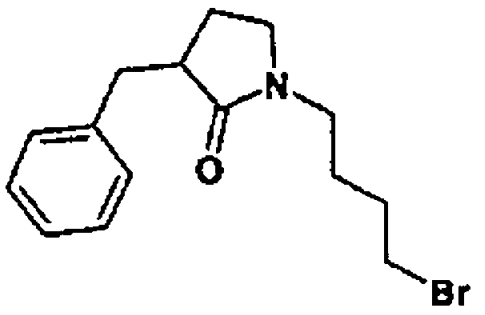
b) 8-cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona



Se prepara con 8-cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona usando 1-(4-bromobutil)-3-(fenilmetil)-2-pirrolidinona como el agente de alquilación, carbonato de potasio como base y se calienta a 50°C durante 18 horas. Rendimiento 86%.

LC/EM: m/z 526 $[MH]^+$.

c) 1-(4-bromobutil)-3-(fenilmetil)-2-pirrolidinona



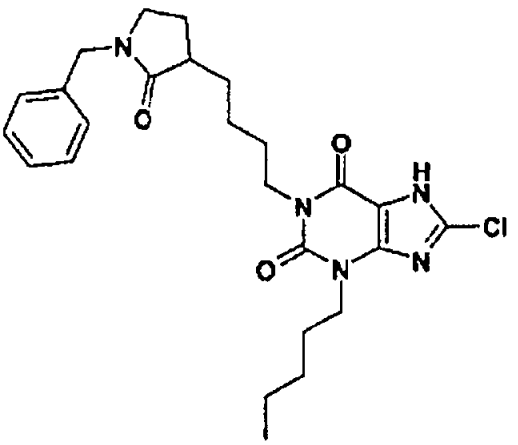
A una solución de 3-(fenilmetil)-2-pirrolidinona (0.23 g, 1.3 mmol) y 1,4-dibromobutano (0.57 g, 4.2 mmol) en DMF (5 ml) se añade t-butóxido de sodio (0.151 g, 1.6 mmol) y la solución se agita durante 18 horas. La solución se concentra y a los residuos se les realiza la cromatografía sobre sílice (SPE de 20 g, eluyendo primero con ciclohexano después con DCM) para proporcionar el compuesto del titulo como un aceite incoloro que contiene una traza de DMF (0.25 g. 61%).

LC/EM: m/z 311 $[MH]^+$.

EJEMPLO 247

8-cloro-1-{4-[2-oxo-1-(fenilmetil)-3-pirrolidinil]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

a) 8-cloro-1-{4-[2-oxo-1-(fenilmetil)-3-pirrolidinil]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

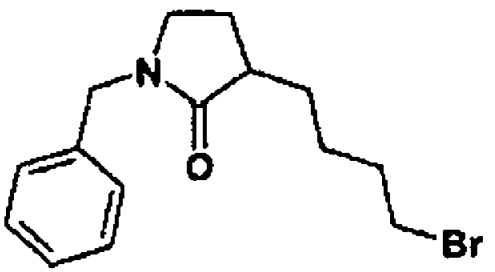


A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (0.086 g, 0.29 mmol) y 3-(4-bromobutil)-1-(fenilmetil)-2-pirrolidinona (0.17 g, 0.55 mmol, mezcla 1:1 con 2-(fenilmetil)-2-azaspiro[4,4]nonan-1-ona) en THF (5 ml) se añade carbonato de potasio (0.08 g, 0.58 mmol) y la mezcla se calienta y se agita a 50°C durante 18 horas. La solución se deja enfriar después se desgasifica (evacuación secuencial seguida por la adición de nitrógeno x 3) y $Pd(PPh_3)_4$ (0.09 g, 0.077 mmol) seguido por morfolina (0.2 ml, 2.2 mmol) se añade y la solución se agita a temperatura ambiente durante 18 horas. La solución se separa entre acetato de etilo y HCl dil y los orgánicos se lavan con salmuera, se secan y se

concentran. La purificación de los residuos usando un SPE de aminopropilo (5 g) eluyendo con MeOH después AcOH/MeOH al 5% produciendo el compuesto del titulo como un aceite amarillo que se cristaliza y se deja reposar bajo éter (0.031 g, 22%).

LC/EM: m/z 486 $[MH]^+$.

b) 3-(4-bromobutil)-1-(fenilmetil)-2-pirrolidinona

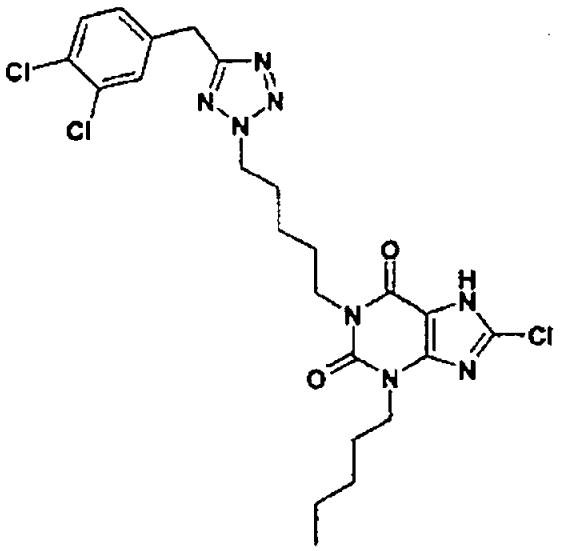


A una solución de 1-(fenilmetil)-2-pirrolidinona (0.47 g, 2.7 mmol) en THF (10 ml) a -78°C se añade hexametildisililazina de litio (2.8 ml, 2.7 mmol, solución 1M) alreddor de 5 minutos. Después de 15 minutos se añade 1,4-dibromobutano (0.32 ml, 2.7 mmol) y la solución se deja unir a temperatura ambiente alrededor de 2 horas después se agita durante 18 horas adicionales. La solución se separa entre acetato de etilo y agua y los orgánicos se aíslan, se secan y se concentran. La cromatografía de sobre sílice (SPE 20 g) eluyendo con ciclohexano después DCM y finalmente el éter provee un aceite claro que es una mezcla 1:1 del compuesto del titulo y 2-(fenilmetil)-2-azaspiro[4,4]nonan-1-ona (0.17 g). Este se usa en la siguiente etapa sin purificación adicional.

LC/EM: m/z 310, 312 $[MH]^+$.

EJEMPLO COMPARATIVO C

8-cloro-1-(5-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}pentil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona



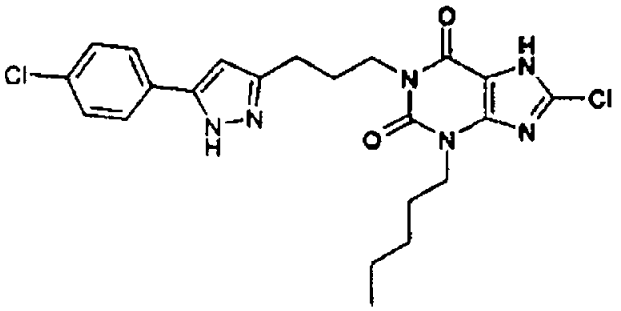
A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona(0.18 g, 0.61 mmol) en THF (5 ml) se añade 5-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}-1-pentanol (0.191 g, 0.61 mmol; se prepara en manera similar al ejemplo 35), trifenilfosfina (0.36 g, 1.3 mmol) y finalmente dibencilazodicarboxilato (0.40 g, 1.3 mmol). La solución se agita durante 18 horas después de lo cual se añade $Pd(PPh_3)_4$ (0.16 g, 0.137 mmol) seguido por morfolina (0.75 ml, 8.3 mmol) y la solución se agita a temperatura ambiente durante 6 horas. La solución se carga en un SPE de aminopropilo (5 g) y se eluye con MeOH después AcOH/MeOH al 5% para producir el compuesto del titulo que contiene impurezas menores. La cromatografía

adicional (SPE de sílice, 20 g) eluyendo con éter produciendo el compuesto del titulo como un sólido blanco (0.061 g, 18%).

LC/EM: m/z 553 $[MH]^+$.

EJEMPLO 248

8-cloro-1-{3-[5-(4-clorofenil)-1H-pirazol-3-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

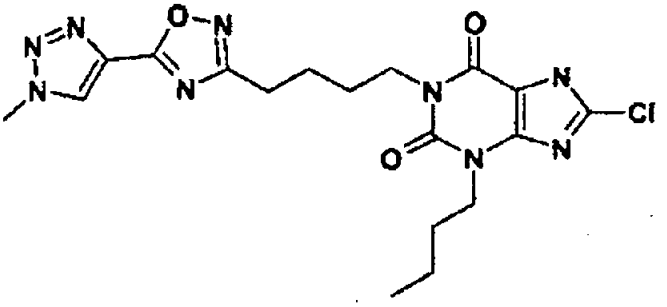


Se prepara con 8-cloro-1-(5-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}pentil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona (ejemplo comparativo C) usando 3-[5-(4-clorofenil)-1H-pirazol-3-il]-1-propanol. El material de producto final se lava con éter para producir el compuesto del titulo como un sólido crema (30%).

LC/EM m/z 475 $[MH]^+$

EJEMPLO 249

3-butil-8-cloro-1-{4-[5-(1-metil-1H-1,2,3-triazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona

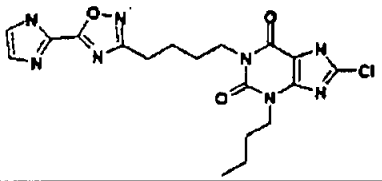
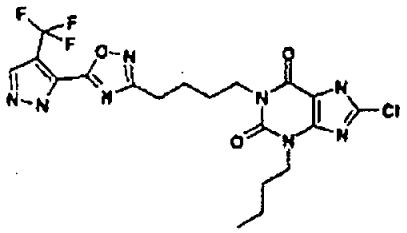
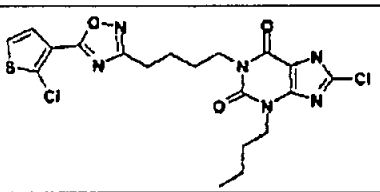
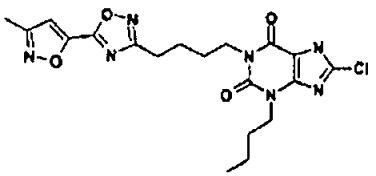
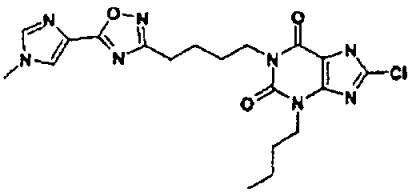
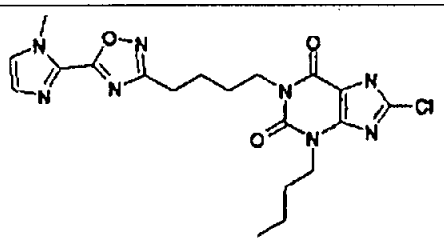


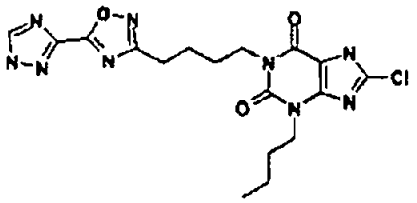
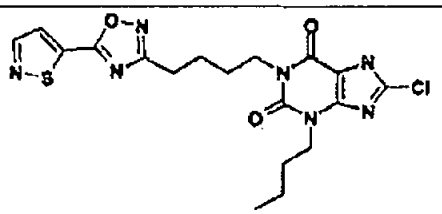
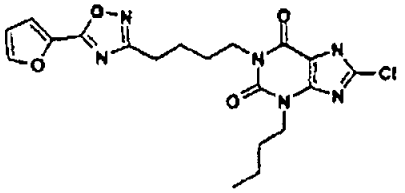
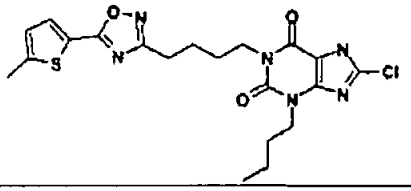
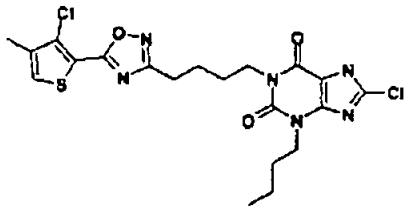
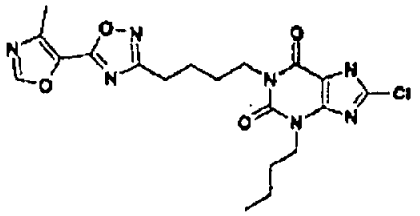
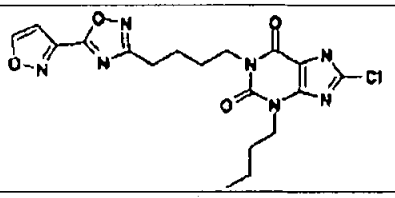
Una solución de acido 1-metil-1H-1,2,3-triazol-4-carboxílico 818 mg, 0.14 mmol) en DMF (0.5 ml) se trata con CDI (23 mg, 0.14 mmol) a temperatura ambiente durante 1 hora. Una solución de (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.14 mmol) en DMSO (0.4 ml) se añade a la mezcla después se calienta a 100°C durante 18 horas. La mezcla de reacción se purifica mediante MDAP para proporcionar el compuesto del titulo como un sólido blanco (18 mg).

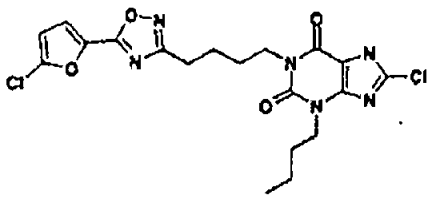
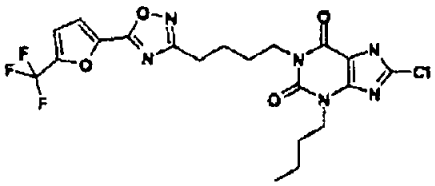
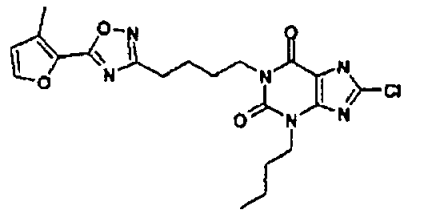
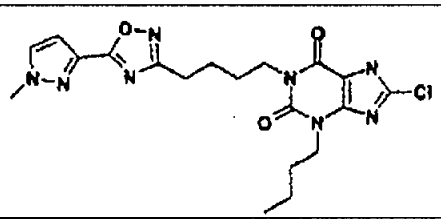
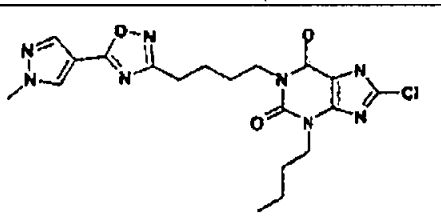
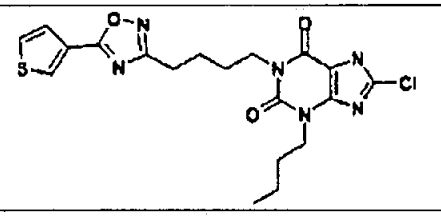
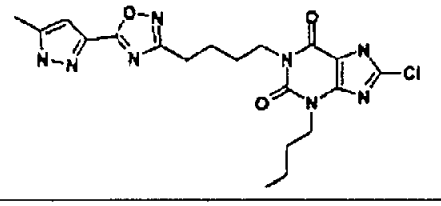
LC/EM: m/z 448 $[MH]^+$, temperatura ambiente 2-86 minutos.

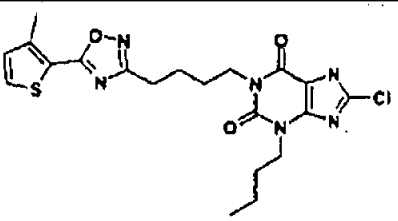
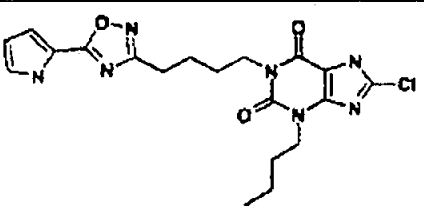
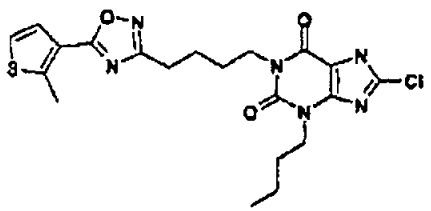
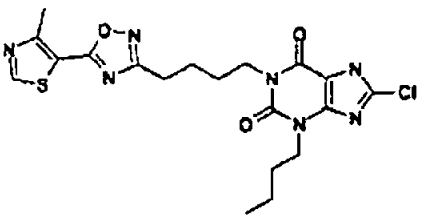
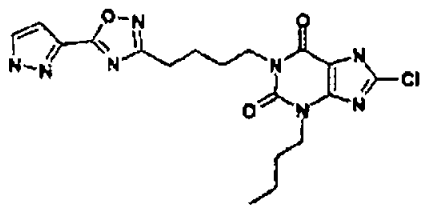
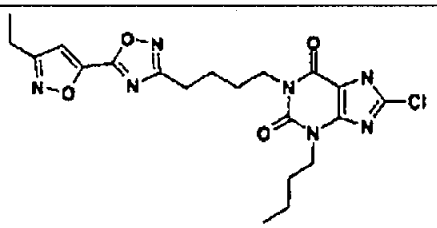
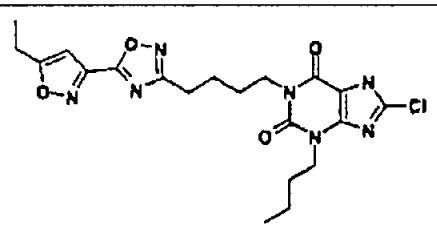
Los siguientes compuestos (cuadro 20) se preparan usando un método análogo al del ejemplo 249, usando el ácido carboxílico apropiado.

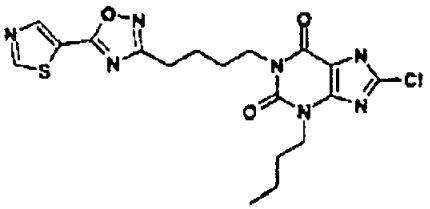
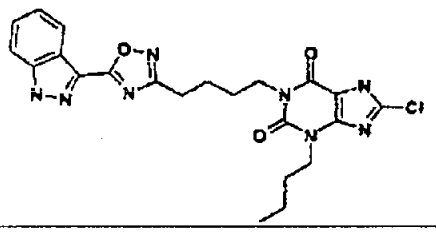
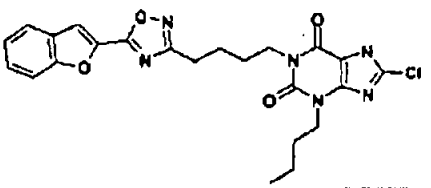
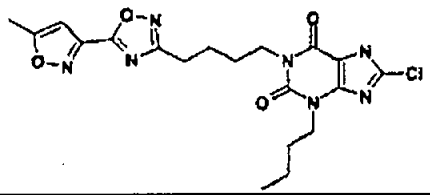
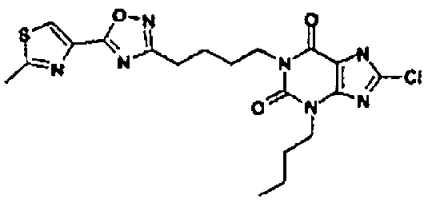
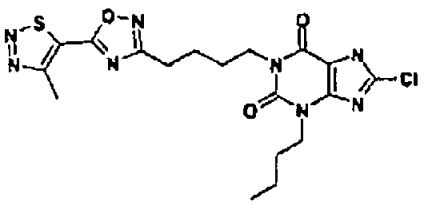
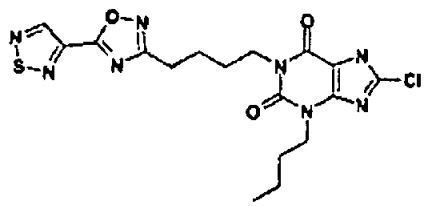
CUADRO 20

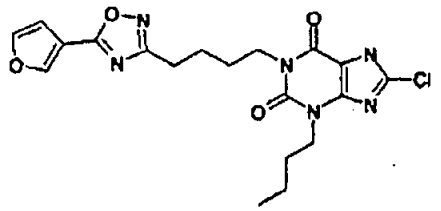
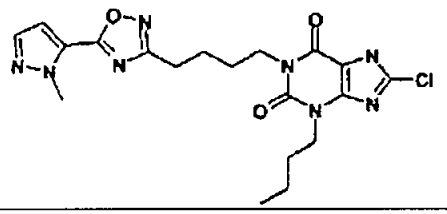
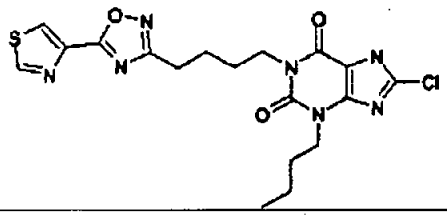
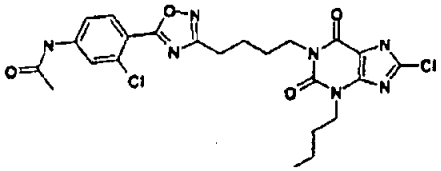
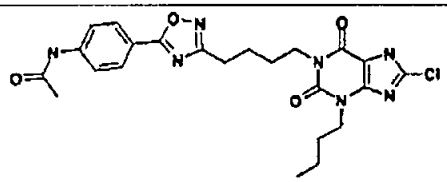
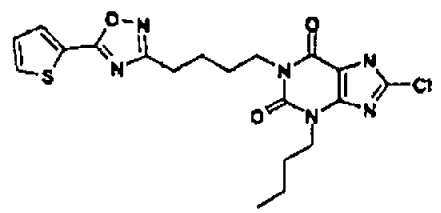
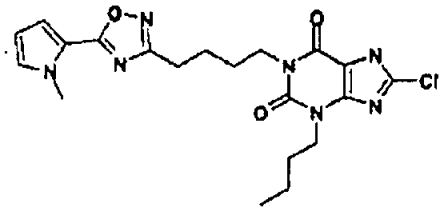
Ej.	Estructura	Nombre	Rend (mg)	LC/EM
250		3-butil-8-cloro-1-{4-[5-(1H-imidazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	16	m/z 433 $[MH]^+$ RT 2.79 min.
251		3-butil-8-cloro-1-(4-{5-[4-(trifluorometil)-1H-pirazol-5-il]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purina-2,6-diona	19	m/z 501 $[MH]^+$ RT 3.28 min.
252		3-butil-8-cloro-1-{4-[5-(2-cloro-3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	26	m/z 483 $[MH]^+$ RT 2.59 min.
253		3-butil-8-cloro-1-(4-[5-(3-metil-5-isoxazolil)-1,2,4-oxadiazol-3-il]butil)-3,7-dihidro-1H-purina-2,6-diona	25	m/z 448 $[MH]^+$ RT 3.21 min.
254		3-butil-8-cloro-1-(4-[5-(1-metil-1H-imidazol-4-il)-1,2,4-oxadiazol-3-il]butil)-3,7-dihidro-1H-purina-2,6-diona	16	m/z 447 $[MH]^+$ RT 2.74 min.
255		3-butil-8-cloro-1-(4-[5-(1-metil-1H-imidazol-2-il)-1,2,4-oxadiazol-3-il]butil)-3,7-dihidro-1H-purina-2,6-diona	9	m/z 447 $[MH]^+$ RT 2.91 min.

256		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-purina-2,6-diona	10	m/z 434 $[MH]^+$ RT 2.73 min.
257		3-butil-8-cloro-1-{4-[5-(5-isotiazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	17	m/z 450 $[MH]^+$ RT 3.34 min.
258		3-butil-8-cloro-1-{4-[5-(2-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	26	m/z 433 $[MH]^+$ RT 3.27min.
259		3-butil-8-cloro-1-{4-[5-(5-metil-2-tienil) -1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	29	m/z 463 $[MH]^+$ RT 3.61 min.
260		3-butil-8-cloro-1-{4-[5-(3-cloro-4-metil-2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	30	m/z 497 $[MH]^+$ RT 3.76 min.
261		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-purina-2,6-diona	25	m/z 448 $[MH]^+$ RT 3.13 min.
262		3-butil-8-cloro-1-{4-[5-(3-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	23	m/z 434 $[MH]^+$ RT 3.20 min.

263		3-butil-8-cloro-1-{4-[5-(5-cloro-2-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	27	m/z 467 $[MH]^+$ RT 3.51 min.
264		3-butil-8-cloro-1-(4-{5--[5-(trifluorometil)-2-furanil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purina-2,6-diona	27	m/z 501 $[MH]^+$ RT 3.61 min.
265		3-butil-8-cloro-1-{4-[5-(3-metil-2-furanil) - 1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	27	m/z 447 $[MH]^+$ RT 3.43 min.
266		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	25	m/z 447 $[MH]^+$ RT 3.02 min.
267		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	8	m/z 447 $[MH]^+$ RT 2.99 min.
268		3-butil-8-cloro-1-{4-[5-(3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	19	m/z 449 $[MH]^+$ RT 3.43 min.
269		3-butil-8-cloro-1-{4-[5-(5-metil-1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	26	m/z 447 $[MH]^+$ RT 3.03 min.

270		3-butil-8-cloro-1-{4-[5-(3-metil-2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	27	m/z 463 $[MH]^+$ RT 3.62 min.
271		3-butil-8-cloro-1-{4-[5-(1H-pirrol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	13	m/z 432 $[MH]^+$ RT 3.26 min.
272		3-butil-8-cloro-1-{4-[5-(2-metil-3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	18	m/z 463 $[MH]^+$ RT 3.64 min.
273		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-purina-2,6-diona	24	m/z 464 $[MH]^+$ RT 3.26 min.
274		3-butil-8-cloro-1-{4-[5-(1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	20	m/z 433 $[MH]^+$ RT 3.00 min.
275		3-butil-8-cloro-1-{4-[5-(3-etil-5-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	20	m/z 462 $[MH]^+$ RT 3.43 min.
276		3-butil-8-cloro-1-{4-[5-(5-etil-3-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	23	m/z 462 $[MH]^+$ RT 3.46 min.

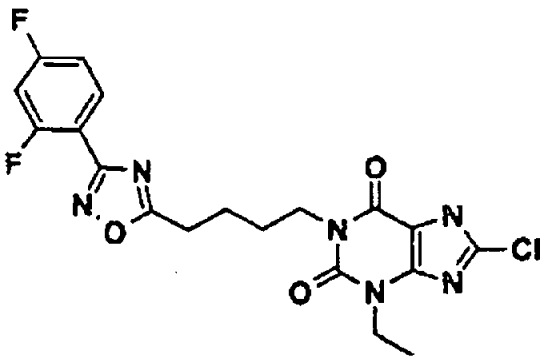
277		3-butil-8-cloro-1-{4-[5-(1,3-tiazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	20	m/z 450 $[MH]^+$ RT 3.13 min.
278		3-butil-8-cloro-1-{4-[5-(1H-indazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	24	m/z 483 $[MH]^+$ RT 3.50 min.
279		1-{4-[5-(1-benzofuran-2-il)-1,2,4-oxadiazol-3-il]butil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	6	m/z 483 $[MH]^+$ RT 3.72 min.
280		3-butil-8-cloro-1-(4-[5-{5-metil-3-isoxazol}-1,2,4-oxadiazol-3-il]butil)-3,7-dihidro-1H-purina-2,6-diona	13	m/z 448 $[MH]^+$ RT 3.30 min.
281		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-purina-2,6-diona	20	m/z 464 $[MH]^+$ RT 3.14 min.
282		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-purina-2,6-diona	14	m/z 465 $[MH]^+$ RT 3.40 min.
283		3-butil-8-cloro-1-{4-[5-(1,2,5-tiadiazol-3-il)-1,2,4-oxadiazol-3-il]butil-3,7-dihidro-1H-purina-2,6-diona	24	m/z 451 $[MH]^+$ RT 3.27 min.

284		3-butil-8-cloro-1-{4-[5-(3-furani)-1,2,4-oxadiazol-3-il]butil}3,7-dihidro-1H-purina-2,6-diona	21	m/z 433 $[MH]^+$ RT 3.29 min.
285		3-butil-8-cloro-1-{4-[5-(1-metil-1H-)-pirazol-5-il]-1,2,4-oxadiazol-3-il}butil}-3,7-dihidro-1H-purina-2,6-diona	23	m/z 447 $[MH]^+$ RT 3.22 min.
286		3-butil-8-cloro-1-{4-[5-(1,3-tiazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	20	m/z 450 $[MH]^+$ RT 3.06 min.
287		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 $[MH]^+$ RT 3.44 min.
288		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 $[MH]^+$ RT 3.23 min.
289		3-butil-8-cloro-1-{4-[5-(2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	27	m/z 449 $[MH]^+$ RT 3.45 min.
290		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirrol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	15	m/z 446 $[MH]^+$ RT 3.45 min.

EJEMPLO 291

8-cloro-1-{4-[3-(2,4-difluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-etil-3,7-dihidro-1H-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-1H-purina-2,6-diona

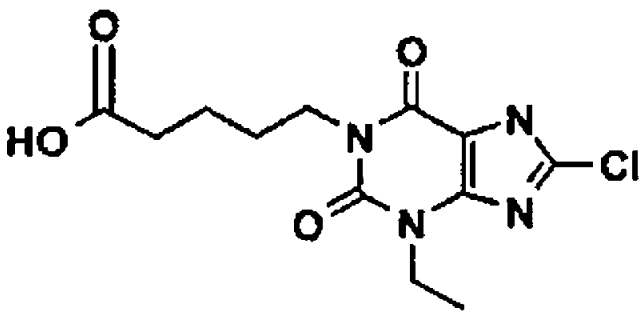


Una solución de ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico (0.05 g, 0.16 mmol) en DMSO (1 ml) se trata con CDI (0.029 g, 0.18 mmol) y la mezcla se agita a temperatura ambiente durante 1 hora. Consecutivamente, la mezcla se trata con 2,4-difluorobenzamidoxima (0.03 g, 0.18 mmol) y después se calienta a 120°C durante 30 minutos. El producto se purifica a partir de la mezcla cruda usando MDAP. Las fracciones que contienen el producto se evaporan usando una corriente de nitrógeno y la goma incolora resultante triturada en éter y se seca para revelar el compuesto del titulo como un soliod blanco (50 mg, 70%).

LC/EM: m/z 451 $[MH]^+$, temperatura ambiente 2.23 minutos.

230

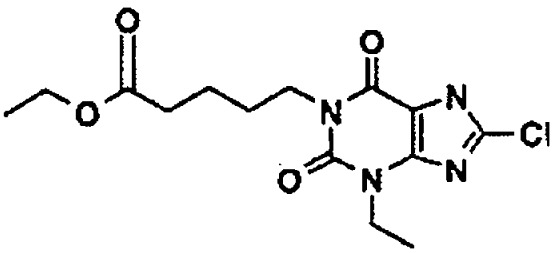
b) ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico



Una solución de 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (2.3 g, 6.7 mmol) en metanol (75 ml) se trata con agua (3 ml) e hidróxido de litio (0.481 g, 20.1 mmol) y la mezcla se agita a 40°C durante 17 horas. La mezcla se evapora a sequedad y el residuo se trata con 50 ml de acetato de etilo y 50 ml de agua. Las 2 fases se separan y la fase acuosa se ajusta a pH 5 usando ácido clorhídrico acuoso el producto precipitado se filtra y se seca para producir ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico como un sólido blanco (1.99 g, 95%).

LC/EM: m/z 315 $[MH]^+$, temperatura ambiente 2.34 minutos.

c) 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo

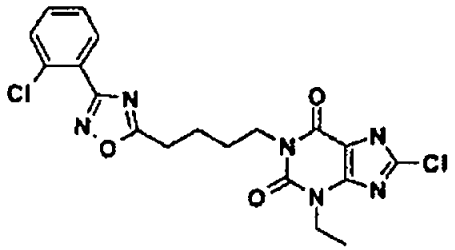
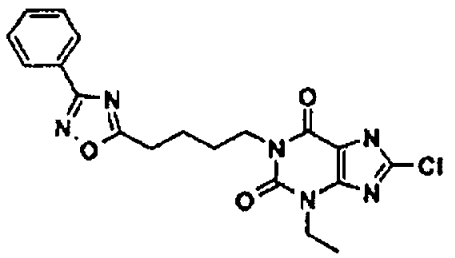
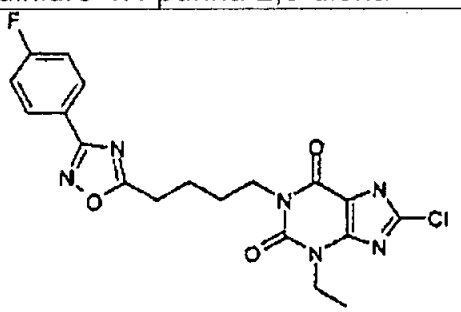


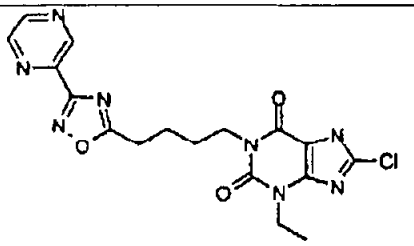
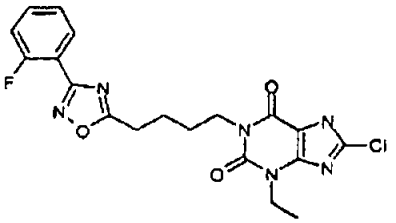
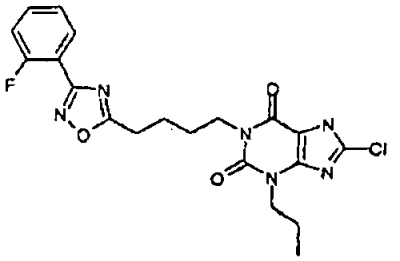
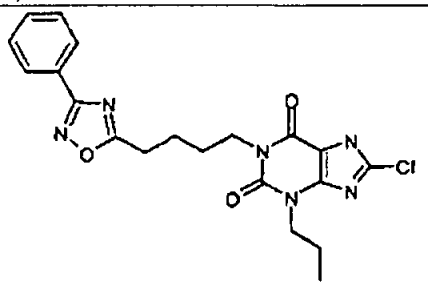
Una solución de 8-cloro-7-(2-propen-1-il)-3-etil-3,7-dihidro-1H-purina-2,6-diona (3g, 11.8 mmol) en DMF (40 ml) se trata con carbonato de potasio (1.9 g, 14.1 mmol) y 5-bromopentanoato de etilo (2.24 ml, 14.1 mmol) y la mezcla se calienta en una atmósfera de nitrógeno a 70°C durante 5 horas y después se enfría. La mezcla se desgasifica por la aplicación repetida de vacío seguido por el rellenado con gas de nitrógeno y después se trata con tetraquis(trifenilfosfina)paladio (0) (1.36 g, 1.1 mmol) y morfolina (10.3 ml, 118 mmol). La mezcla se agita en una atmósfera de nitrógeno durante 4 horas y después se evapora a sequedad. El residuo se divide entre 100 ml de acetato de etilo y 100 ml de agua. La fase acuosa se re-extrae con 100 ml de acetato de etilo y los orgánicos combinados se secan sobre sulfato de magnesio, se filtran y se evaporan. El residuo se tritura en dietiléter, se filtra y se seca para revelar 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%).

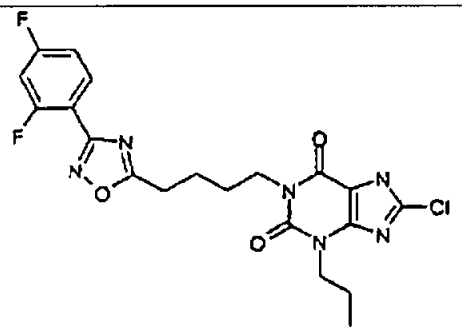
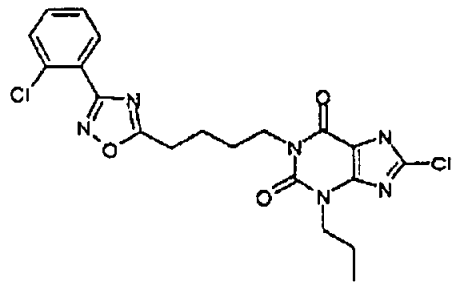
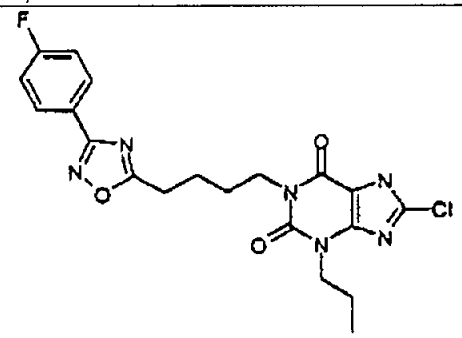
LC/EM: m/z 343 $[MH]^+$, temperatura ambiente 2.73 minutos.

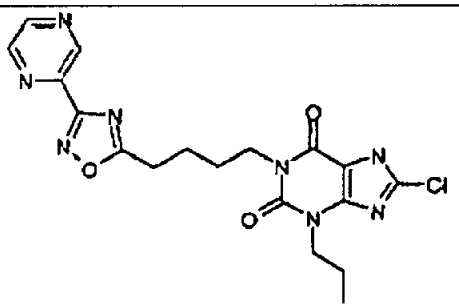
Los siguientes compuestos (cuadro 21) se preparan por un método análogo al del ejemplo 291.

CUADRO 21

Ej.	Estructura	Precursor	Rend. (mg)	LC/EM
292	 8-cloro-1-{4-[3-(2-clorofenil)-1,2,4-oxadiazol-5-il]butil}-3-etil-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	33	m/z 449 $[MH]^+$ RT 3.27 min.
293	 8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3-etil-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	32	m/z 415 $[MH]^+$ RT 3.22 min.
294	 8-cloro-3-etil-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purin-2,6-diona	Ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	31	m/z 433 $[MH]^+$ RT 3.26 min.

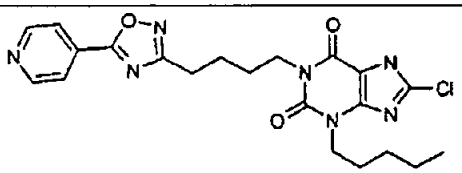
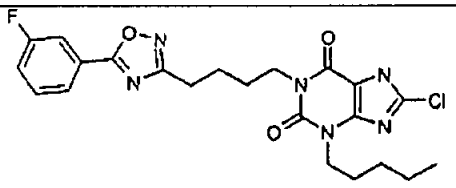
295	 8-cloro-3-etil-1-{4-[3-(2-pirazinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	2	m/z 417 $[MH]^+$ RT 2.54 min.
296	 8-cloro-3-etil-1-{4-[3-(2-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	38	m/z 433 $[MH]^+$ RT 3.12 min.
297	 8-cloro-1-{4-[3-(2-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	29	m/z 447 $[MH]^+$ RT 3.28 min.
298	 8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol.5.il)butil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	11	m/z 429 $[MH]^+$ RT 3.35 min.

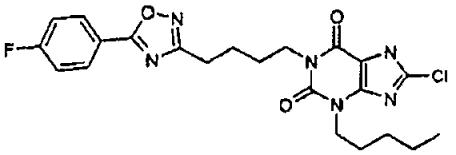
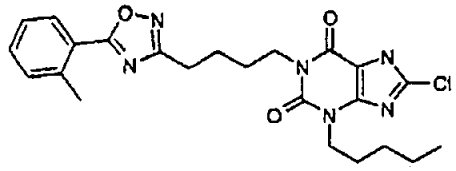
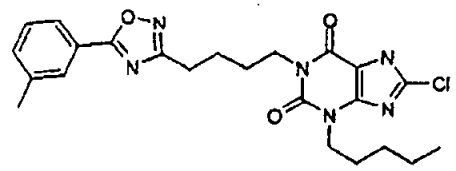
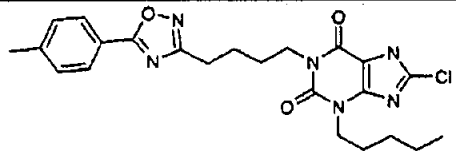
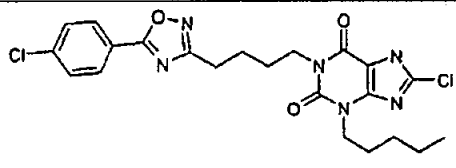
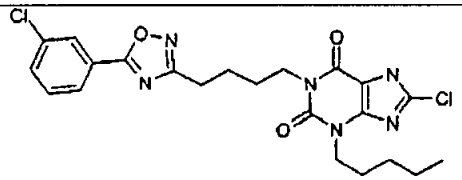
299	 8-cloro-1-{4-[3-(2,4-difluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	32	m/z 465 $[MH]^+$ RT 3.40 min.
300	 8-cloro-1-{4-[3-(2-clorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H--purina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	25	m/z 463 $[MH]^+$ RT 3.40 min.
301	 8-cloro-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1Hpurina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	26	m/z 447 $[MH]^+$ RT 3.44 min.

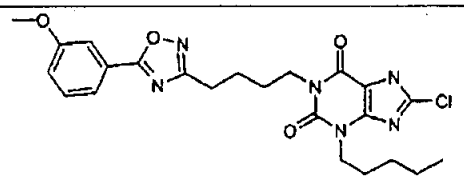
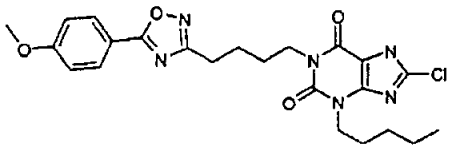
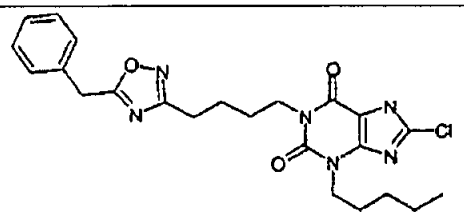
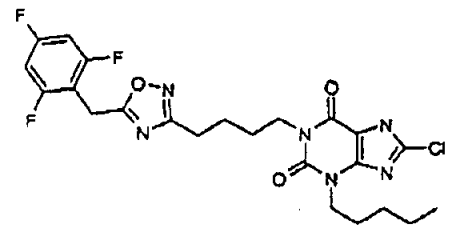
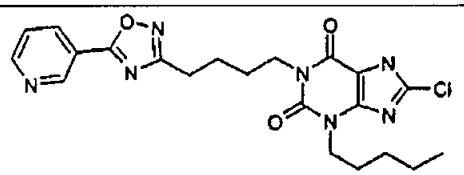
302	 8-cloro-3-propil-1-{4-[3-(2-pirazinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	Ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanóico	26	m/z 431 $[MH]^+$ RT 3.09 min.

Los siguientes compuestos (cuadro 22) se preparan usando un método análogo al del ejemplo 127, usando el ácido apropiado

CUADRO 22

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
303		8-cloro-3-pentil-1-{4-[5-(4-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	8.0	m/z 458 $[MH]^+$ RT 3.25 min.
304		8-cloro-1-{4-[5-(3-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	9.1	m/z 475 $[MH]^+$ RT 3.25 min.

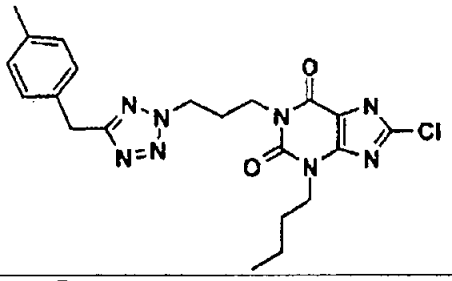
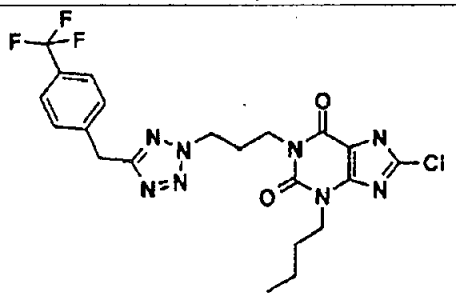
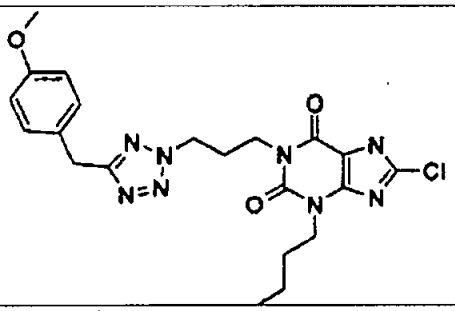
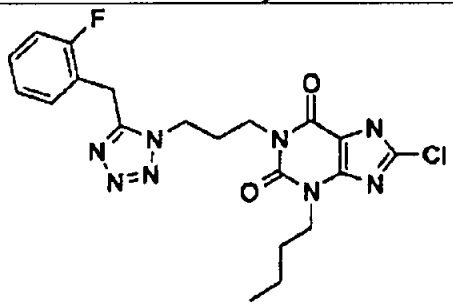
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
305		8-cloro-1-{4-[5-(4-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6,-diona	16.1	m/z 475 $[MH]^+$ RT 3.69 min.
306		8-cloro-1-{4-[5-(2-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	22.9	m/z 471 $[MH]^+$ RT 3.82 min.
307		8-cloro-1-{4-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	18.0	m/z 471 $[MH]^+$ RT 3.81 min.
308		8-cloro-1-{4-[5-(4-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	25.0	m/z 471 $[MH]^+$ RT 3.80 min.
309		8-cloro-1-{4-[5-(4-clorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	16.6	m/z 491 $[MH]^+$ RT 3.89 min.
310		8-cloro-1-{4-[5-(3-clorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	12.8	m/z 491 $[MH]^+$ RT 3.91 min.

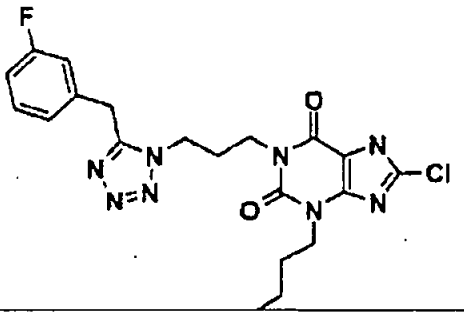
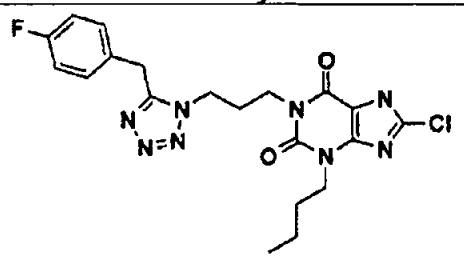
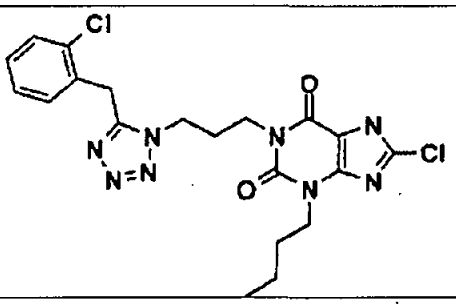
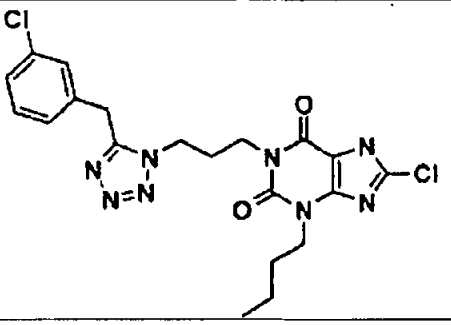
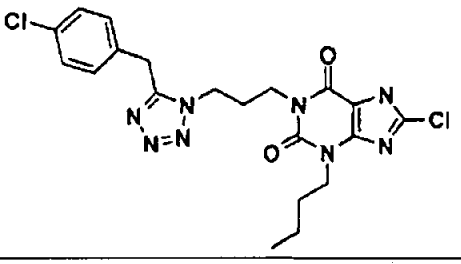
Ej.	Estructura	Precursor	Rend. (mg)	LC/EM
311		8-cloro-1-(4-{5-[3-(metiloxi)fenil]-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	23.0	m/z 487 $[MH]^+$ RT 3.71 min.
312		8-cloro-1-(4-{5-[4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	15.9	m/z 487 $[MH]^+$ RT 3.67 min.
313		8-cloro-3-pentil-1-(4-{5-(fenilmetil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	21.0	m/z 471 $[MH]^+$ RT 3.55 min.
314		8-cloro-3-pentil-1-(4-{5-[(2,4,6-trifluorofenil)metil]-1,2,4-oxadiazol-3-il9butil}-3,7-dihidro-1H-purina-2,6-diona		m/z 525 $[MH]^+$ RT 3.62 min.
315		8-cloro-3-pentil-1-(4-[5-(3-piridinil)-1,2,4-oxadiazol-3-il]butil)-3,7-dihidro-1H-purina-2,6-diona		m/z 458 $[MH]^+$ RT 3.23 min.

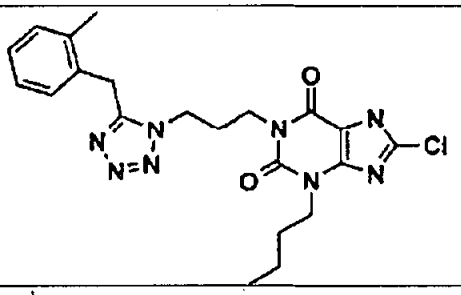
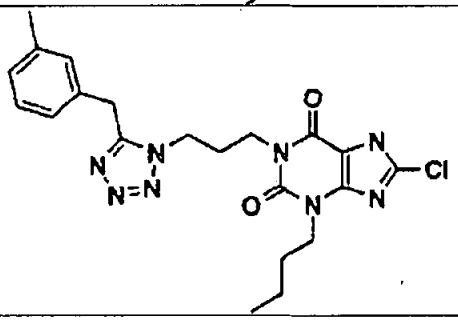
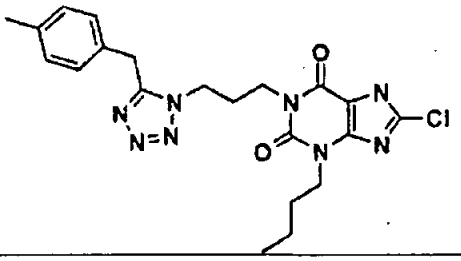
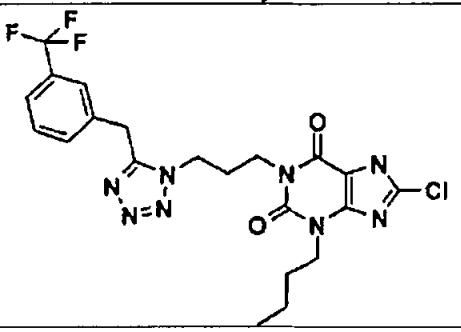
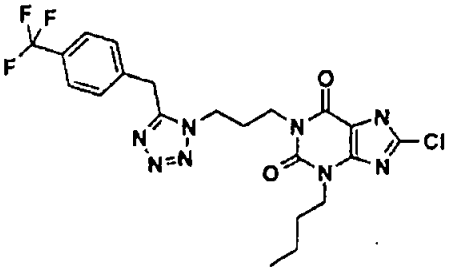
Los siguientes compuestos (cuadro 23) se preparan usando un método análogo al del ejemplo 19, usando el tetrazol apropiado y metanosulfonato de 3-[3-alquil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]propil. Se emplea MDAP para purificación adicional de aquellos compuestos insuficientemente puros siguiendo cromatografía de fase

normal

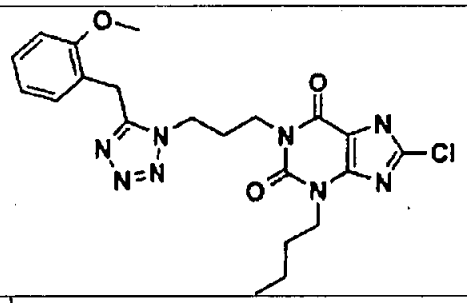
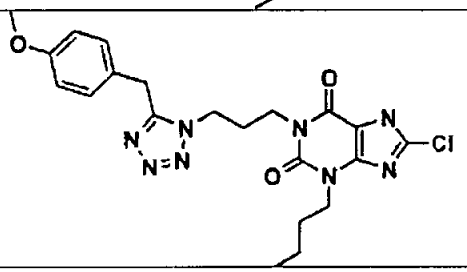
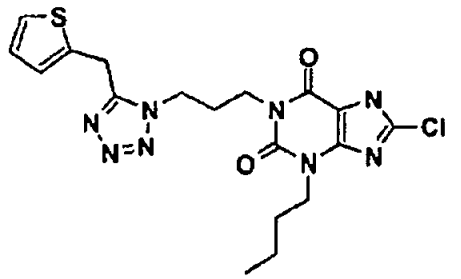
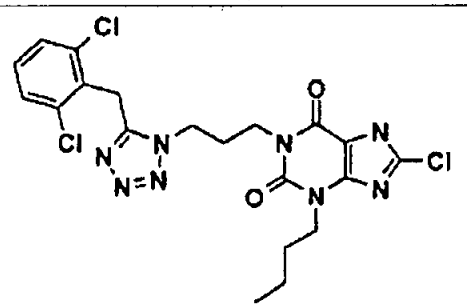
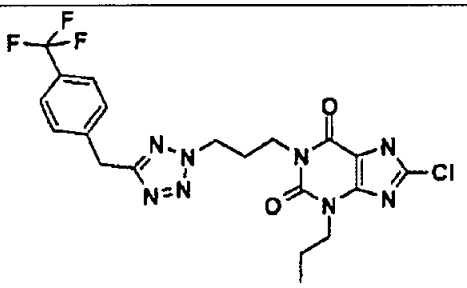
CUADRO 23

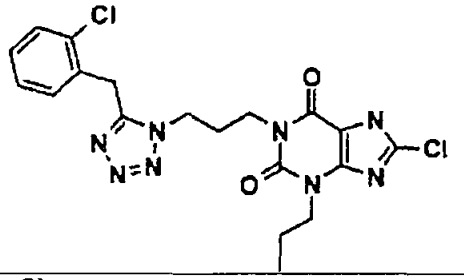
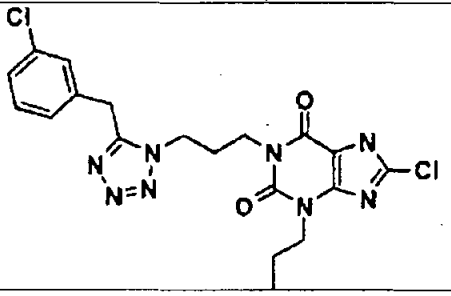
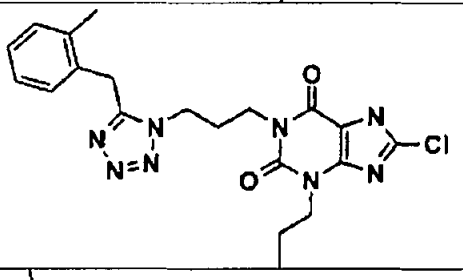
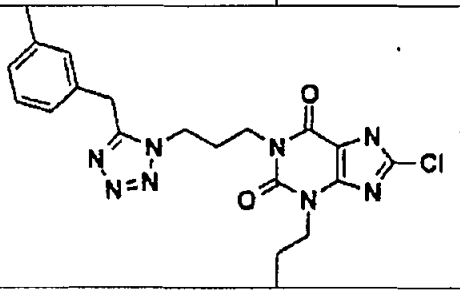
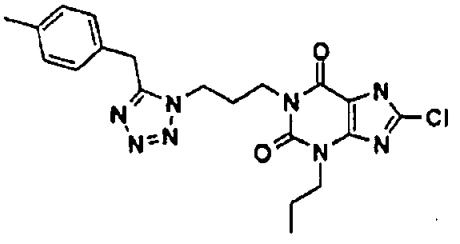
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
316		3-butil-8-cloro-1-(3-{5-[(4-metilfenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	35.1	m/z 457 $[MH]^+$ RT 3.40 min.
317		3-butil-8-cloro-1-(3-{5-[(4-(trifluorometil)fenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	43.6	m/z 511 $[MH]^+$ RT 3.52 min.
318		8-butil-8-cloro-1-[3-(5-{[4-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	38.2	m/z 473 $[MH]^+$ RT 3.24 min.
319		8-butil-8-cloro-1-[3-(5-{[2-fluorofenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	13.7	m/z 461 $[MH]^+$ RT 3.07 min.

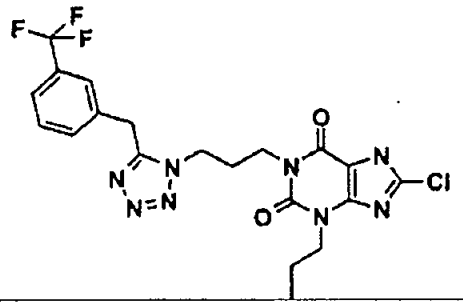
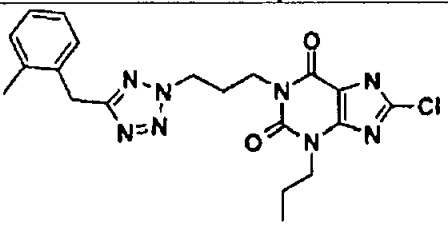
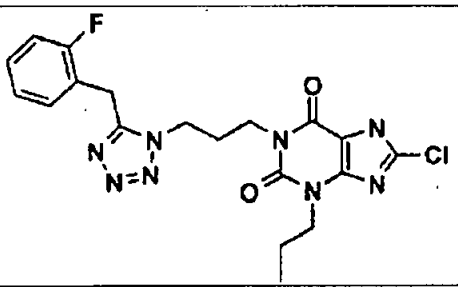
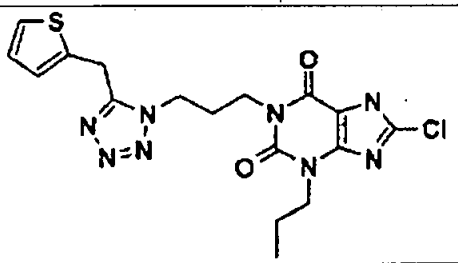
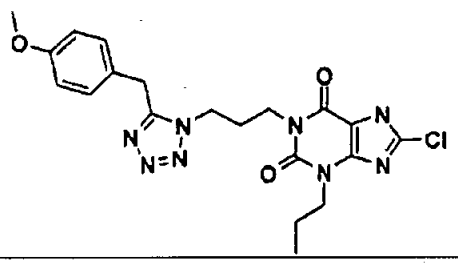
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
320		3-butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	15.0	m/z 461 $[MH]^+$ RT 3.10 min.
321		3-butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.7	m/z 461 $[MH]^+$ RT 3.10 min.
322		3-butil-8-cloro-1-(3-{5-[(2-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	8.4	m/z 477 $[MH]^+$ RT 3.17 min.
323		3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	16.4	m/z 477 $[MH]^+$ RT 3.23 min.
324		3-butil-8-cloro-1-(3-{5-[(4-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.0	m/z 477 $[MH]^+$ RT 3.24 min.

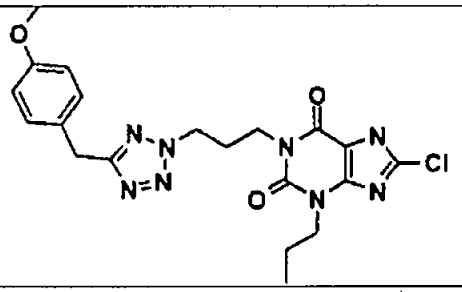
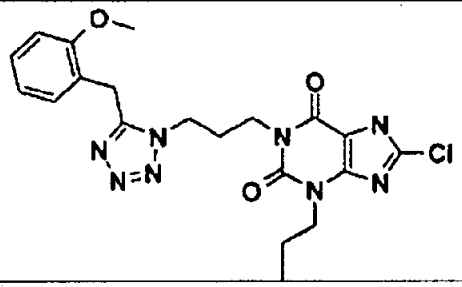
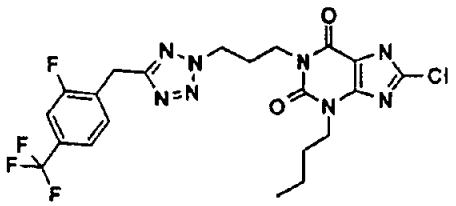
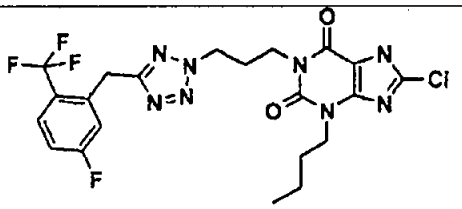
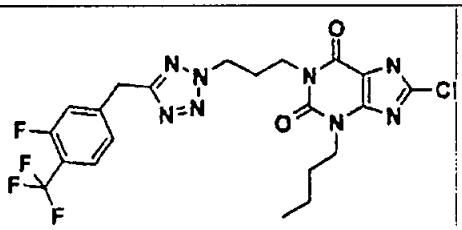
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
325		3-butil-8-cloro-1-(3-{5-[(2-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	15.1	m/z 457 $[MH]^+$ RT 3.15 min.
326		3-butil-8-cloro-1-(3-{5-[(3-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	18.6	m/z 457 $[MH]^+$ RT 3.18 min.
327		3-butil-8-cloro-1-(3-{5-[(4-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	16.3	m/z 457 $[MH]^+$ RT 3.19 min.
328		3-butil-8-cloro-1-(3-{5-[(3-trifluorometil)fenil]metil}-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.7	m/z 511 $[MH]^+$ RT 3.31 min.
329		3-butil-8-cloro-1-[3-(5-{[4-(trifluorometil)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	21.6	m/z 511 $[MH]^+$ RT 3.33 min.

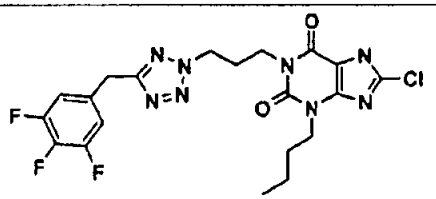
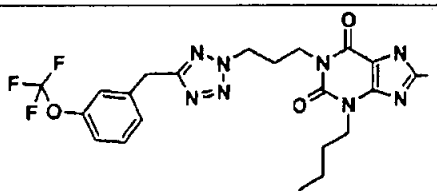
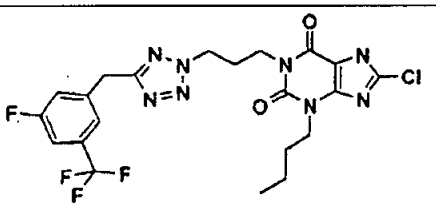
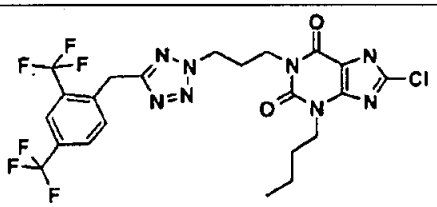
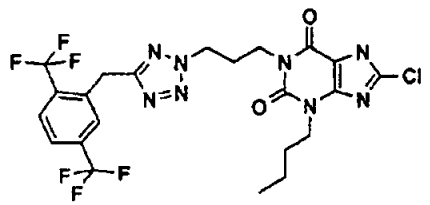
490

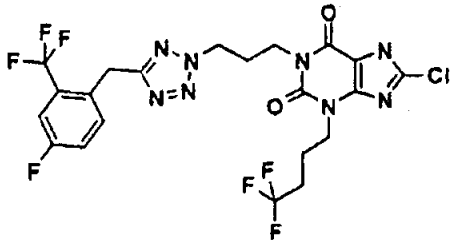
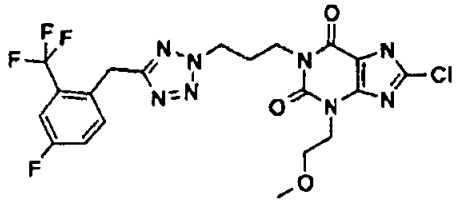
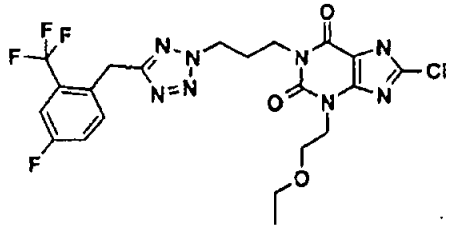
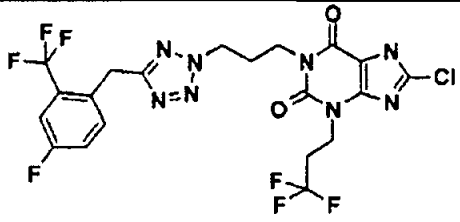
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
330		3-butil-8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	16.3	m/z 473 $[MH]^+$ RT 3.10 min.
331		3-butil-8-cloro-1-[3-(5-{[4-(metiloxi)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	20.8	m/z 473 $[MH]^+$ RT 3.05 min.
332		3-butil-8-cloro-1-{3-[5-(2-tienilmetil)-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	11.8	m/z 448 $[MH]^+$ RT 3.02 min.
333		3-butil-8-cloro-1-(3-{5-[(2,6-diclorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purina-2,6-diona	12.4	m/z 512 $[MH]^+$ RT 3.27 min.
334		8-cloro-1-3-propil-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	15.5	m/z 497 $[MH]^+$ RT 3.38 min.

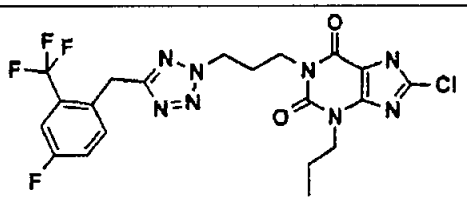
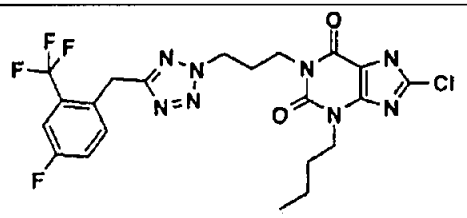
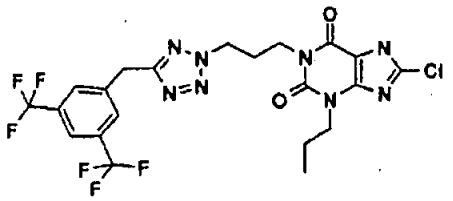
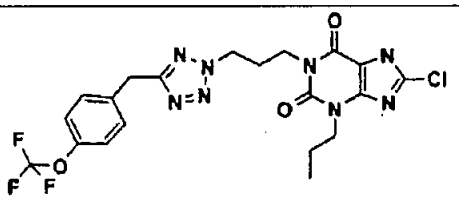
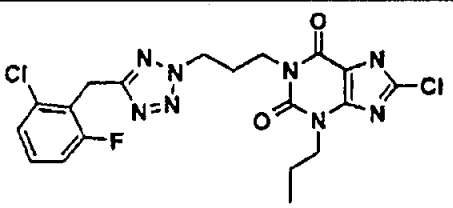
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
335		8-cloro-1-(3-{5-[(2-clorofenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	1.6	m/z 463 $[MH]^+$ RT 3.00 min.
336		8-cloro-1-(3-{5-[(3-clorofenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	7.1	m/z 463 $[MH]^+$ RT 3.06 min.
337		8-cloro-1-(3-{5-[(2-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	7.2	m/z 443 $[MH]^+$ RT 2.97 min.
338		8-cloro-1-(3-{5-[(3-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	5.7	m/z 443 $[MH]^+$ RT 3.01 min.
339		8-cloro-1-(3-{5-[(4-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	5.5	m/z 443 $[MH]^+$ RT 3.01 min.

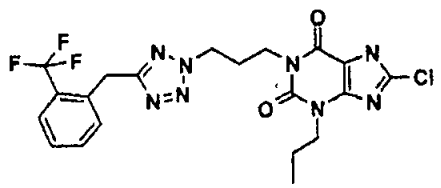
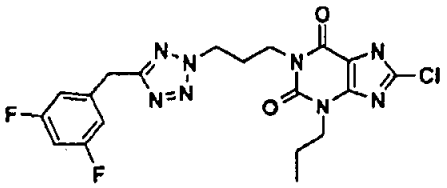
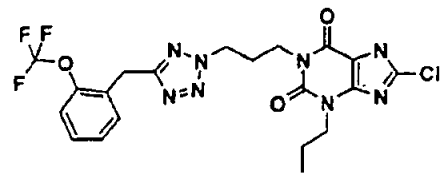
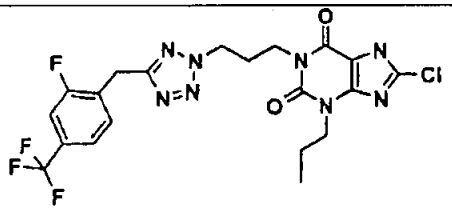
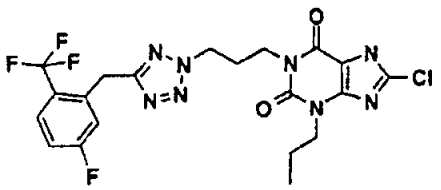
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
340		8-cloro-3-propil-1-[3-(5-{[3-(trifluorometil)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purina-2,6-diona	3.3	m/z 497 $[MH]^+$ RT 3.16 min.
341		8-cloro-1-(3-{5-[(2-metilfenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	24.1	m/z 443 $[MH]^+$ RT 3.20 min.
342		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	1.3	m/z 447 $[MH]^+$ RT 2.89 min.
343		8-cloro-3-propil-1-{3-[5-(2-tienilmetil)-1H-tetrazol-1-il]propil}-3,7-dihidro-1H-purina-2,6-diona	5.2	m/z 435 $[MH]^+$ RT 2.83 min.
344		8-cloro-1-[3-(5-{[4-(metiloxi)fenil]metil}-1H-tetrazol-1-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	1.2	m/z 459 $[MH]^+$ RT 2.87 min.

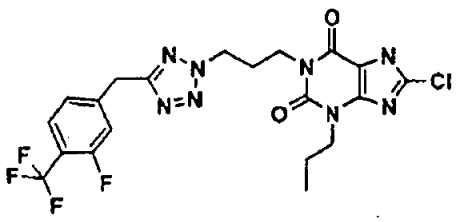
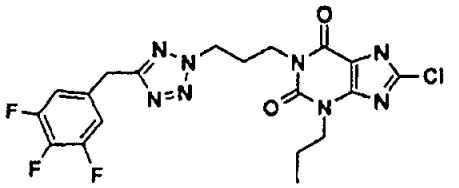
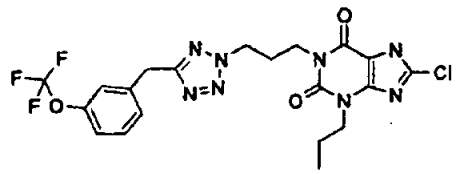
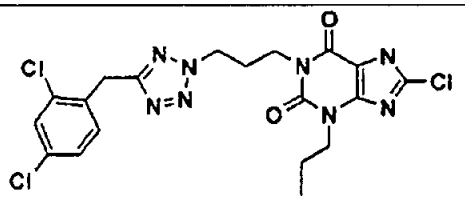
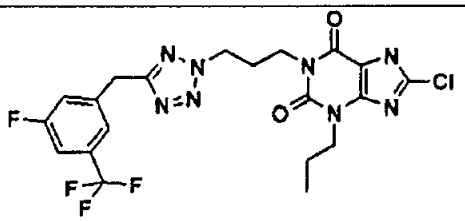
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
345		8-cloro-1-[3-(5-{[4-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	19.7	m/z 459 $[MH]^+$ RT 3.07 min.
346		8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-1H-tetrazol-1-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	1.9	m/z 459 $[MH]^+$ RT 2.92 min.
347		3-butil-8-cloro-1-[3-(5-{[2-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	24.5	m/z 529 $[MH]^+$ RT 3.22 min.
348		3-butil-8-cloro-1-[3-(5-{[5-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	25.3	m/z 529 $[MH]^+$ RT 3.51 min.
349		3-butil-8-cloro-1-[3-(5-{[3-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	11.5	m/z 529 $[MH]^+$ RT 3.56 min.

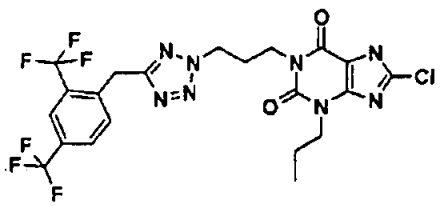
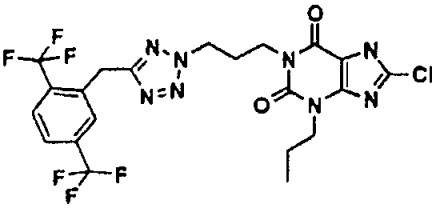
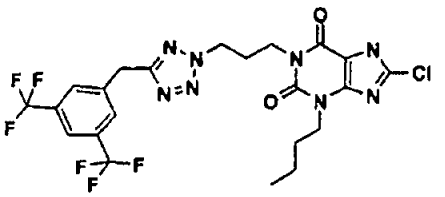
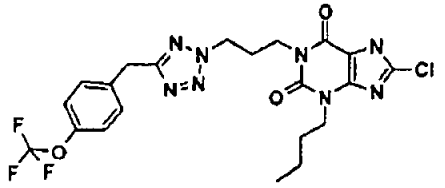
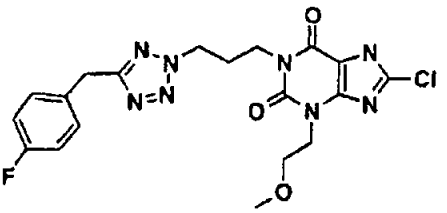
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
350		3-butil-8-cloro-1-(3-{5-[(3,4,5-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	19.4	m/z 497 $[MH]^+$ RT 3.45 min.
351		3-butil-8-cloro-1-{3-[5-({3-[(trifluorometil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	27.2	m/z 527 $[MH]^+$ RT 3.55 min.
352		3-butil-8-cloro-1-[3-(5-{[3-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	19.8	m/z 529 $[MH]^+$ RT 3.56 min.
353		1-[3-(5-{[2,4-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	36.6	m/z 579 $[MH]^+$ RT 3.72 min.
354		1-[3-(5-{[2,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	50.3	m/z 579 $[MH]^+$ RT 3.65 min.

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
355		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-purina-2,6-diona	25.0	m/z 583 $[MH]^+$ RT 3.50 min.
356		8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	23.0	m/z 531 $[MH]^+$ RT 3.16 min.
357		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	13.1	m/z 545 $[MH]^+$ RT 3.30 min.
358		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-purina-2,6,-diona	36.3	m/z 569 $[MH]^+$ RT 3.46 min.

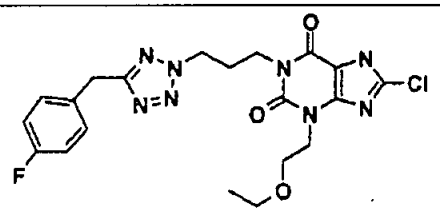
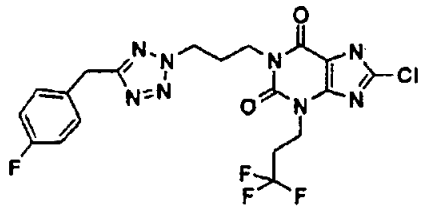
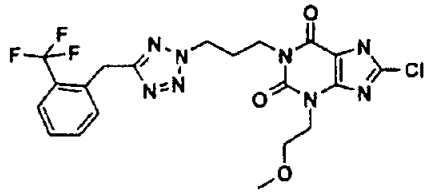
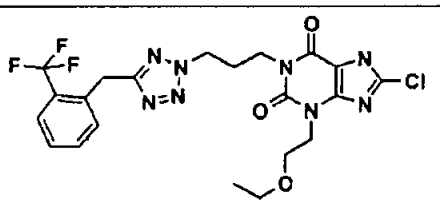
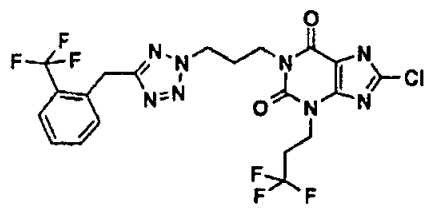
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
359		8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	32.0	m/z 515 $[MH]^+$ RT 3.37 min.
360		3-butil-8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	30.3	m/z 529 $[MH]^+$ RT 3.53 min.
361		1-[3-(5-{[3,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purina-2,6-diona	22.9	m/z 565 $[MH]^+$ RT 3.54 min.
362		8-cloro-3-propil-1-{3-[5-({4-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	21.6	m/z 513 $[MH]^+$ RT 3.42 min.
363		8-cloro-1-(3-{5-[(2-cloro-6-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	12.4	m/z 481 $[MH]^+$ RT 3.20 min.

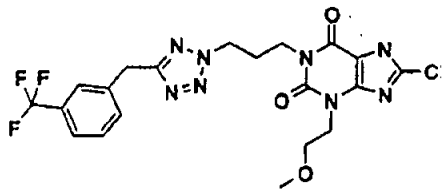
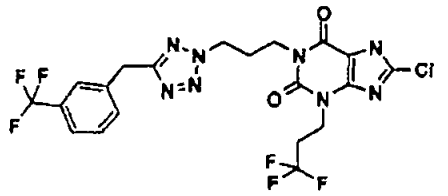
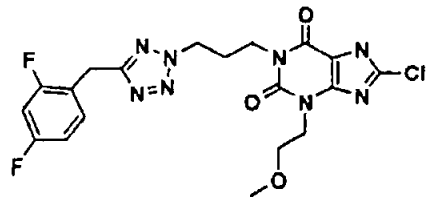
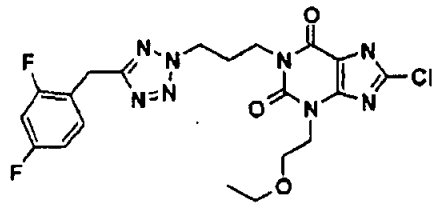
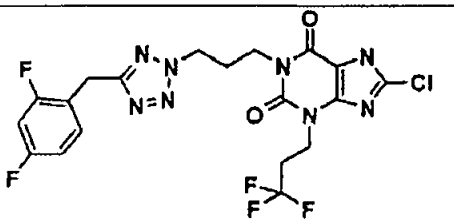
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
364		8-cloro-3-propil-1-[3-{5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il}propil]-3,7-dihidro-1H-purina-2,6-diona	17.7	m/z 497 $[MH]^+$ RT 3.26 min.
365		8-cloro-1-(3-{5-[(3,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	21.6	m/z 465 $[MH]^+$ RT 3.16 min.
366		8-cloro-3-propil-1-{3-[5-({2-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	22.3	m/z 513 $[MH]^+$ RT 3.27 min.
367		8-cloro-1-[3-(5-{[2-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	9.7	m/z 515 $[MH]^+$ RT 3.40 min.
368		8-cloro-1-[3-(5-{[5-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	26.8	m/z 515 $[MH]^+$ RT 3.26 min.

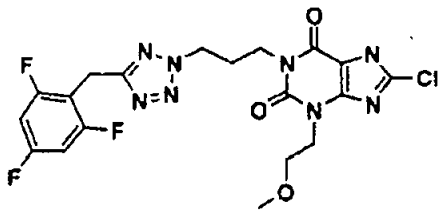
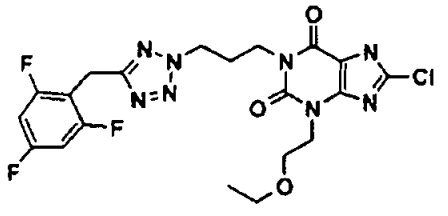
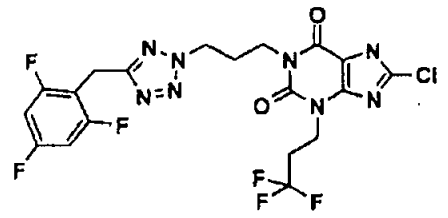
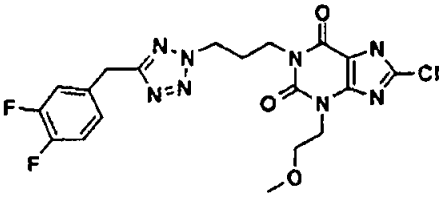
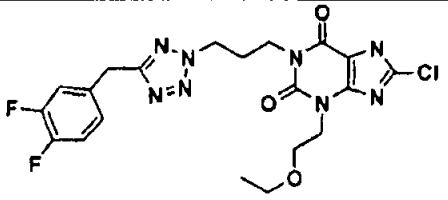
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
369		8-cloro-1-[3-(5-{[3-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	20.7	m/z 515 $[MH]^+$ RT 3.31 min.
370		8-cloro-3-propil-1-(3-{5-[(3,4,5-trifluorofenil)metil]-2H-tetrazol-2-il}propil}3,7-dihidro-1H-purina-2,6-diona	10.2	m/z 513 $[MH]^+$ RT 3.35 min.
371		8-cloro-3-propil-1-{3-[5-({3-[(trifluorometil)oxi]-fenil}metil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	9.8	m/z 515 $[MH]^+$ RT 3.26 min.
372		8-cloro-1-(3-{5-[(2,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2,6-diona	27.6	m/z 515 $[MH]^+$ RT 3.26 min.
373		8-cloro-1-[3-(5-{[3-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purina-2,6-diona	17.6	m/z 515 $[MH]^+$ RT 3.26 min.

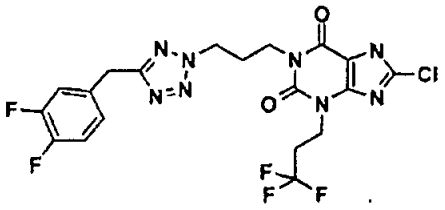
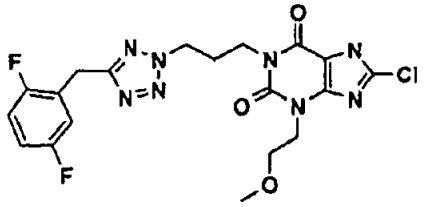
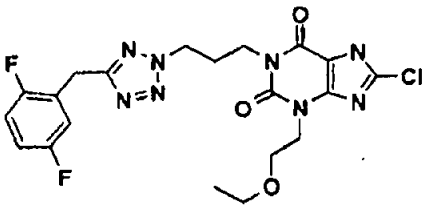
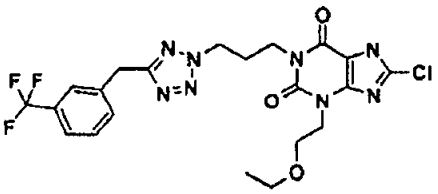
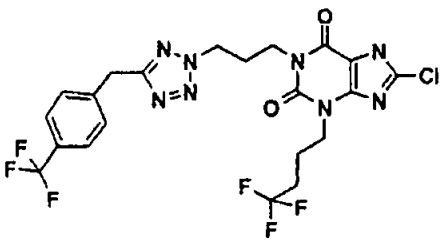
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
374		1-[3-(5-{[2,4-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purina-2,6-diona	21.0	m/z 565 $[MH]^+$ RT 3.40 min.
375		1-[3-(5-{[2,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purina-2,6-diona	9.7	m/z 565 $[MH]^+$ RT 3.50 min.
376		1-[3-(5-{[3,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	28.1	m/z 579 $[MH]^+$ RT 3.68 min.
377		3-butil-8-cloro-1-{3-[5-({4-[(trifluorometil)oxi]-fenil]metil}-2H-tetrazol-2-il)propil}-3,7-dihidro-1H-purina-2,6-diona	32.1	m/z 527 $[MH]^+$ RT 3.57 min.
378		8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	15.0	m/z 463 $[MH]^+$ RT 2.89 min.

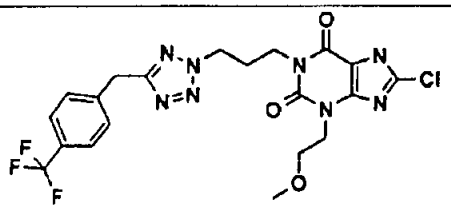
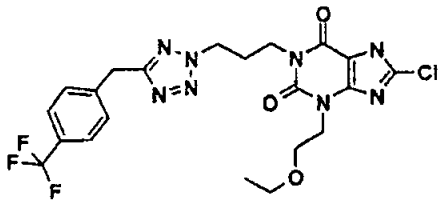
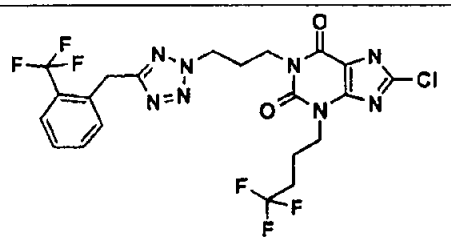
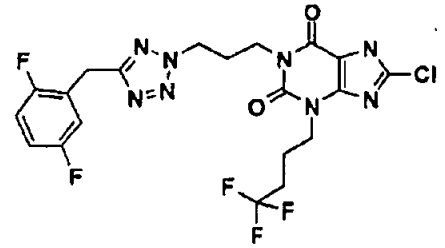
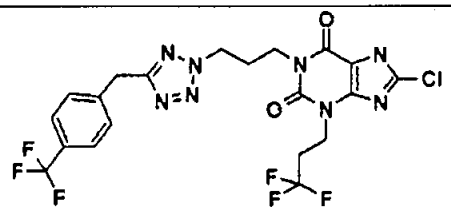
450

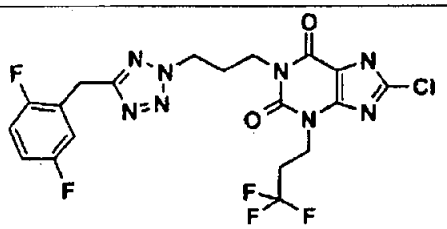
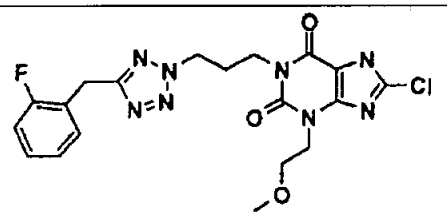
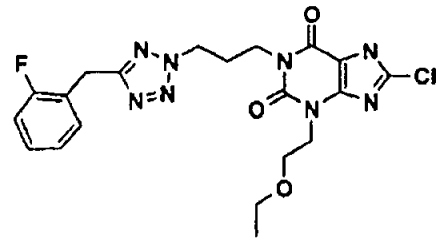
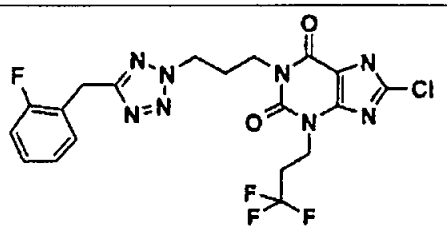
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
379		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	12.6	m/z 477 $[MH]^+$ RT 3.03 min.
380		8-cloro-1-83-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	17.8	m/z 501 $[MH]^+$ RT 3.21 min.
381		8-cloro-3-[2-(metiloxi)etil]-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	14.2	m/z 513 $[MH]^+$ RT 3.10 min.
382		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	20.8	m/z 527 $[MH]^+$ RT 3.18 min.
383		8-cloro-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	35.8	m/z 551 $[MH]^+$ RT 3.35 min.

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
384		8-cloro-3-[2-]metiloxi)etil]-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	15.3	m/z 513 $[MH]^+$ RT 3.14 min.
385		8-cloro-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	29.4	m/z 551 $[MH]^+$ RT 3.42 min.
386		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	17.8	m/z 481 $[MH]^+$ RT 2.96 min.
387		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	14.4	m/z 495 $[MH]^+$ RT 2.86 min.
388		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	29.9	m/z 519 $[MH]^+$ RT 3.19 min.

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
389		8-cloro-3-[2-(metiloxi)etil]-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	21.3	m/z 513 $[MH]^+$ RT 3.14 min.
390		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	15.5	m/z 513 $[MH]^+$ RT 2.93 min.
391		8-cloro-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	32.3	m/z 537 $[MH]^+$ RT 3.29 min.
392		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	14.5	m/z 481 $[MH]^+$ RT 2.97 min.
393		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	7.2	m/z 495 $[MH]^+$ RT 3.06 min.

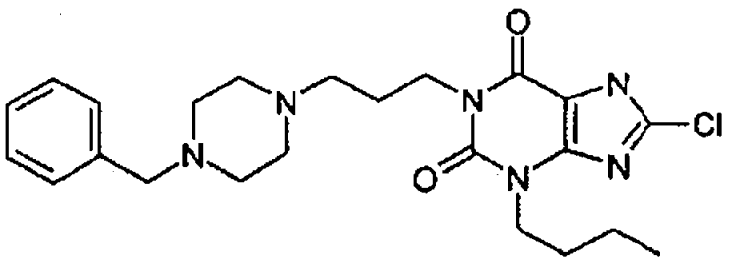
Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
394		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	27.8	m/z 519 $[MH]^+$ RT 3.27 min.
395		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	17.1	m/z 481 $[MH]^+$ RT 2.89 min.
396		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	13.5	m/z 495 $[MH]^+$ RT 3.05 min.
397		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	14.6	m/z 527 $[MH]^+$ RT 3.26 min.
398		8-cloro-(4,4,4-trifluorobutil)-1-[3-(5-{[4-(trifluorofenil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	12.1	m/z 565 $[MH]^+$ RT 3.51 min.

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
399		8-cloro-3-[2-(metiloxi)etil]-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina	17.3	m/z 513 $[MH]^+$ RT 3.17 min.
400		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina	15.2	m/z 527 $[MH]^+$ RT 3.30 min.
401		8-cloro-3-(4,4,4-trifluorobutil)-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purina-2,6-diona	5.8	m/z 565 $[MH]^+$ RT 3.46 min.
402		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona	14.7	m/z 533 $[MH]^+$ RT 3.34 min.
403		8-cloro-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	26.1	m/z 551 $[MH]^+$ RT 3.46 min.

Ej.	Estructura	Nombre	Rend. (mg)	LC/EM
404		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	18.0	m/z 519 $[MH]^+$ RT 3.29 min.
405		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	3.4	m/z 463 $[MH]^+$ RT 2.84 min.
406		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	8.2	m/z 477 $[MH]^+$ RT 2.85 min.
407		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purina-2,6-diona	32.7	m/z 501 $[MH]^+$ RT 3.25 min.

EJEMPLO 408

3-butil-8-cloro-1-{3-[4-(fenilmetil)-1-piperazinil]propil}-3,7-dihidro-1H-purina-2,6-diona



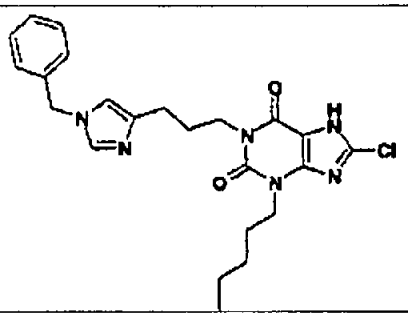
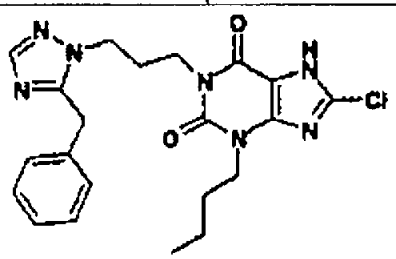
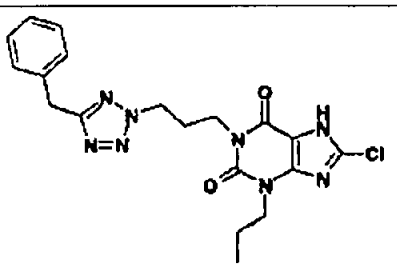
Una solución de metanosulfonato 3-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]propilo (0.08 g, 0.19 mmol) en DMF (5 ml) se trata con carbonato de potasio (0.08 g, 0.6 mmol) y 1-bencilpiperazina (0.04 g, 0.23 mmol) y después se calienta a 70°C durante 2 horas. La mezcla se enfría, se evapora a sequedad y se divide entre 10 ml de DCM y 10 ml de agua. La fase orgánica se evapora a sequedad y el residuo se disuelve en THF anhidro (5 ml). La solución se desgasifica cautelosamente por la aplicación repetida de vacío a la mezcla de reacción y consecutivamente se rellena con gas nitrógeno y después se trata con tetraquis(trifenilfosfina)paladio (0) (0.010 g, 0.009 mmol) y morfolina (0.200 ml, 2.3 mmol) y la mezcla se agita durante 2 horas en una atmósfera de nitrógeno. La mezcla se evapora y el residuo se toma en 5 ml de metanol y se añade a un cartucho SPE de aminopropilo de 2g que después se lava con metanol y el producto se eluye usando solución al 3% de ácido acético en metanol. Las fracciones que contienen el producto se agrupan y se evaporan a sequedad. El producto después se purifica mediante cromatografía

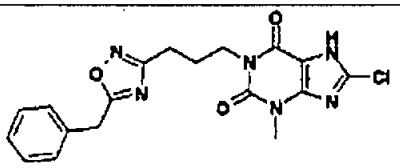
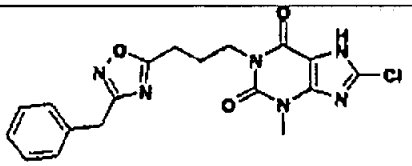
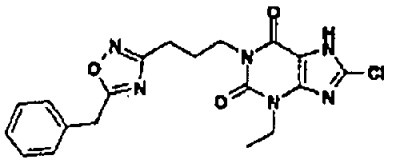
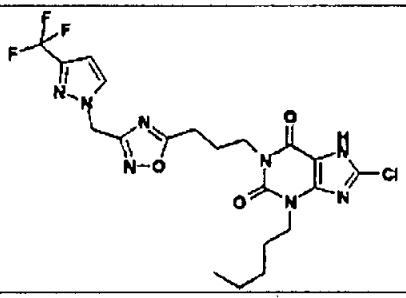
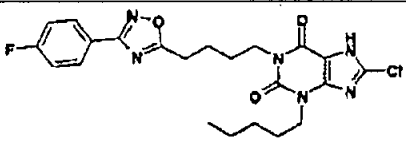
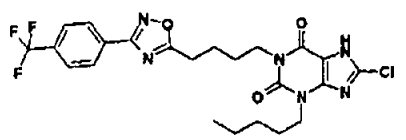
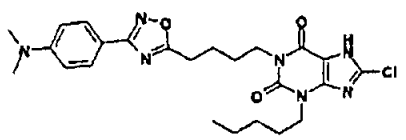
instantánea usando una elusión de gradiente de DCM/ácido acético al 2% a DCM (MeOH al 20%/ácido acético al 2% y el producto final se seca por congelamiento a partir de 1,4-dioxan para proporcionar el compuesto del titulo como un sólido blanco (0.021 g, 24%).

LC/EM: m/z 459 $[MH]^+$, temperatura ambiente 2.37 minutos.

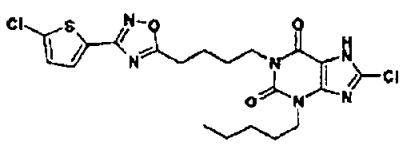
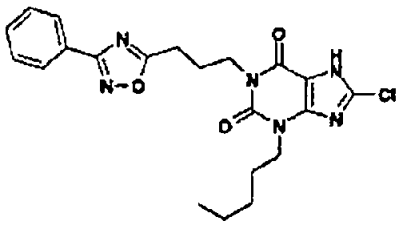
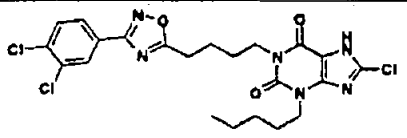
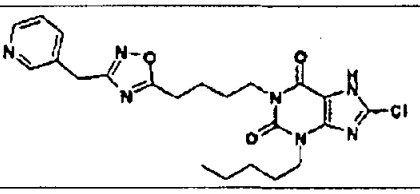
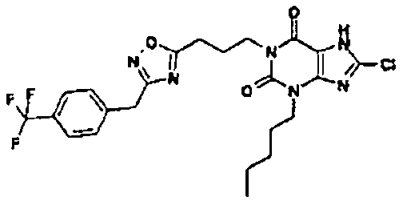
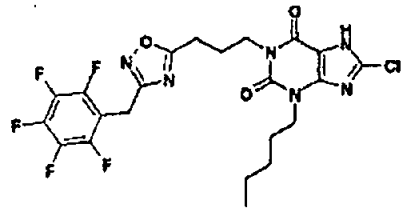
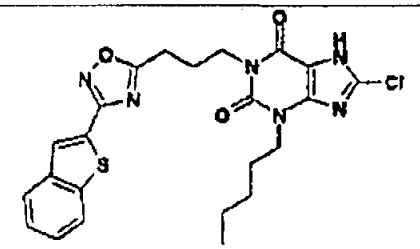
Los siguientes compuestos (cuadro 24) se preparan mediante la metodología general apropiada descrita anteriormente.

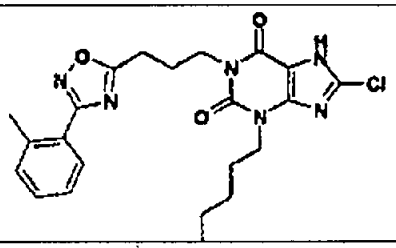
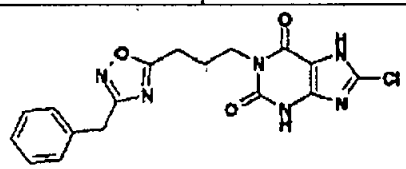
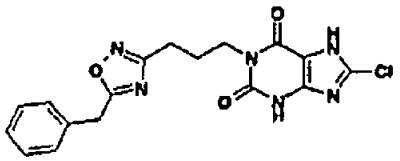
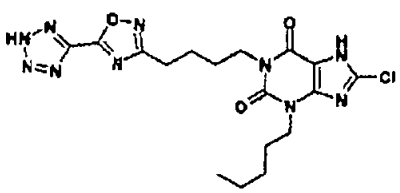
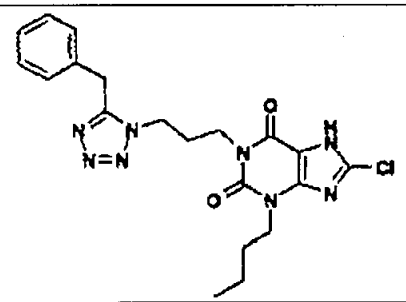
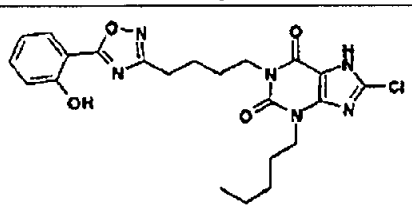
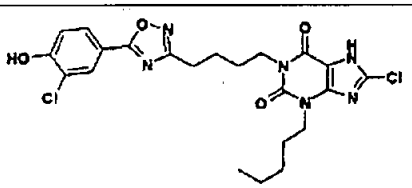
CUADRO 24

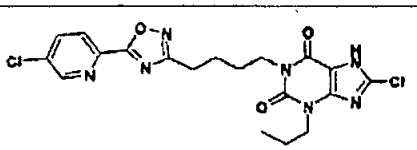
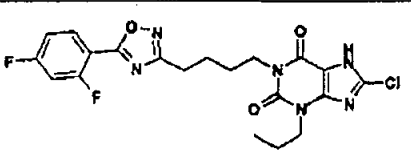
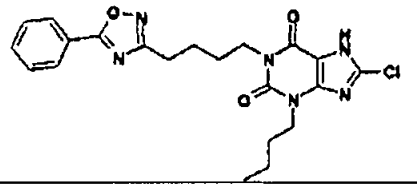
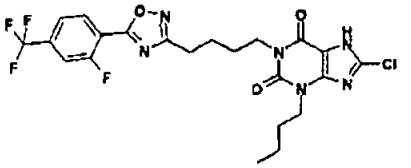
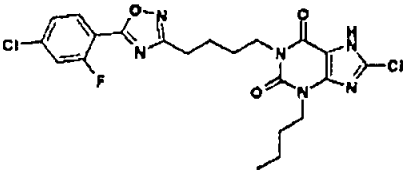
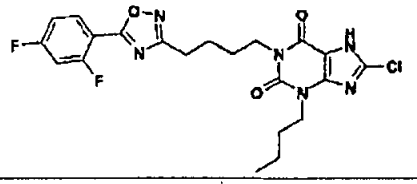
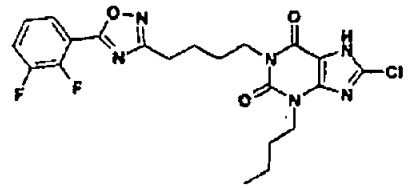
Ej.	Estructura	Nombre	LC/EM
409		8-cloro-3-pentil-1-{3-[1-(fenilmetil)-1H-imidazol-4-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 455 $[MH]^+$ RT 2.61 min.
410		3-butil-8-cloro-1-{3-[5-(fenilmetil)-1H-1,2,4-triazol-1-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 442 $[MH]^+$ RT 2.94 min.
411		8-cloro-1-{3-[5-(fenilmetil)-2H-tetrazol-2-il]propil}-3-propil-3,7-dihidro-1H-purina-2,6-diona	m/z 429 $[MH]^+$ RT 3.14 min.

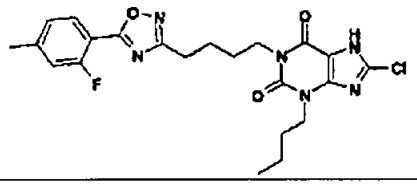
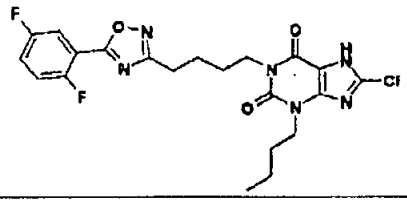
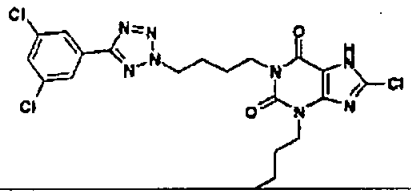
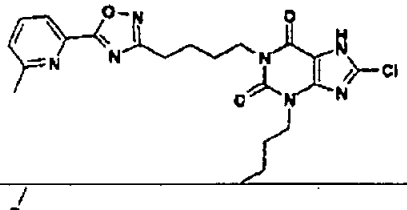
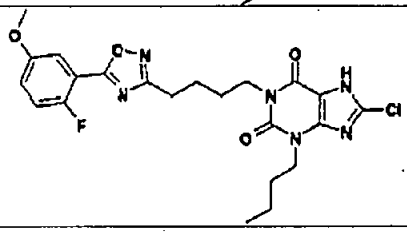
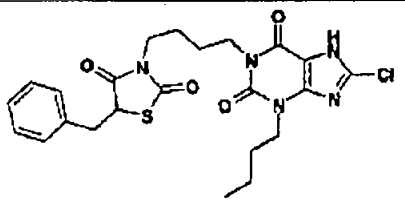
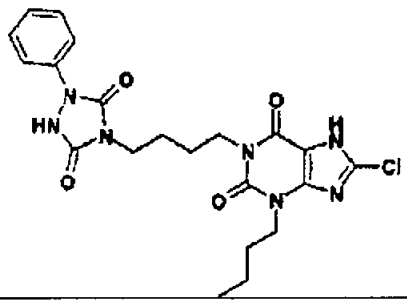
Ej.	Estructura	Nombre	LC/EM
412		8-cloro-3-metil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 401 $[MH]^+$ RT 2.88 min.
413		8-cloro-3-metil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 401 $[MH]^+$ RT 2.89 min.
414		8-cloro-3-etil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 415 $[MH]^+$ RT 2.97 min.
415		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-purina-2,6-diona	m/z 515 $[MH]^+$ RT 3.43 min.
416		8-cloro-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 475 $[MH]^+$ RT 3.71 min.
417		8-cloro-3-pentil-1-(4-{3-[4.(trifluorometil)fenil]-1,2,4-oxadiazol-5-il}butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 525 $[MH]^+$ RT 3.92 min.
418		8-cloro-1-(4-{3-[4-(dimetilamino)fenil]-1,2,4-oxadiazol-5-il}butil9-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 500 $[MH]^+$ RT 3.73 min.

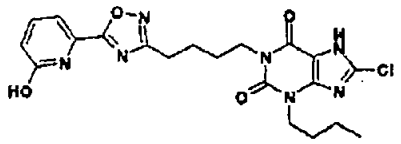
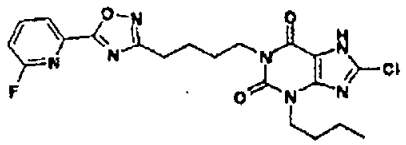
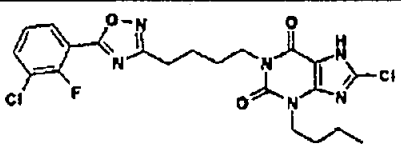
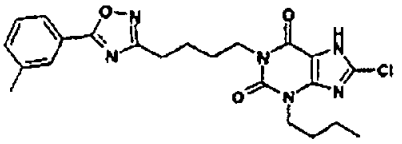
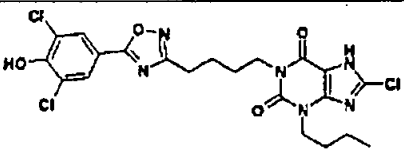
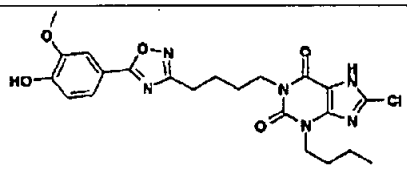
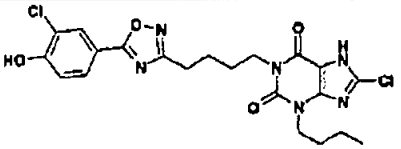
460

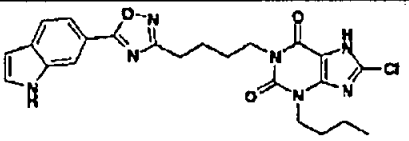
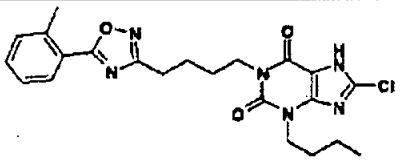
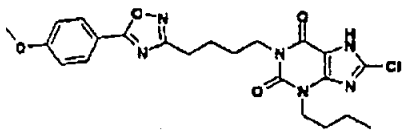
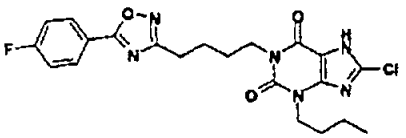
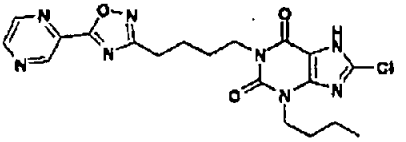
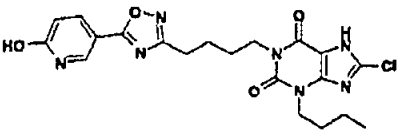
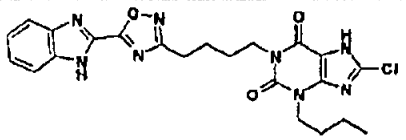
Ej.	Estructura	Nombre	LC/EM
419		8-cloro-1-{4-[3-(5-cloro-2-tienil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 497 $[MH]^+$ RT 3.88 min.
420		8-cloro-3-pentil-1-[3-(3-fenil-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	m/z 443 $[MH]^+$ RT 3.51 min.
421		8-cloro-1-{4-[3-(3,4-diclorofenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 525 $[MH]^+$ RT 4.12 min.
422		8-cloro-3-pentil-1-{4-[3-(piridin-3-ilmetil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 472 $[MH]^+$ RT 2.90 min.
423		8-cloro-3-pentil-1-[3-(3-{[4-(trifluorometil)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	m/z 525 $[MH]^+$ RT 3.69 min.
424		8-cloro-1-(3-{3-[(pentafluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 547 $[MH]^+$ RT 3.66 min.
425		1-{3-[3-(1-benzotien-2-il)-1,2,4-oxadiazol-5-il]propil}-8-cloro-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 499 $[MH]^+$ RT 3.77 min.

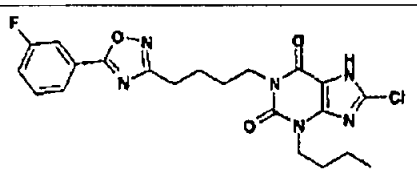
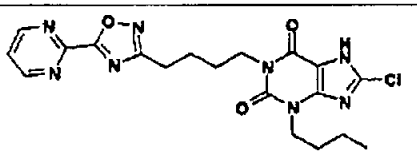
Ej.	Estructura	Nombre	LC/EM
426		8-cloro-1-{3-[3-(2-metilfenil)-1,2,4-oxadiazol-5-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 457 $[MH]^+$ RT 3.62 min.
427		8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 387 $[MH]^+$ RT 2.63 min.
428		8-cloro-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 387 $[MH]^+$ RT 2.65 min.
429		8-cloro-3-pentil-1-{4-[5-(1H-tetrazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 449 $[MH]^+$ RT 4.03 min.
430		3-butil-8-cloro-1-{3-(5-(fenilmetil)-1H-tetrazol-1-il)propil}-3,7-dihidro-1H-purina-2,6-diona	m/z 443 $[MH]^+$ RT 3.11 min.
431		8-cloro-1-{4-[5-(2-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.84 min.
432		8-cloro-1-{4-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	m/z 507 $[MH]^+$ RT 3.74 min.

Ej.	Estructura	Nombre	LC/EM
433		8-cloro-1-{4-[5-(5-cloropiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1H-purina-2,6-diona	m/z 464 $[MH]^+$ RT 3.30 min.
434		8-cloro-1-{4-[5-(2,4-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1H-purina-2,6-diona	m/z 465 $[MH]^+$ RT 3.48 min.
435		3-butil-8-cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 443 $[MH]^+$ RT 3.49 min.
436		3-butil-8-cloro-1-(4-{5-[2-fluoro-4-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 529 $[MH]^+$ RT 3.71 min.
437		3-butil-8-cloro-1-{4-[5-(4-cloro-2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 495 $[MH]^+$ RT 3.64 min.
438		3-butil-8-cloro-1-{4-[5-(2,4-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 479 $[MH]^+$ RT 3.49 min.
439		3-butil-8-cloro-1-{4-[5-(2,3-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 479 $[MH]^+$ RT 3.53 min.

Ej.	Estructura	Nombre	LC/EM
440		3-butil-8-cloro-1-{4-[5-(2-fluoro-4-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 475 $[MH]^+$ RT 3.51 min.
441		3-butil-8-cloro-1-{4-[5-(2,5-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 479 $[MH]^+$ RT 3.50 min.
442		3-butil-8-cloro-1-{4-[5-(3,5-diclorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 511 $[MH]^+$ RT 3.92 min.
443		3-butil-8-cloro-1-{4-[5-(6-metilpiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 458 $[MH]^+$ RT 3.12 min.
444		3-butil-8-cloro-1-{4-[5-[2-fluoro-5-(metiloxi)fenil]-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 491 $[MH]^+$ RT 3.51 min.
445		3-butil-8-cloro-1-{4-[2,4-dioxo-5-(fenilmetil)-1,3-tiazolidin-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 504 $[MH]^+$ RT 3.36 min.
446		3-butil-8-cloro-1-[4-(3,5-dioxo-1-fenil-1,2,4-triazolidin-4-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 474 $[MH]^+$ RT 2.91 min.

Ej.	Estructura	Nombre	LC/EM
447		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-purina-2,6-diona	m/z 460 $[MH]^+$ RT 2.86 min.
448		3-butil-8-cloro-1-{4-[5-(6-fluoropiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 462 $[MH]^+$ RT 3.23 min.
449		3-butil-8-cloro-1-{4-[5-(3-cloro-2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 495 $[MH]^+$ RT 3.69 min.
450		3-butil-8-cloro-1-{4-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 457 $[MH]^+$ RT 3.67 min.
451		3-butil-8-cloro-1-{4-[5-(3,5-dicloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 527 $[MH]^+$ RT 3.92 min.
452		3-butil-8-cloro-1-{4-{5-[4-hidroxi-3-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 489 $[MH]^+$ RT 3.27 min.
453		3-butil-8-cloro-1-{4-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 493 $[MH]^+$ RT 3.61 min.

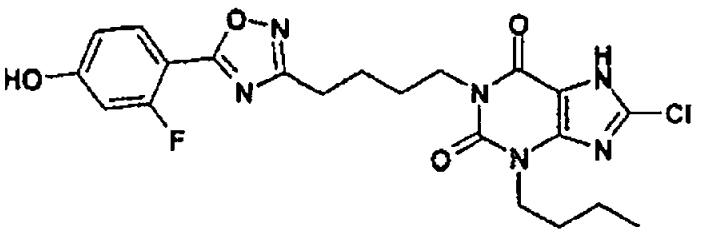
Ej.	Estructura	Nombre	LC/EM
454		3-butil-8-cloro-1-{4-[5-(1H-indol-6-il)-1,2,4-oxadiazol-3-il]butil-3,7-dihidro-1H-purina-2,6-diona	m/z 482 $[MH]^+$ RT 3.55 min.
455		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-1,2,4-oxadiazol-3-ilñ]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 457 $[MH]^+$ RT 3.67 min.
456		3-butil-8-cloro-1-(4-{5-[4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.51 min.
457		3-butil-8-coro-1-{4-[5-(4-fluorofenil)-1,2,4-oxadiazol-3-il]butil-}3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.54 min.
458		3-butil-8-cloro-1-[4-(5-pirazin-2-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 445 $[MH]^+$ RT 2.96 min.
459		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-purina-2,6-diona	m/z 460 $[MH]^+$ RT 3.78 min.
460		1-{4-[5-(1H-bencimidazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	m/z 483 $[MH]^+$ RT 3.22 min.

Ej.	Estructura	Nombre	LC/EM
461		3-butil-8-cloro-1-{4-[5-(3-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.58 min.
462		3-butil-8-cloro-1-[4-(5-pirimidin-2-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 445 $[MH]^+$ RT 2.84 min.

EJEMPLO 463

3-butil-8-cloro-1-{4-[5-(2-fluoro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-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-1H-purina-2,6-diona



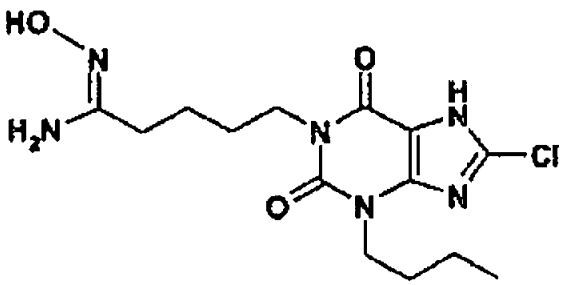
Se añade CDI (45 mg, 0.28 mmol) en DMSO anhidro (0.5 ml) a ácido 2-fluoro-4-hidroxibenzoico (40 mg, 0.25 mmol) y se agita a temperatura ambiente durante 2 horas. Se añade 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmol) en DMSO (0.4 ml) y al mezcla resultante se calienta a 90°C durante 18 horas. La purificación mediante MDAP produce el compuesto del titulo como un sólido

(38 mg, 28%).

LC/EM: m/z 477 $[MH]^+$, temperatura ambiente 3.39 minutos.

^{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 (d, 1H), 14.45 (br s, 1H).

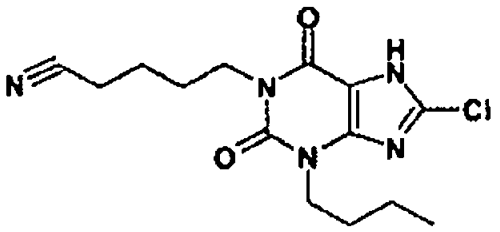
b) 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida



Se disuelve 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanonitrilo (8.5 g, 26 mmol) en EtOH (100 ml). Se añade hidroxilamina (50% en agua; 2.6 ml, 39 mmol) y la mezcla se calienta a 80°C durante 48 bajo nitrógeno. La mezcla de reacción se concentra *in vacuo*, el sólido resultante se lava con metanol y se seca para proporcionar el compuesto del titulo como un sólido (5.9 g, 47%).

LC/EM: m/z 357 $[MH]^+$, temperatura ambiente 2.17 minutos.

c) 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanonitrilo



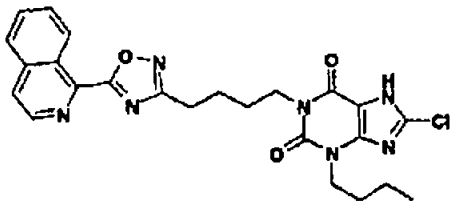
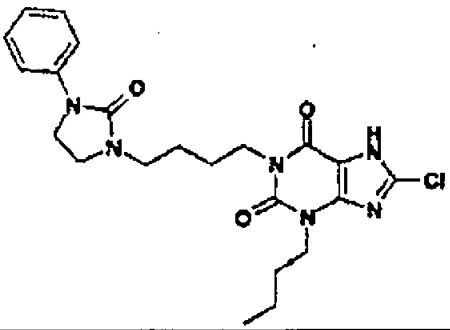
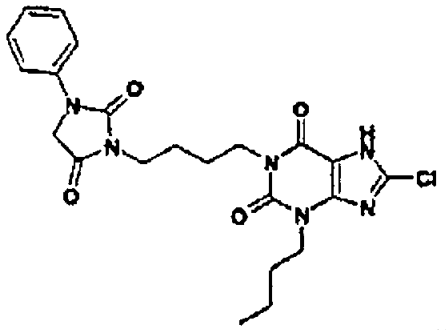
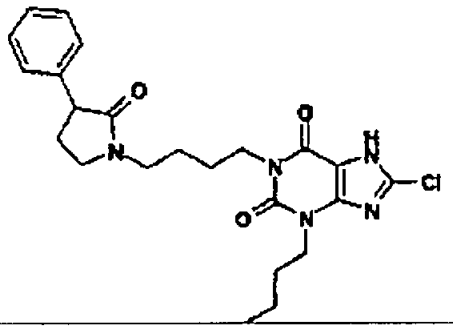
Se añade 5-bromopentanonitrilo (4.54 ml, 39 mmol) y carbonato de cesio (12.7 g) se añade a una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona (10 g, 35 mmol) en DMF (100 ml) y la mezcla se agita bajo nitrógeno a 40°C toda la noche y se deja enfriar.

La mezcla después se desgasifica mediante la aplicación sucesiva repetida de un vacío y después a presión de nitrógeno. La mezcla después se trata con tetraquis(trifenilfosfina)paladio (0) 82.86 g, 2.5 mmol) y morfolina (30.8 ml, 350 mmol). La mezcla se agita en una atmósfera de nitrógeno durante 3 horas y después se divide entre EtOAc y ácido clorhídrico 2M. La capa acuosa se separa y se extrae con EtOAc (x2). Las fases orgánicas combinadas se concentran *in vacuo* para proporcionar un sólido que se lava con éter, se filtra y se seca. El filtrado se concentra y se purifica en una columna de aminopropilo eluyendo con MeOH seguido por AcOH/MeOH al 3%. Las fracciones que contienen el producto se combinan y se concentran para proporcionar un sólido, que se combina con el producto filtrado. El compuesto del titulo se obtiene como un sólido (10.5 g, 93%).

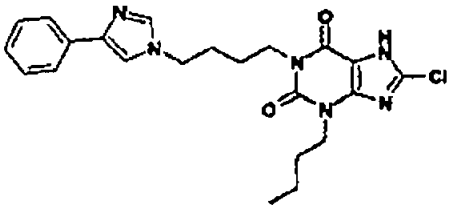
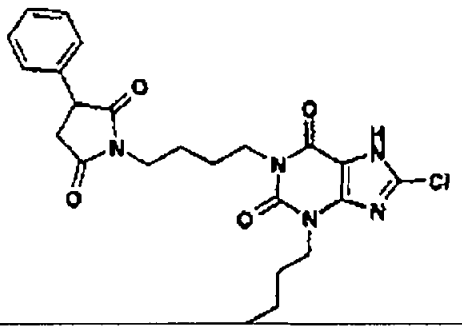
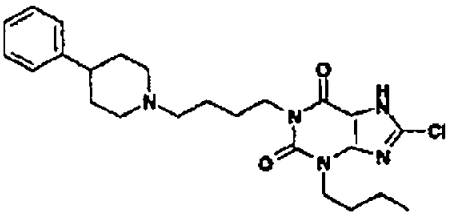
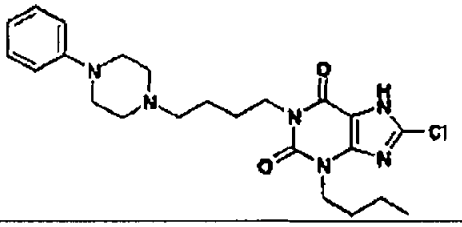
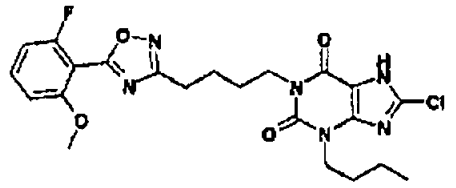
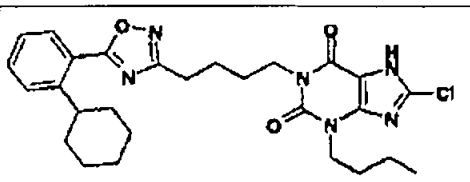
LC/EM: m/z 324 $[MH]^+$, temperatura ambiente 2.75 minutos.

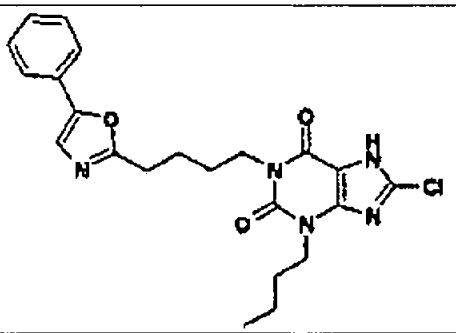
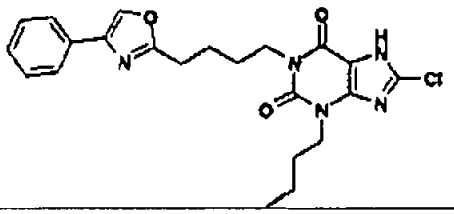
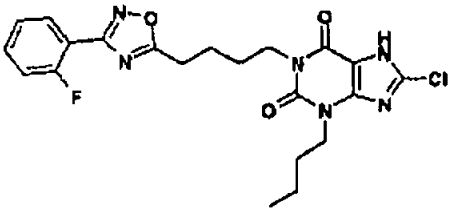
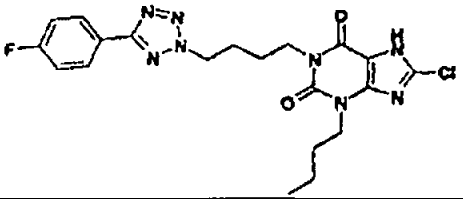
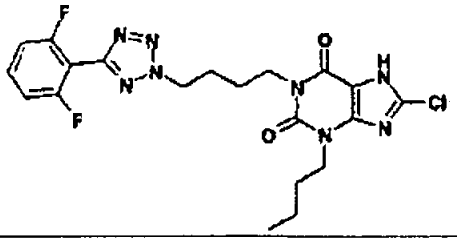
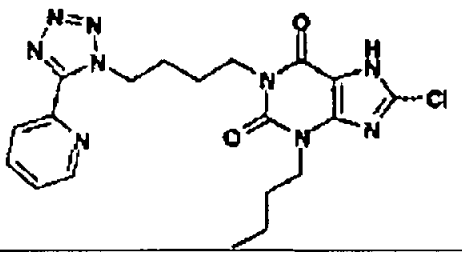
Los siguientes compuestos (cuadro 25) se preparan usando un método análogo al del ejemplo 463, usando el ácido carboxílico apropiado.

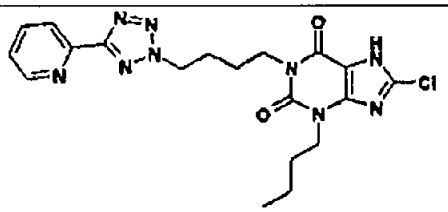
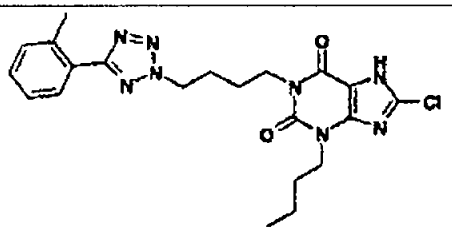
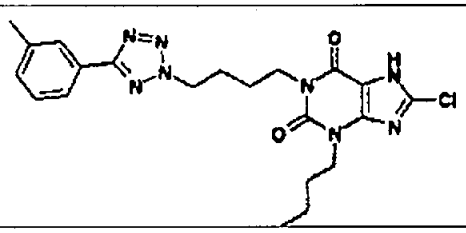
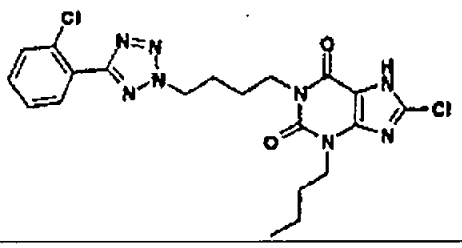
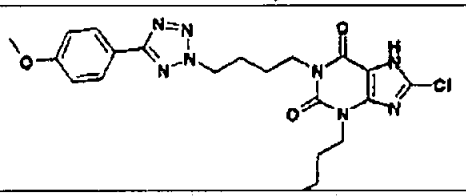
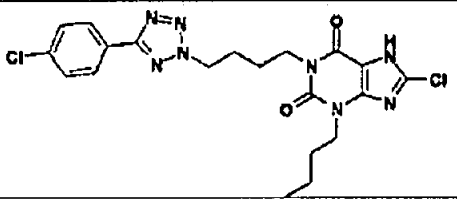
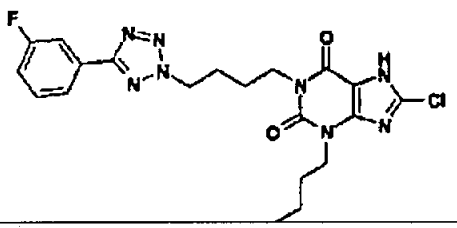
CUADRO 25

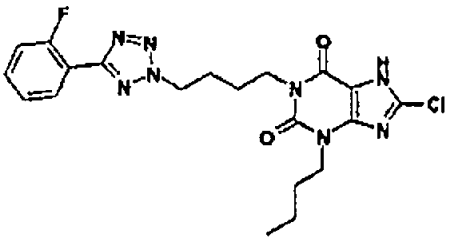
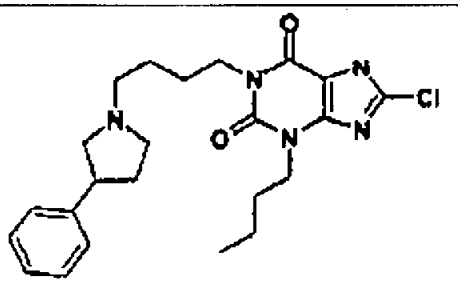
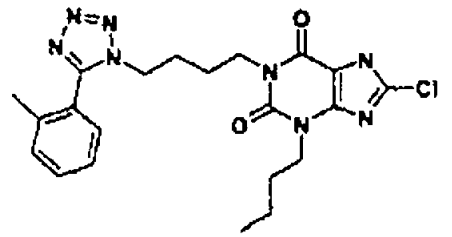
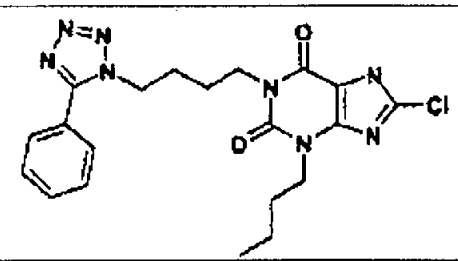
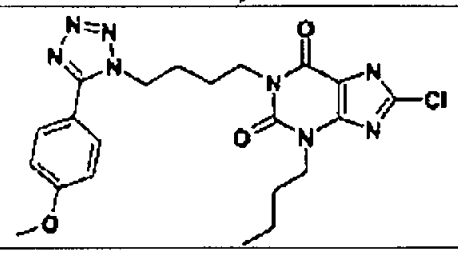
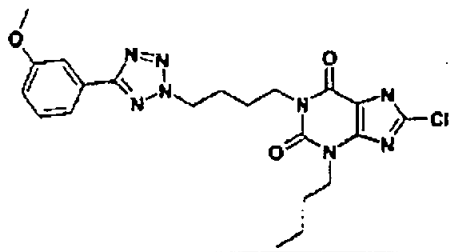
Ej	Estructura	Nombre	LC/EM
464		3-butil-8-cloro-1-[4-(5-isoquinolin-1-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 494 $[MH]^+$ RT 3.49 min.
465		3-butil-8-cloro-1-[4-(2-oxo-3-fenilimidazolidin-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 459 $[MH]^+$ RT 3.23 min.
466		3-butil-8-cloro-1-[4-(2,5-dioxo-3-fenilimidazolidin-1-il)-butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.19 min.
467		3-butil-8-cloro-1-[4-(2-oxo-3-fenilpirrolidin-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 458 $[MH]^+$ RT 3.12 min.

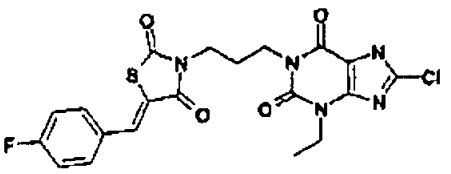
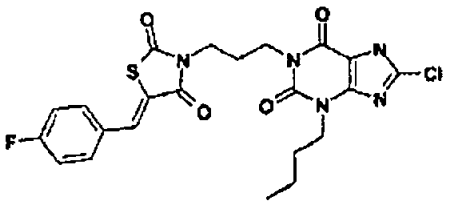
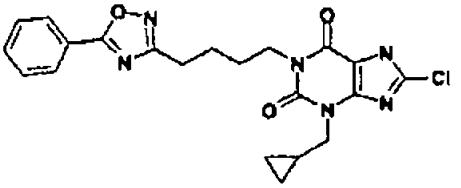
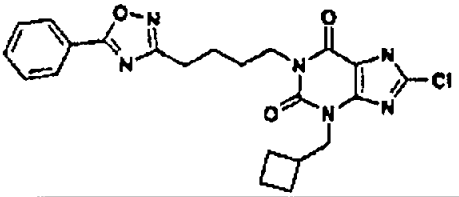
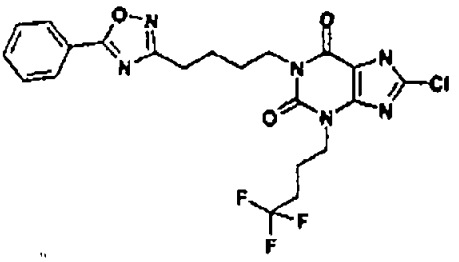
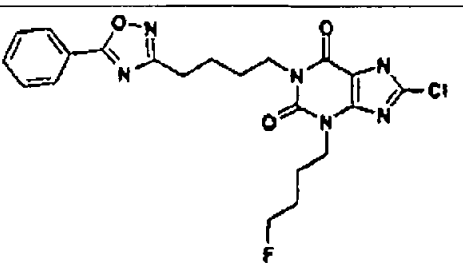
470

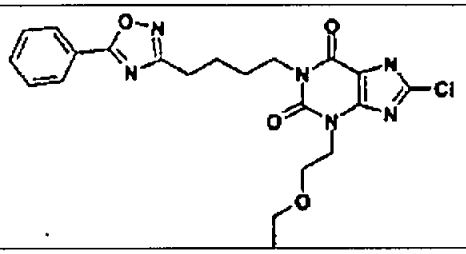
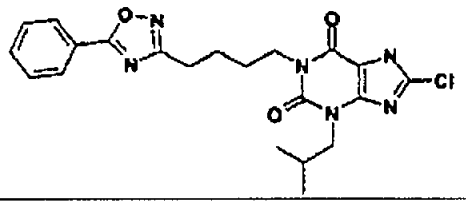
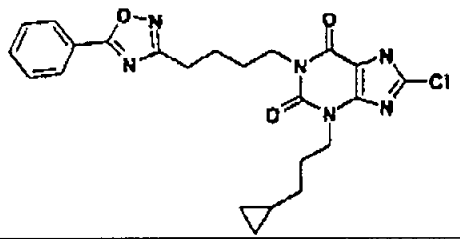
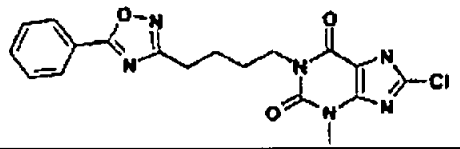
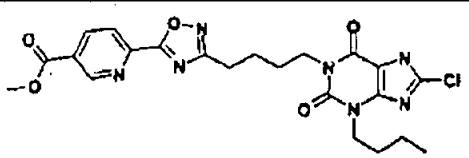
Ej	Estructura	Nombre	LC/EM
468		3-butil-8-cloro-1-[4-(4-fenil-1H-imidazol-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 441 $[MH]^+$ RT 2.80 min.
469		3-butil-8-1-[4-(2,5-dioxo-3-fenil)pirrolidin-1-il]butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 472 $[MH]^+$ RT 3.20 min.
470		3-butil-8-cloro-1-[4-(4-fenilpiperidin-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 458 $[MH]^+$ RT 2.56 min.
471		3-butil-8-cloro-1-[4-(4-fenilpiperazin-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 459 $[MH]^+$ RT 2.49 min.
472		3-butil-8-cloro-1-(4-{5-[2-fluoro-6-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 491 $[MH]^+$ RT 3.33 min.
473		3-butil-8-cloro-1-{4-[5-(2-ciclohexil)fenil]-1,2,4-oxadiazol-3-ilbutil}-3,7-dihidro-1H-purina-2,6-diona	m/z 525 $[MH]^+$ RT 4.18 min.

Ej	Estructura	Nombre	LC/EM
474		3-butil-8-cloro-1-[4-(5-fenil-1,3-oxazol-2-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 442 $[MH]^+$ RT 3.46 min.
475		3-butil-8-cloro-1-{4-(4-fenil-1,3-oxazol-2-il)butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 442 $[MH]^+$ RT 3.48 min.
476		3-butil-8-cloro-1-{4-[3-(2-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.45 min.
477		3-butil-8-cloro-1-{4-[5-(4-fluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.47 min.
478		3-butil-8-cloro-1-{4-[5-(2,6-difluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 479 $[MH]^+$ RT 3.32 min.
479		3-butil-8-cloro-1-[4-(5-piridin-2-il-1H-tetrazol-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 444 $[MH]^+$ RT 2.94 min.

Ej	Estructura	Nombre	LC/EM
480		3-butil-8-cloro-1-[4-(5-piridin-2-il-2H-tetrazol-2-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 444 $[MH]^+$ RT 3.07 min.
481		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purina-2,6,diona	m/z 457 $[MH]^+$ RT 3.54 min.
482		3-butil-8-cloro-1-{4-[5-(3-metilfenil)-2H-tetrazol-2il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 457 $[MH]^+$ RT 3.56 min.
483		3-butil-8-cloro-1-{4-[5-(2-clorofenil)-2H-tetrazol-2il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 477 $[MH]^+$ RT 3.68 min.
484		3-butil-8-cloro-1-{4-[5-[4-(metiloxi)fenil]-2H-tetrazol-2il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.40 min.
485		3-butil-8-cloro-1-{4-[5-(4-clorofenil)-2H-tetrazol-2il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 477 $[MH]^+$ RT 3.68 min.
486		3-butil-8-cloro-1-{4-[5-(3-fluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.51 min.

Ej	Estructura	Nombre	LC/EM
487		3-butil-8-cloro-1-{4-[5-(2-fluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H--purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.34 min.
488		3-butil-8-cloro-1-[4-(3-fenil-1-pirrolidinil)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 444 $[MH]^+$ RT 2.51 min.
489		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-1H-tetrazol-1-il]butil-3,7-dihidro-1H-purina-2,6-diona	m/z 457 $[MH]^+$ RT 3.16 min.
490		3-butil-8-cloro-1[4-(5-fenil-1H-tetrazol-1-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 443 $[MH]^+$ RT 3.08 min.
491		3-butil-8-cloro-1-(4-{5-[4-(metiloxi)fenil]-1H-tetrazol-1-il}butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.10 min.
492		3-butil-8-cloro-1-(4-{5-[3-(metiloxi)fenil]-2H-tetrazol-2-il}butil)-3,7-dihidro-1H-purina-2,6-diona	m/z 473 $[MH]^+$ RT 3.40 min.

Ej	Estructura	Nombre	LC/EM
493		8-cloro-3-etil-1-(3-{(5Z)-5-[(4-fluorofenil)metilideno]-2,4-dioxo-1,3-tiazolidin-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona	m/z 478 $[MH]^+$ RT 3.31 min.
494		3-butil-8-cloro-1-(3-{(5Z)-5-[(4-fluorofenil)metilideno]-2,4-dioxo-1,3-tiazolidin-3-il}propil)-3,7-dihidro-1H-purina-2,6-diona	m/z 506 $[MH]^+$ RT 3.63 min.
495		8-cloro-3-(ciclopropilmetil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 441 $[MH]^+$ RT 3.38 min.
496		8-cloro-3-(ciclobutilmetil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 455 $[MH]^+$ RT 3.53 min.
497		8-cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona	m/z 497 $[MH]^+$ RT 3.46 min.
498		8-cloro-3-(4-fluorobutil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 461 $[MH]^+$ RT 3.26 min.

Ej	Estructura	Nombre	LC/EM
499		8-cloro-3-[2-(etiloxi)etil]-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 459 $[MH]^+$ RT 3.16 min.
500		8-cloro-3-(2-metilpropil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 443 $[MH]^+$ RT 3.16 min.
501		8-cloro-3-(3-ciclopropilpropil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 469 $[MH]^+$ RT 3.63 min.
502		8-cloro-3-metil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purina-2,6-diona	m/z 401 $[MH]^+$ RT 2.98 min.
503		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-piridinacarboxilato de metilo	m/z 502 $[MH]^+$ RT 3.22 min.

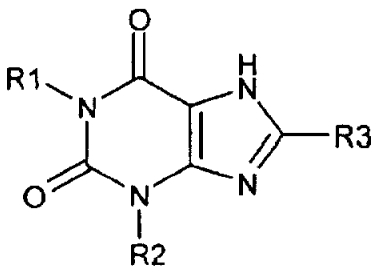
Los materiales de inicio anterior se pueden adquirir comercialmente y/o se hacen de acuerdo con los procedimientos que son disponibles en la literatura.

Todas las publicaciones, incluyendo pero sin limitarse a patentes y solicitudes de patente, citadas en esta especificación se incorporan aquí para referencia como si cada publicación individual fuera indicada

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Al menos una entidad química seleccionada de los compuestos de fórmula (I)



(I)

y derivados farmacéuticamente aceptables de los mismos, en donde R^1 representa -(alquileno)$_m$-X-(alquileno)$_n$-Y; en donde m y n representan el número de átomos de carbono en la cadena alquileno; en donde X representa un grupo seleccionado de heteroarilo y heterociclilo; en donde Y representa un grupo seleccionado de arilo, heteroarilo y O-arilo; que se puede sustituir opcionalmente por uno o más grupos seleccionados independientemente de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, -$(CH_2)_qNR^5R^7$, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$N(R^5)C(O)OR^8$, -$(CH_2)_q$-$N(R^5)C(O)R^8$, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$C(O)NR^5R^6$, -$(CH_2)_q$-$N(R^5)C(O)NR^5R^6$, -$(CH_2)_q$-$C(O)N((CH_2)_mOH)R^5$, -$(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, -CH_2-$S(O)_2NR^5R^6$, -haloalquilo 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; R^2 representa alquilo de C_{1-6} que se puede sustituir opcionalmente por uno o más

grupos seleccionados independientemente de cicloalquilo, haloalquilo de C_{1-6}, halógeno, -CN y $-OR^4$; R^3 representa halógeno; R^4 representa un grupo seleccionado 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 alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_t$ cicloalquilo, $-(CH_2)_t$ cicloalquenilo, $-(CH_2)_t$ heterociclilo, $-(CH_2)_t$arilo, y $-(CH_2)_t$ heteroarilo; R^8 representa 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 número entero seleccionado de 3 y 4; n representa un número entero seleccionado de 0 y 1; p representa un número entero seleccionado de 0 y 1; q representa un número entero seleccionado de 0, 1 y 2; y t representa un número entero seleccionado de 1 y 2.

2.- Al menos una entidad química de conformidad con la reivindicación 1, caracterizada además porque X representa un grupo seleccionado de heteroarilo.

3.- Al menos una entidad química de conformidad con la reivindicación 1 o 2, caracterizada además porque R^2 se selecciona de alquilo de C_{3-6}.

4.- Al menos una entidad química de conformidad con la reivindicación 2 o 3, caracterizada además porque X representa un grupo

seleccionado de heteroarilo que comprende un heteroátomo de nitrógeno.

5.- Al menos una entidad química de conformidad con la reivindicación 4, caracterizada además porque X representa oxadiazolilo o tetrazol.

6.- Al menos una entidad química de conformidad con cualquier reivindicación anterior, caracterizada además porque Y representa un grupo seleccionado de arilo y heteroarilo.

7.- Al menos una entidad química de conformidad con cualquier reivindicación anterior, caracterizada además porque Y se sustituye opcionalmente por uno o más de halógeno y haloalquilo de C_{1-6}.

8.- Al menos una entidad química de conformidad con cualquier reivindicación anterior, caracterizada además porque R^3 representa cloro.

9.- Al menos una entidad química de conformidad con cualquier reivindicación anterior, caracterizada además porque Y representa fenilo y m es 3 y n es 1.

10.- Al menos una entidad química de conformidad con la reivindicación 9, caracterizada además porque X representa tetrazolilo, R^2 representa butilo y R^3 representa cloro.

11.- Al menos una entidad química de conformidad con la reivindicación 8, caracterizada además porque X representa oxadiazolilo, Y representa piridinilo, R^2 representa butilo, R^3 representa cloro y m es 4 y n es 0.

12.- Al menos una entidad química de conformidad con cualquier

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reivindicación anterior para usarse en medicina humana o veterinaria.

13.- Al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11, para usarse en el tratamiento de trastornos de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia y/o de enfermedades o condiciones inflamatorias.

14.- Al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11 para usarse en el tratamiento de dislipidemia diabética, dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad, enfermedad de la arteria coronaria, trombosis, angina, deficiencia renal crónica, enfermedad vascular periférica o apoplejía.

15.- Al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11 para usarse en la elaboración de un medicamento para el tratamiento de dislipidemia diabética, dislipidemia mixta, deficiencia cardiaca, hipercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus tipo II, diabetes tipo I, resistencia a la insulina, hiperlipidemia, anorexia nervosa, obesidad, enfermedad de la arteria coronaria, trombosis, angina, deficiencia renal crónica o apoplejía.

16.- Un método para el tratamiento de un sujeto humano o animal con una condición donde la sub-activación del receptor HM74A

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contribuye a la condición o donde la activación del receptor será benéfica, dicho método comprende la administración a dicho sujeto humano o animal de una cantidad efectiva de al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 7.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque el sujeto humano o animal tiene un trastorno de metabolismo lipídico incluyendo dislipidemia e hiperlipoproteinemia o una enfermedad o condición inflamatoria.

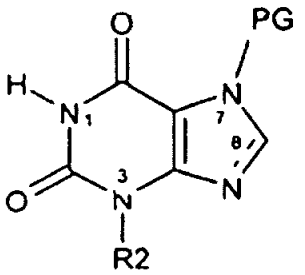
18.- Una formulación farmacéutica que comprende al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11 y al menos un diluyente, excipiente o portador farmacéuticamente aceptable.

19.- Una combinación para la administración junta o separadamente, consecutivamente o simultáneamente en formulaciones farmacéuticas separadas o combinadas, dicha combinación comprendiendo al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11 junto con al menos un agente terapéuticamente activo.

20.- Una formulación farmacéutica que comprende: (i) al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11; (ii) uno o más agentes terapéuticamente activos seleccionado de estatinas, fibratos, resinas de unión a ácido biliar y ácido nicotínico; y (iii) uno o más de un diluyente, excipiente o portador farmacéuticamente aceptable.

21.- Un método para la preparación de al menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 11 de una

material de inicio apropiado, por ejemplo compuesto o compuestos de la fórmula (II):



(II)

en donde PG= grupo protector, el método comprendiendo: (i) alquilación en N1 de una xantina N7 protegida; (ii) alquilación en N3 de una xantina N7 protegida; (iii) halogenación en C8; y (iv) desprotección de N7; en cualquier orden que provea desprotección se realiza después de la alquilación.

RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos de fórmula (I) que son derivados de xantina, procedimientos para la elaboración de dichos derivados, formulaciones farmacéuticas que contienen estos, compuestos y el uso de los compuestos en la terapia, por ejemplo, en el tratamiento de enfermedades donde la sub-activación del receptor HM74A contribuye a la enfermedad o donde la activación del receptor será benéfica.

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Figura 1

intensidad (conteos)

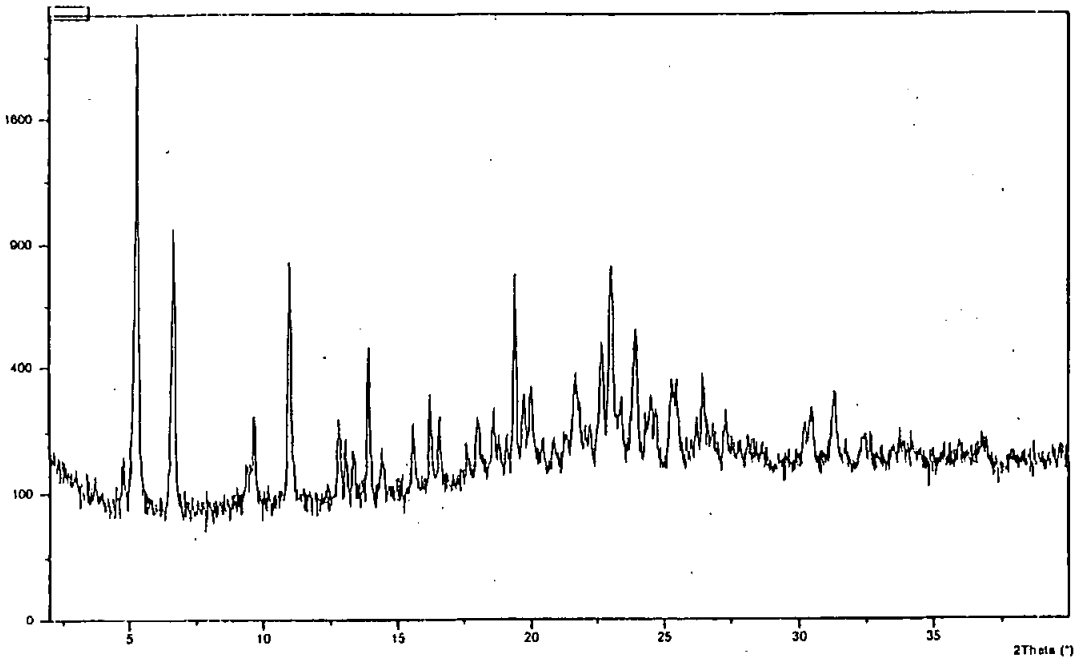

figura 1: datos XRPD de la forma 1 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina

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Figura 2

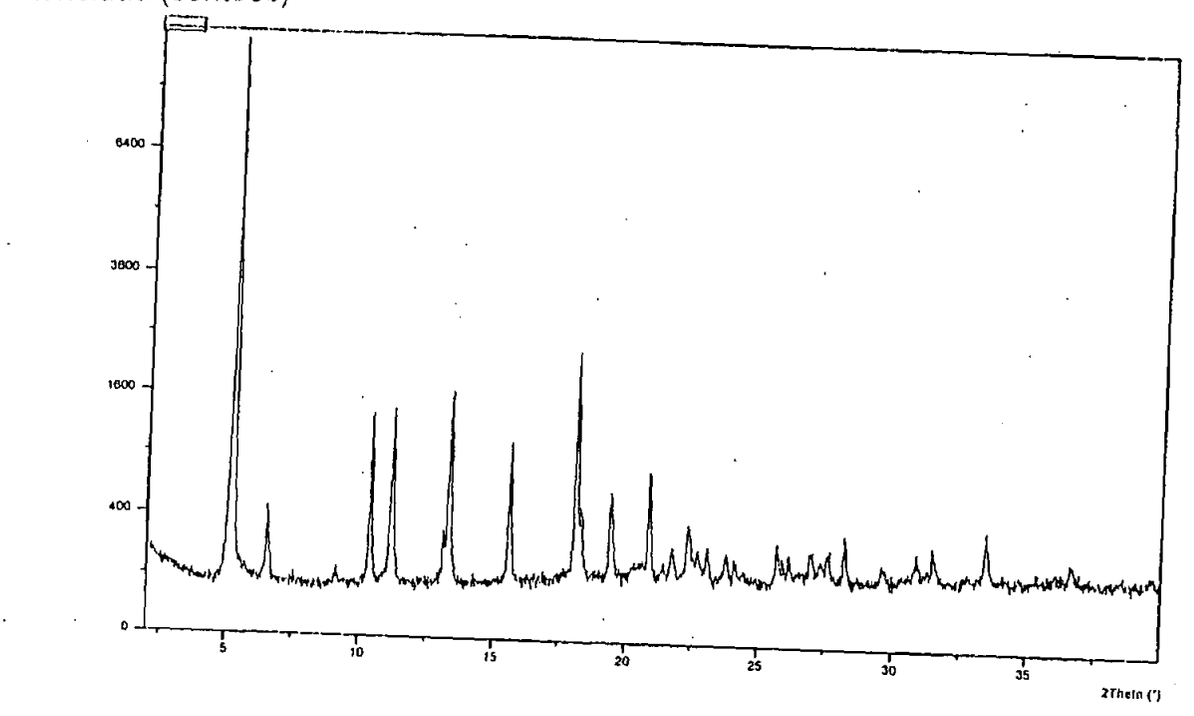

figura 2: datos XRPD de la forma 2 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona sustancialmente cristalina

Figura 3

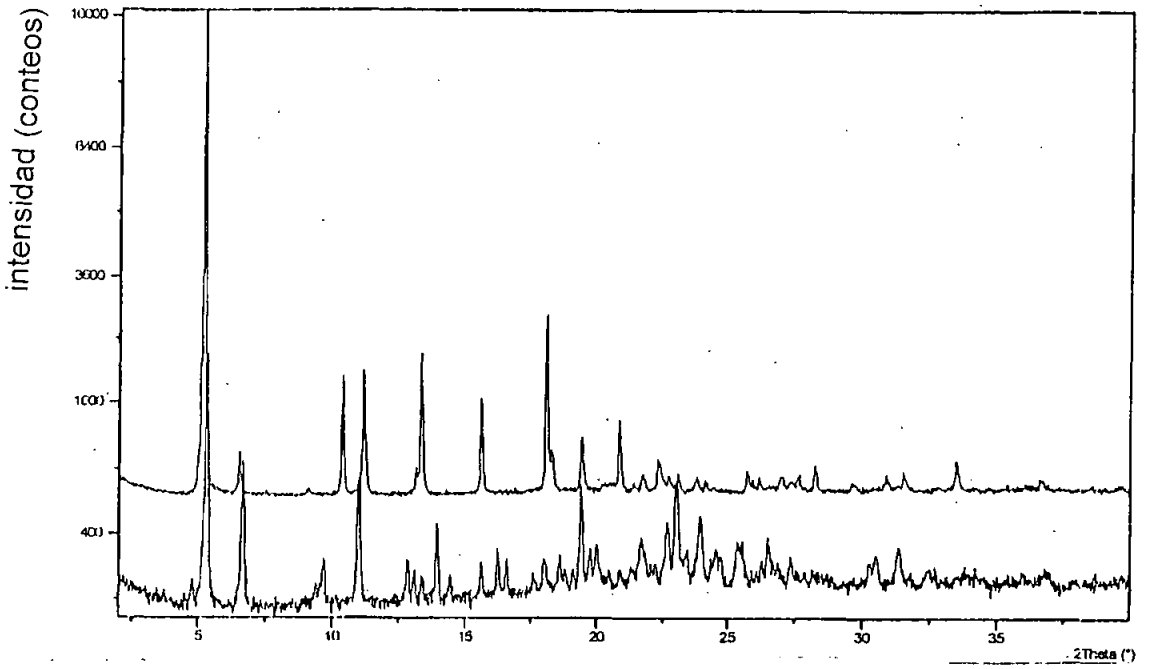

Figura 3 sobreposición de datos de la forma 1 (fondo), forma 2 (superior) (los datos se han desplazado para claridad).

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	1-21
A	WO 2005/016870 A (SMITHKLINE BEECHAM CORP [US]; CAMPBELL MATHEW [GB]; HATLEY RICHARD JON) 24 February 2005 (2005-02-24) the whole document	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 2006	22/11/2006

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/007865

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-17,19 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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No 08 013175 00000 0000

Fecha 2008 02 11 12 33 22 Dep 2020 NUECREACIONI
Tra 11 PATENTEIYII Lve 378 FASENACIONALI
Act 411 PRESENTACION Folios 489

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 [ ]

Firma Responsable

Fecha 11 FEB 2003

Carrera 13 No 27-00 Piso 5, 7 y 10
Conmutador 3 82 08 40
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491

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SMITHKLINE BEECHAM CORPORATION

REFERENCIA	Radicación No.	8 13175
	Solicitud internacional	PCT/EP2006/007865
	Fecha inicio fase nacional	10/03/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	3950

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 14 MAR. 2008
adpa11