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Industria y Comercio
SUPERINTENDENCIA

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Radicacion : 03018834 02220808 Folios: 252
Fecha (AMD): 2003-03-05 16:42:33
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-151 85 Sodertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Julie B. Bartlett, Sue Freeman, Peter Kenny, Andrew Morley, Paul Whittamore Dirección: AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido; (Respectivamente) Nacionalidad o Domicilio: Reino Unido (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/SE01/01880 Fecha 31-08-2001
Publicación Internacional No. WO 02/20530 A1 Fecha 14-03-2002

8 Título (54): PIRROLILAMIDAS BICÍCLICAS COMO INHIBIDORES DE GLUCÓGENO FOSFORILASA

7 Clasificación Internacional (51) A 61 K 31/403

6 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GB	06-09-2000	0021831.3

9 Comprobante de pago No. 03-2.632, 03-2.574 **Fecha** 05-03-2003

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

A 2

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [x] Comprobante de pago por reivindicación de prioridad. $112.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- [ ] 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)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar 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 12x12.
- [ ] 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.
- [ ] Otros

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

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

Industria y Comercio

SUPERINTENDENCIA

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Radicacion : 03018834 00000000 Folios: 262
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Tramite : 011 PCT-PATENT 279 FASE MACT A11 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

NIT : 800170...-2

RECIBO OFICIAL DE CAJA : 03 - 3...
FECHA : ...

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	V. PAGO
...ERRADA & CASTRO LTDA	CONSIGNACION	BANCO POPU...	050-...-6	...7050	18/01/2003	$2,...,...,...

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

CANT.	PERTINETICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 CONSTITUCC	35 INVENCION DE UNA PERTINEN EN MI	$ ...,...,...
		TOTAL :	$ ...,...,...

SON: SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE PAGO ANEXADO AL EXPEDIENTE No._____

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Industria y Com rcio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

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Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 6,574

FECHA : ENERO 31 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7417227	31/01/2003	1,051,360.00
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7417228	31/01/2003	13,573,160.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50009-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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foto y tarjeta
propietario
2020 SC Julio 9 2003

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(71) Solicitante *(para todos los países destinatarios con excepción de los Estados Unidos)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE)

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: BARTLETT, Julie, B. [GB/GB]; AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). FREEMAN, Sue [GB/GB]; AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). KENNY, Peter [GB/GB]; AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MORLEY, Andrew [GB/GB]; AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WHITTAMORE, Paul [GB/GB]; AstraZeneca R & D Alderley, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agente : ASTRAZENECA AB; Global Intellectual Property, S-151 85 Södertälje (SE)

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

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

Declaración bajo regla 4.17:
— de actividad inventiva *(regla 4.17(iv) para los Estados Unidos únicamente*

publicada:
— *con informe de búsqueda internacional*
— *antes de la expiración del límite cronológico para modificar las reivindicaciones y tiene que volverse a publicar en la eventualidad de recibo de las modificaciones*

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

WO 02/20530 A1

(54) Título: PIRROLILAMIDAS BICÍCLICAS COMO INHIBIDORES DE GLUCÓGENO FOSFORILASA

(57) Extracto: Derivados de amida heterocíclica, de fórmula (I): en donde -X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^5-CR^4=CR^5- y -CR^4=CR^5-NR^5-; o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*; (con condiciones); poseen actividad inhibidora de glucógeno fosforilasa y, en consecuencia, son útiles en el tratamiento de estados patológicos asociados con un aumento en la actividad de glucógeno fosforilasa. Se describen procesos para la manufactura de dichos derivados de amida heterocíclica y composiciones farmacéuticas que los contienen.

Pirrolilamidas bicíclicas como inhibidores de glucógeno fosforilasa

La presente invención se refiere a derivados de amidas heterocíclicas, sus sales de aceptación farmacéutica y sus ésteres hidrolizables *in vivo*. Estas amidas heterocíclicas poseen actividad inhibidora de glicógeno fosforilasa y, en consecuencia, son útiles en el tratamiento de estados patológicos asociados con una mayor actividad glicógeno fosforilasa y, por lo tanto, son potencialmente útiles en métodos para el tratamiento de un animal de sangre caliente como el hombre. La invención tiene que ver igualmente con procesos para la manufactura de dichos derivados de amidas heterocíclicas, composiciones farmacéuticas que las contienen y su uso en la manufactura de medicamentos para inhibir actividad de glicógeno fosforilasa en un animal de sangre caliente como el hombre.

El hígado es el principal órgano que regula la glicemia en el estado pos-absorbente. Adicionalmente, aunque juega un papel menor en la contribución a niveles de glucosa pos-prandial en la sangre, la respuesta del hígado a fuentes exógenas de glucosa plasmática es clave para una capacidad de mantener la glicemia. Se considera que una mayor producción de glucosa hepática (HGO) juega un papel importante en mantener los niveles elevados de glucosa plasmática en ayunas observados en diabéticos tipo 2; particularmente aquellos con una FPG >140mg/dl (7.8mM). (Weyer y colaboradores, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., y colaboradores, (1992) Diabetes Care 15; 318-355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

Puesto que las terapias actuales orales anti-diabéticas fallan en llevar los niveles FPG a un rango no-diabético dentro de lo normal y puesto que niveles FPG (y glycHbA1c) elevados constituyen factores de riesgo tanto para enfermedad macrovascular (Charles, M.A. y colaboradores (1996) Lancet 348, 1657-1658; Coutinho, M. y colaboradores (1999) Diabetes Care 22; 233-240; Shaw, J.E. y colaboradores (2000) Diabetes Care 23, 34-39) y microvascular (DCCT Research Group (1993) New. Eng. J. Med.

329; 977-986), la disminución y normalización de niveles FPG continúa siendo una meta de tratamiento en la diabetes tipo 2.

Se ha estimado que, luego de un ayuno nocturno, el 74% de la HGO se deriva de glucogenólisis, derivándose el resto de precursores gluconeogénicos (Hellerstein y colaboradores (1997) Am J Physiol, 272: E163). La glicógeno fosforilasa es una enzima clave en la generación por glucogenólisis de glucosa-1-fosfato y, por lo tanto, la glucosa en el hígado y también en otros tejidos tales como músculos y tejido neuronal.

La actividad de la glicógeno fosforilasa del hígado es elevada en modelos diabéticos animales incluyendo el ratón db/db y la rata fa/fa (Aiston S y colaboradores (2000). Diabetologia 43, 589-597).

Se ha demostrado que la inhibición de la glicógeno fosforilasa con inhibidores de cloroindol (CP91149 y CP320626) reduce tanto la glucogenólisis estimulada por el glucagón y la producción de glucosa en hepatocitos (Hoover y colaboradores (1998) J Med Chem 41, 2934-8; Martin y colaboradores (1998) PNAS 95, 1776-81, WO 96/39384 y WO 96/39385). Adicionalmente, se reduce la concentración de glucosa plasmática, en una forma relativa a la dosis, en ratones db/db y ob/ob a raíz del tratamiento con estos compuestos.

Estudios en perros conscientes con exposición al glucagón en ausencia y presencia de otro inhibidor de glicógeno fosforilasa, Bay K 3401, demuestran también la utilidad potencial de dichos agentes en donde hay elevados niveles de glucagón en circulación, como en la diabetes Tipo y Tipo 2. En presencia de R 3401, la producción de glucosa hepática y los niveles de glucosa plasmática arterial luego de una exposición al glucagón se redujeron significativamente (Shiota y colaboradores, (1997), Am J Physiol, 273: E868).

ES 2,081,747 divulga que ciertos derivados de amida de 4*H*-tieno[3,2-b]pirroles y 4*H*-tieno[2,3-b]pirroles son antagonistas CCK y son útiles en el tratamiento de desórdenes de secreción gástrica y en la

regulación del apetito. Los compuestos divulgados en este documento se excluyen de las reivindicaciones de compuestos de la presente invención.

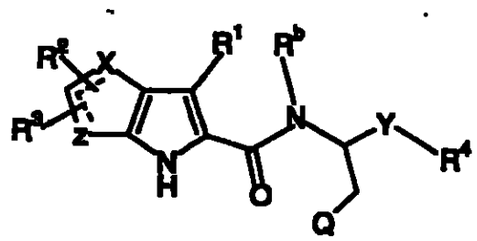
US 3,706,810 divulga que ciertos derivados *N*-(aminoalquil) de tieno[3,2-b]pirrol-5-carboxamida son útiles como agentes analgésicos y anti-depresivos. Los compuestos divulgados en este documento se excluyen de las reivindicaciones de compuestos de la presente invención.

US 4,751,231 divulga que ciertas tieno[2,3-b]pirrol-5-sulfonamidas son útiles en el tratamiento de presión intraocular elevada y glaucoma. Ciertas amidas se divulgan como intermedios. Los compuestos divulgados en este documento se excluyen de las reivindicaciones de compuestos de la presente invención.

US 4,794,120 divulga hidrazida de ácido 4*H*-tieno[3,2-b]pirrol-5-carboxílico e hidracida de ácido 6*H*-tieno[2,3-b]pirrol-5-carboxílico como intermedios en la preparación de (5-nitro-2-furanil)metilenohidrazidas que son antibacteriales, fungicidas y protozoacidas. Los compuestos divulgados en este documento se excluyen de las reivindicaciones de compuestos de la presente invención.

La solicitud co-pendiente EP 1088824 divulga que un compuesto de Fórmula A:

un estereoisómero, su sal de aceptación farmacéutica o su profármaco, o una sal de aceptación farmacéutica



A

del profármaco,

en donde

Q es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

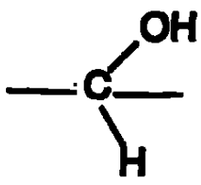
cada uno de z y X son independientemente (C, CH o CH_2), N, O ó S;

X^1 es NR^a, $-CH_2-$, O ó S;

cada ---- es independientemente un enlace o está ausente, con la condición que ambos ---- no sean simultáneamente enlaces;

R^1 es hidrógeno, halógeno, $-OC_1-C_8$alquilo, $-SC_1-C_8$alquilo, $-C_1-C_8$alquilo, $-CF_3$, $-NH_2$, $-NHC_1-C_8$alquilo, $-N(C_1-C_8alquil)_2$, $-NO_2$, -CN, $-CO_2H$, $-CO_2C_1-C_8$alquilo, $-C_2-C_8$alquenilo, o $-C_2-C_8$alquinilo;

cada R^a y R^b son independientemente hidrógeno o $-C_1-C_8$alquilo; Y es

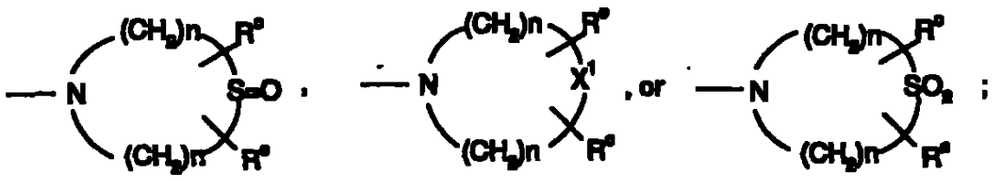


o está ausente;

R^2 y R^3 son independientemente hidrógeno, halógeno, $-C_1-C_8$alquilo, -CN, $-C\equiv C-Si(CH_3)_3$, $-OC_1-C_8$alquilo, $-SC_1-C_8$alquilo, $-CF_3$, $-NH_2$, $-NHC_1-C_8$alquilo,$-N(C_1-C_8alquil)_2$, $-NO_2$, $-CO_2H$, $-CO_2C_1-C_8$alquilo, $-C_2-C_8$alquenilo, o $-C_2-C_8$alquinilo, o R^2 y R^3 juntos con los átomos en el anillo al cual se unen forman un anillo de cinco o seis miembros que contienen de 0 a 3 heteroátomos y de 0 a 2 enlaces dobles;

R^4 es -C(=O)-A;

A es $-NR^dR^d$, $-NR^aCH_2CH_2OR^a$,



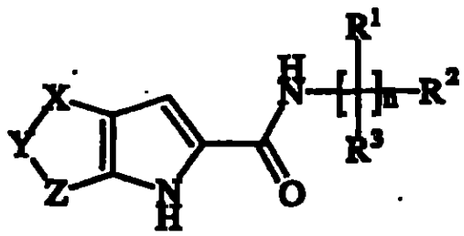
cada R^d es independientemente hidrógeno, C_1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido; cada R^c es independientemente hidrógeno, $-C(=O)OR^a$,$-OR^a$, $-SR^a$, o $-NR^aR^a$; y cada n es independientemente 1-3,

son útiles en tratar diabetes, resistencia a la insulina, neuropatía diabética, nefropatía diabética, retinopatía diabética, cataratas, hiperglicemia,

hipercolesterolemia, hipertensión, hiperinsulinemia, hiperlipidemia, aterosclerosis, o isquemia de tejido tisular. Estos compuestos se excluyen de la presente solicitud.

Las amidas heterocíclicas de la presente invención poseen actividad inhibidora de glicógeno fosforilasa y, en consecuencia, se espera que sean útiles en el tratamiento de diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca y obesidad, particularmente diabetes tipo 2.

La presente invención proporciona un compuesto de fórmula (I):



(I)

en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4=N, -NR^6- CR^4=CR^5 -CR^4=CR^5 -NR^6.-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquilsulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

R^6 es hidrógeno o C_{1-6}alquilo;

R^1 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino; C_{3-8}cicloalquilo, C_{3-8}cicloalquilo, C_{1-6}alquilo, arilo, arilC_{1-6}alquilo, grupo heterocíclico y (grupo heterocíclico)C_{1-6}alquilo; en donde R^1 puede sustituirse opcionalmente por uno o más grupos seleccionados de P y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R;

R^2 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo,
C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, sulfamoilamino, *N*-(C_{1-6}alquil)sulfamoilamino, *N,N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonilaminocarbonilo, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino y un grupo -E-F-G-H;

en donde E y G se seleccionan independientemente de u enlace directo, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- y -C(O)NR^aSO_2-; en donde R^a y

R^b se seleccionan independientemente de hidrógeno o C_{1-6}alquilo que se sustituye opcionalmente por un grupo V ;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

R^3 es hidrógeno o C_{1-6}alquilo;

n se selecciona de 0-4; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes;

P, S y Q se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*-*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*-*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N*-*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, arilo y un grupo heterocíclico; en donde P, S y Q pueden sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-

etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N-N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

R, T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonilo, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo en donde R, T y U pueden sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V;

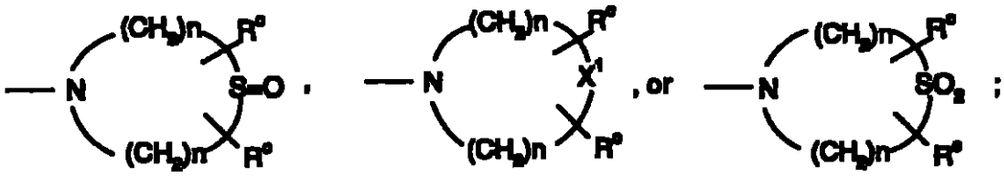
o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*; con las condiciones:

i) cuando -X-Y-Z- es -S-CH=CH-, R^2-(CR^1R^3)$_n$- no puede ser amino, 1-fenil-5-metil-1H-1,5-benzodiazepina-2,4(3H,5H)dion-3-ilo, 1-metil-5-fenil-2-oxo- 2,3-dihidro-1H- benzo(E)(1,4)diazepin-3-ilo, 2-(4-fenil-1,2,5,6-tetrahidropirid-1-il)etilo, 3-(4-fenil-1,2,5,6-tetrahidropirid-1-il)propilo, 2-(4-fenilpiperazin-1-il)etilo, 2-(*N*-metilamino)etilo, 2-morfolinoetilo o 2-(*N*-metil-*N*-bencilamino)etilo;

ii) cuando -X-Y-Z- es -CH=CH-S-, R^2-(CR^1R^3)$_n$- no puede ser amino o 1-metil-5-fenil-2-oxo- 2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo;

iii) cuando -X-Y-Z- es -CH=C(SO_2NH_2)-S-, R^2-(CR^1R^3)$_n$- no puede ser metilo o isobutilo; y

iv) cuando -X-Y-Z- es como se definió inicialmente, n es 1, R^1 es arilmetilo, arilmetilo sustituido, (grupo heterocíclico)metilo y (grupo heterocíclico)metilo sustituido y R^3 es hidrógeno entonces R^2 no es un grupo -C(=O)-A o un grupo -CH(OH)-C(=O)-A en el cual A es NR^dR^d, $NR^aCH^2CH^2OR^a$, o



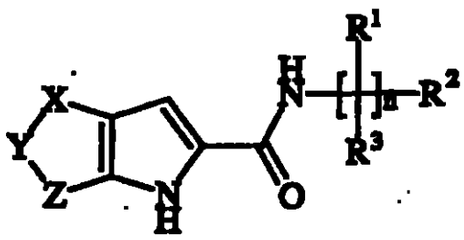
cada R^a y R^b es independientemente hidrógeno o -C_1-C_8alquilo;

cada R^d es independientemente hidrógeno, C_1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^c es independientemente hidrógeno, -C(=O)OR^a, -OR^a, -SR^a, o -NR^aR^a; y cada n es independientemente 1-3, y

X^1 es NR^a, -CH_2-, O ó S.

En otro aspecto la presente invención provee un compuesto de fórmula (I):



(I)

(1) en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-,-N=CR^4-S-, -S-CR^4=N-, -NR^6-R^4=CR^5- y -CR^4-CR^5-NR^6-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi; C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N*-(C_{1-6}alquilsulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

R^6 es hidrógeno o C_{1-6}alquilo;

R^1 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, C_{3-8}cicloalquilC_{1-6}alquilo, arilo, arilC_{1-6}alquilo, grupo heterocíclico y (grupo heterocíclico)C_{1-6}alquilo; en donde R^1 puede sustituirse opcionalmente por uno o más grupos seleccionados de P y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R;

R^2 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, sulfamoilamino, *N*-(C_{1-6}alquil)sulfamoilamino, *N,N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonilaminocarbonilo, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino y un grupo -E-F-G-H;

en donde **E** y **G** se seleccionan independientemente de un enlace directo, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- y -C(O)NR^aSO_2-; en donde R^a y R^b se seleccionan independientemente de hidrógeno o C_{1-6}alquilo;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

R^3 es hidrógeno o C_{1-6}alquilo;

n se selecciona de 0-4; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes;

P, S y Q se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo; C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, arilo y grupo heterocíclico; en donde P, S y Q pueden sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

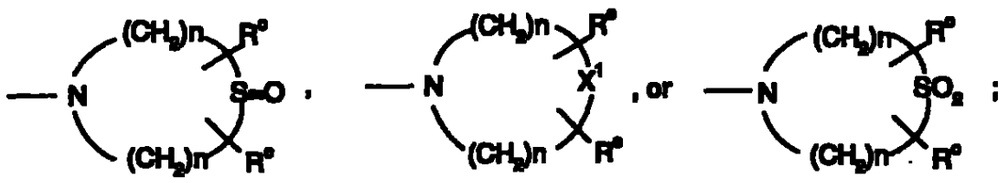
V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-

etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo;

R, T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonilo, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*;

con las condiciones: i) cuando -X-Y-Z- es -S-CH=CH-, R_2-(CR^1R^3)$_n$- no puede ser amino, 1-fenil-5-metil-1H-1,5-benzodiazepina-2,4(3H,5H)dion-3-ilo, 1-metil-5-fenil-2-oxo-2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo, 2-(4-fenil-1,2,5,6-tetrahidropirid-1-il)etilo, 3-(4-fenil-1,2,5,6-tetrahidropirid-1-il)propilo, 2-(4-fenilpiperazin-l-il)etilo, 2-(*N*-metilamino)etilo, 2-morfolinoetilo o 2-(*N*-metil-*N*-bencilamino)etilo;

ii) cuando X-Y-Z- es -CH=CH-S-, R^2-(CR^1R^3)$_n$- no puede ser amino o 1-metil-5-fenil-2-oxo- 2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo; iii) cuando -X-Y-Z- es -CH=C(SO_2NH_2)-S-, R^2-(CR^1R^3)$_n$- no puede ser metilo o isobutilo; y iv) cuando -X-Y-Z- es como se definió inicialmente, n es 1, R^1 es arilmetilo, arilmetilo sustituido, (grupo heterocíclico)metilo y (grupo heterocíclico)metilo sustituido y R^3 es hidrógeno entonces R^2 no es un grupo -C(=O)-A o un grupo -CH(OH)-C(=O)-A e el cual A es NR^dR^d, -$NR^aCH_2CH_2OR^a$, o



cada R^a y R^b es independientemente hidrógeno o -C_1-C_8alquilo;

cada R^d es independientemente hidrógeno, C1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^c es independientemente hidrógeno, -C(=O)OR^a, -OR^a, -SR^a, o -NR^aR^a; y cada n es independientemente 1-3, y

X^1 es NR^a, -CH_2-, O ó S.

En esta especificación el término "alquilo" incluye grupos alquilo de cadena recta y ramificada pero referencias a grupos alquilo individuales tales como "propilo" son específicos únicamente de la versión de cadena recta. Por ejemplo, "C_{1-6}alquilo" incluye C_{1-4}alquilo, propilo, isopropilo y *t*-butilo. No obstante, referencias a grupos alquilo individuales tales como 'propilo' son específicos de la versión de cadena recta únicamente y referencias a grupos alquilo individuales de cadena ramificada tales como 'isopropilo' son específicos de la versión de cadena ramificada únicamente. Una convención similar se aplica a otros radicales, por ejemplo "arilC_{1-6}alquilo" incluye arilC_{1-4}alquilo, bencilo, 1-feniletilo y 2-feniletilo. El término "halo" se refiere a fluoro, cloro, bromo y yodo.

Donde sustituyentes opcionales se eligen de "uno o más" grupos hay que entender que esta definición incluye todos los sustituyentes que se escogen de uno de los grupos especificados o los sustituyentes que se escogen de dos o más de los grupos especificados.

Un "grupo heterocíclico" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado que contiene 4-12 átomos de los cuales por lo menos un átomo se elige de nitrógeno, azufre u oxígeno, que pueden, a menos que se especifique otra cosa, enlazarse a carbono o nitrógeno, en donde un grupo -CH_2- puede reemplazarse opcionalmente por un -C(O)- y un átomo de azufre en el anillo puede oxidarse opcionalmente para formar el S-óxido(s). Ejemplos de valores apropiados del término "grupo heterocíclico" son morfolino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, indolilo, quinolilo, tienilo, 1,3-benzodioxolilo, 1,3-dioxolanilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, 2-oxazolidinonilo, 5-isoxazolonilo, benz-3-azepinilo, 1,4-benzodioxanilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, 3-pirazolin-5-onilo, tetrahidropiranilo, bencimidazolilo, benztiazolilo, imidazo[1,2-a]piridilo, pirimidilo, pirazinilo, piridazinilo, isoxazolilo, 4-piridona, 1-isoquinolon1, 2-pirrolidon1, 4-tiazolidona 2,3-dihidro-1,5-benzotiazepin-4(5H)-ona. Preferiblemente un "grupo heterocíclico" es piridilo, imidazolilo, tiazolilo, quinolilo, tienilo,

1,3-benzodioxolilo, 1,3-dioxolanilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, 2-oxazolidinonilo, 5-isoxazolonilo, benz-3-azepinilo, hidantoinilo, 1,4-benzodioxanilo, tiomorfolino, 3-pirazolin-5-onilo, bencimidazolilo, benztiazolilo, imidazo[1,2-a]piridilo, pirimidilo, pirazinilo, y 2,3-dihidro-1,5-benzotiazepin-4(5H)-ona.

"Arilo" es un anillo mono o bicíclico parcialmente saturado o insaturado que contiene 4-12 átomos de carbono, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un -C(O)-. Preferiblemente arilo es fenilo, naftilo, 1,2,3,4-tetrahidronaftilo (tetralinilo) o indanilo. Más preferiblemente arilo es fenilo, naftilo o 1,2,3,4-tetrahidronaftilo. Muy preferiblemente arilo es fenilo, o naftilo.

Un ejemplo de "C_{1-6}alcanoiloxi" es acetoxi. Ejemplos de "C_{1-6}alcoxicarbonilo" incluyen C_{1-4}alcoxicarbonilo, metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo. Ejemplos de "C_{1-6}alcoxicarbonilamino" incluyen metoxicarbonilamino, etoxicarbonilamino, *n*- y *t*-butoxicarbonilamino. Ejemplos de "C_{1-6}alcoxi" incluyen metoxi, etoxi y propoxi. Ejemplos de "C_{1-6}alcanoilamino" incluyen formamido, acetamido y propionilamino. Ejemplos de "C_{1-6}alquil$S(O)_a$ en donde a es 0 a 2" incluyen C_{1-4}alquilsulfonilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo. Ejemplos de "C_{1-6}alquilsulfonilamino" incluyen metilsulfonilamino, etilsulfonilamino y propilsulfonilamino. Ejemplos de "C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino" incluyen metilsulfonil-*N*-metilamino, etilsulfonil-*N*-metilamino y propilsulfonil-*N*-etilamino. Ejemplos de "C_{1-6}alcanoilo" incluyen C_{1-4}alcanoilo, propionilo y acetilo. Ejemplos de "*N*-(C_{1-6}alquil)amino" incluyen metilamino y etilamino. Ejemplos de *N*-*N*-(C_{1-6}alquil)2amino" incluyen di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino. Ejemplos de "C_{2-6}alquenilo" son vinilo, alilo y 1-propenilo. Ejemplos de "C_{2-6}alquinilo" son etinilo, 1-propinilo y 2-propinilo. Ejemplos de "*N*-(C_{1-6}alquil)sulfamoilo" son *N*-(metil)sulfamoilo y *N*-(etil)sulfamoilo. Ejemplos de "*N*-(C_{1-6}alquil)$_2$ sulfamoilo" son *N*,*N*-(dimetil)sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo.

Ejemplos de "*N*-(C_{1-6}alquil)carbamoilo" son *N*-(C_{1-4}alquil)carbamoilo, metilaminocarbonilo y etilaminocarbonilo. Ejemplos de *N,N*-(C_{1-6}alquil)$_2$carbamoilo" son *N,N*-(C_{1-4}alquil)carbamoilo, dimetilaminocarbonilo y metiletilaminocarbonilo. Ejemplos de "anillo C_{3-8}cicloalquilo" son ciclopropilo y ciclohexilo. Ejemplos de "(grupo heterocíclico)C_{1-6}alquilo" incluyen piridilmetilo, 3-morfolinopropilo y 2-pirimid-2-iletilo. Ejemplos de "C_{3-8}cicloalquilC_{1-6}cicloalquilo" incluyen ciclopropilmetilo y 2-ciclohexilpropilo. "*N*-(C_{1-6}alquil)sulfamoilamino" son *N*-(metil)sulfamoilamino y *N*-(etil)sulfamoilamino. Ejemplos de "*N*-(C_{1-6}alquil)$_2$sulfamoilamino" son *N,N*-(dimetil)sulfamoilamino y *N*-(metil)-*N*-(etil)sulfamoilamino. Ejemplos de "C_{1-6}alquilsulfonilaminocarbonilo" incluyen metilsulfonilaminocarbonilo, etilsulfonilaminocarbonilo y propilsulfonilaminocarbonilo.

Una sal apropiada de aceptación farmacéutica de un compuesto de la invención es, por ejemplo, una sal de adición de ácido de un compuesto de la invención que es suficientemente básica, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhídrico, bromhídrico, sulfúrico, fosfórico, trifluoroacético, cítrico o maleico. Adicionalmente una sal apropiada de aceptación farmacéutica de un compuesto de la invención que es suficientemente acídica es una sal de metal alcalino, por ejemplo una sal de potasio o sodio, una sal de metal alcalinotérreo, por ejemplo una sal de magnesio o calcio, una sal de amonio o una sal con una base orgánica que proporciona un catión de aceptación fisiológica, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Un éster hidrolizable *in vivo* de un compuesto de la fórmula (I) que contiene un grupo carboxi o hidroxi es, por ejemplo, un éster de aceptación farmacéutica que se hidroliza en el organismo humano o animal para producir el ácido o alcohol original. Ésteres apropiados de aceptación farmacéutica para carboxi incluyen ésteres C_{1-6}alcoximetilo por ejemplo metoximetilo, ésteres C_{1-6}alcanoiloximetilo por ejemplo pivaloiloximetilo,

ésteres ftalidilo, ésteres C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquilo por ejemplo 1-ciclohexilcarboniloxietilo; ésteres 1,3-dioxolen-2-onilmetilo por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres C_{1-6}alcoxicarboniloxietilo por ejemplo 1-metoxicarboniloxietilo y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Un éster hidrolizable *in vivo* de un compuesto de la fórmula (I) que contiene un grupo hidroxi incluye esters inorgánicos tales como esters de fosfato y éteres α-aciloxialquilo y compuestos relacionados que, como resultado de la hidrólisis *in vivo* de la descomposición esteárica para producir el grupo hidroxi original. Ejemplos de éteres α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de un éster hidrolizable *in vivo* que forma grupos para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para producir ésteres de carbonato alquilo), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo. Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un átomo de nitrógeno en anillo mediante un grupo metileno a la posición 3- ó 4- del anillo benzoilo.

Algunos compuestos de la fórmula (I) pueden tener centros quirales y/o centros isoméricos geométricos (isómeros E- y Z-), y hay que entender que la invención comprende todos aquellos isómeros geométricos y diastereoisómeros ópticos, que poseen actividad inhibidora de glucógeno fosforilasa.

La invención se refiere a cualesquiera y a todas las formas tautoméricas de los compuestos de la fórmula (I) que poseen actividad inhibidora de glucógeno fosforilasa.

Hay que entender también que ciertos compuestos de la fórmula (I) pueden existir en formas solvatadas así como no solvatadas como, por ejemplo, formas hidratadas. Hay que entender que la invención comprende

todas las formas solvatadas que poseen actividad inhibidora de glucógeno fosforilasa.

Valores preferidos de R^1, R^2, R^3, -X-Y-Z- y n son los siguientes. Dichos valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más adelante en el texto.

Preferiblemente -X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5- y -N=CR^4-S-.

More preferiblemente -X-Y-Z- se selecciona de -S-CR^4=CR^5- y -CR^4=CR^5-S-.

En un aspecto de la invención preferiblemente -X-Y-Z- se selecciona de -S-CR^4=CR^5-.

En otro aspecto de la invención preferiblemente -X-Y-Z- se selecciona de -CR^4=CR^5-S-.

Preferiblemente R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

Más preferiblemente R^4 y R^5 se seleccionan independientemente de hidrógeno, cloro, bromo o metilo.

Particularmente R^4 y R^5 se seleccionan independientemente de hidrógeno o cloro.

Más particularmente R^4 y R^5 son ambos cloro.

Preferiblemente -X-Y-Z- se selecciona de -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH-, -N=C(Me)-S- y -S-CH=CCl-. Más preferiblemente -X-Y-Z- se selecciona de -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH- y -N=C(Me)-S-.

Muy preferiblemente -X-Y-Z- se selecciona de -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH- y -S-CH=C(Cl)-.

Particularmente -X-Y-Z- se selecciona de -S-C(Cl)=C(Cl)-.

En un aspecto de la invención, preferiblemente R^6 es hidrógeno.

En otro aspecto de la invención, preferiblemente R^6 es C_{1-6}alquilo.

Preferiblemente R^1 se selecciona de hidrógeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxicarbonilo, arilC_{1-6}alquilo y (grupo heterocíclico)C_{1-6}alquilo; en donde R^1 puede sustituirse opcionalmente en carbono por uno o más grupos seleccionados de P; y

P se selecciona de hidroxi y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alkil)amino.

Más preferiblemente R^1 se selecciona de hidrógeno, hidroxi, metilo, metoxicarbonilo, bencilo e imidazol-4-ilmetilo; en donde R^1 puede sustituirse opcionalmente por uno o más grupos seleccionados de P; y

P se selecciona de hidroxi y mesil-*N*-(metil)amino.

Particularmente R^1 se selecciona de hidrógeno, hidroxi, metilo, metoxicarbonilo, mesil-*N*-(metil)aminometilo, bencilo, hidroximetilo e imidazol-4-ilmetilo.

Más particularmente R^1 se selecciona de hidrógeno, mesil-*N*-(metil)aminometilo o bencilo.

Preferiblemente R^2 se selecciona de *N,N*-(C_{1-4}alquil)$_2$carbamoilo, *N*-*N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilaminocarbonilo y un grupo -E-F-G-H;

en donde E y G se seleccionan independientemente de un enlace directo, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- y -NR^aC(O)O-; en donde R^a es hidrógeno;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

S se selecciona de halo, hidroxi, trifluorometilo, sulfamoilo, ureido, C_{1-6}alquilo, C_{1-6}alcoxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino y arilo; en donde S puede sustituirse opcionalmente por uno o más grupos seleccionados de V;

Q es hidroxi;

V es carbamoil; y

T se selecciona independientemente de C_{1-4}alquilo o fenilo.

Más preferiblemente R^2 se selecciona de *N,N*-dimetilcarbamoilo, *N,N*-dimetilsulfamoilamino, mesilaminocarbonilo y un grupo -E-F-G-H;

en donde E y G se seleccionan independientemente de un enlace directo, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- y -$NR^aC(O)O$-; en donde R^a es hidrógeno;

F es metileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de fenilo, naftilo, ciclopropilo, tiomorfolino, piridilo, tiazolilo, isotiazolilo, morfolinilo, 2,3-dihidro-1,5-benzotiazepin-4(5H)-onilo, 5-oxo- 3-pirazolinilo, 2-oxazolidinonilo, 5-hidroxi-1,3,4,5-tetrahidro-benzo[b]azepin-2-onilo, 5-oxo-2-isoxazolinilo, imidazo[1,2-a]piridinilo, benzotiazolilo, 2,5-dioxoimidazolidinilo, pirazinilo, piridazinilo, imidazolilo, bencimidazolilo, tetrazolilo, quinolilo, 1,3-dioxolanilo y tienilo; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si un grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

S se selecciona de fluoro, cloro, hidroxi, trifluorometilo, sulfamoilo, ureido, metilo, etilo, metoxi, *N,N*-dimetilamino, acetamido y fenilo; en donde S puede sustituirse opcionalmente por uno o más grupos seleccionados de V;

Q es hidroxi;

V es carbamoilo; y

T se selecciona independientemente de metilo o fenilo.

Particularmente R^2 se selecciona de *N,N*-dimetilcarbamoilo, *N,N*-dimetilsulfamoilamino, mesilaminocarbonilo, 2-metoxifenilo, fenoxi, 2-fenilciclopropilo, tien-2-ilo, 4-fluorofenilo, benzoilo, tiomorfolino, anilinocarbonilo, pirid-2-ilamino, tiazol-2-ilo, bencilsulfonilamino, 2,3-dihidro-1,5-benzotiazepin-4(5H)-ona-3-ilo, 1-fenil-2,3-dimetil-5-oxo-3-

pirazolin-4-ilo, 3-fenil-2-oxazolidinon-5-ilo, 5-hidroxi-1,3,4,5-tetrahidro-benzo[b]azepin-2-onilo, 3-fenil-5-oxo-2-isoxazolin-4-ilo, imidazo[1,2-a]piridin-2-ilo, benzotiazol-2-ilo, 2,5-dioxoimidazolidin-3-ilo, naft-2-ilaminocarbonilo, fenilo, 4-sulfamoilfenetilo, 4-(*N*,*N*-dimetilamino)fenilo, 4-sulfamoilfenilo, anilino, 4-hidroxifenilo, quinolin-3-ilo, 4-clorofenilo, 2-metoxipirid-5-ilo, 3-metilisotiazol-5-ilo, 3-trifluorometilpirid-2-ilo, tetrazol-5-ilo, benciloxicarbonilamino, benzimidazol-2-ilo, 2- trifluorometilpirid-5-ilo, piridazin-2-ilo, piridazin-3-iloxi, pirid-2-ilo, imidazol-5-ilo, 4-acetamidofenoxi, 2-ureidotiazol-4-ilo, benciltio, 2-fenil-1,3-dioxolan-2-ilo, 4- carbamoilmetilfenoxi, (*N*-bencilcarbamoilmetil), fenetilo, 3-fenilpropilo, [2-(2-hidroxifenil)etil], -(α,α-dimetilfennetil), (1-fenilciclobutil)metil), (β-metilfenetil), (1,2,3,4-tetrahidronaft-2-il), bencilo, (*N*-bencil-*N*-metilcarbamoilmetil), (*N*-metil-*N*-fenilcarbamoilmetil), [*N*-(2-cianoetil)-*N*-fenilcarbamoilmetil], [*N*-(4-metoxifenil)carbamoilmetil], [*N*-(4-fluorofenil)carbamoilmetil], [*N*-(4-nitrofenil)carbamoilmetil], [*N*-(2,6-dimetilfenil)carbamoilmetil], [*N*-metil-*N*-(4-metilfenil) carbamoilmetil], [*N*-metil-*N*-(3- metilfenil)carbamoilmetil], [*N*-(3-clorofenil)-*N*-metilcarbamoil-metil], [*N*-(2-hidroxietil)-*N*-fenilcarbamoilmetil], [*N*-(1,1-dimetil-2-hidroxietil)carbamoilmetil], [*N*-(2-hidroxietil)-*N*-metilcarbamoilmetil], [*N*-(2-hidroxietil)carbamoilmetil], [*N*-(3-hidroxipropil)carbamoilmetil], [*N*-(4-hidroxibutil)carbamoilmetil], {*N*-[bis(hidroximetil)metil]carbamoilmetil}, [*N*-(2,3-dihidroxipropil)carbamoilmetil], [N-(4-hidroximetilfenil)-carbamoilmetil], [*N*-(5-isoquinolil)carbamoilmetil], [*N*-(3-hidroximeti)lfenil]-carbamoilmetil], {*N*-[4-(2-hidroxietil)fenil]carbamoil-metil}, [*N*-(2,4-difluorofenil)-*N*-metilcarbamoilmetil], [(1,2,3,4-tetrahidro-1-quinolil)carbonilmetil], [*N*-(2-cianoetil)-*N*-metilcarbamoilmetil], [*N*-(4-hidroxipiperidino)carbamoilmetil], (*N*-ciclopentilcarbamoilmetil), (*N*-isopropilcarbamoilmetil), (*N*-isopropil-*N*-metilcarbamoilmetil), (tiomorfolincarbonilmetil), (morfolinocarbonilmetil), [(1,1-dioxotiomorfolino)carbonilmetil], [(l-oxotiomorfolino)-carbonilmetil], (2-indanil), (benz[1,2]oxazol-3-ilmetil), {2-[2-(hidroximetil)fenil]-etil}, (4-fenilisoxazol-3-ilmetil), {2-[2-(2-morfolino-etoxi)fenil]etil}, {2-[2-

(metoxicarbonil-metoxi)fenil]etil}, {2-[2-(carboxi-metoxi)fenil]etil}, [2-(3-metoxifenil)etil], (2-oxo-1,2,3,4-tetrahidroquinol-3-il), {2-[2-(2-metoxietoxi)fenil]etil}, {2-[2-(carbamoilmetoxi)fenil]etil}, {2-[2-(*N*-metilcarbamoilmetoxi)fenil]etil}, {2-[2-(*N*,*N*-dimetilcarbamoil-metoxi)fenil]etil}, 2-[2-(morfolinocarbonilmetoxi)-fenil]etilo, 2-[2-(*N*-bencilcarbamoilmetoxi)fenil]etilo, 2-[2-(4-hidroxipiperidinocarbonilmetoxi)-fenil]etilo, [1-(5-etoxicarbonil-1,3,4-oxadiazo-2-il)-2-feniletil], [1-(4-metoxicarbonil-oxazo-5-il)-2-feniletil], [2-feniletil-1-(pirid-3-il)], [2-feniletil-1-(3-fenil-1,2,4-oxadiazo-5-il)], (1-hidroxiindan-2-il), [(1*S*,2*S*)-2-indan-1-ol], [(1*R*,2*R*)- 2-indan-1-ol], (3-indanil), (1-hidroxi-l,2,3,4-tetrahidronaft-2-il), (6-fluoro-1-hidroxiindan-2-il), (7-metoxi-1-oxo-1,2,3,4-tetrahidronaft-2-il), -(3-metilisoxazol-5-il)metil], (4-hidroxi-1,1-dioxotetrahidrotiofen-3-il), -{*N*-metil-*N*-[(1-oxo-l,2,3,4-tetrahidronaft-2-il)metil]carbamoilmetil}, (3-metilisoxazol-5-il)metil], (4-hidroxi-1,1-dioxotetrahidrotiofen-3-il), {n-metil-*N*-[(1-oxo-1,2,3,4-tetrahidronaft-2-il)metil]carbamoilmetil}, (2-oxo-1,2,3,4-tetrahidroquinol-3-il), (1,2,3,4-tetrahidroquinol-3-il), (1-metil-2-oxo-1,2,3,4-tetrahidroquinol-3-il), (3-oxo-2,3,4,5-tetrahidro-1H-benz[2]azepin-4-il), (1-metoxiindan-2-il), {l-[*N*-(1,1-dimetiletoxi)carbonilamino]indan-2-il}, (1-aminoindan-2-il)], (1-acetamidoindan-2-il), [1-(metanosulfonamido)indan-2-il], [1-(metilamino)indan-2-il], o [1-(*N*-metilacetamido)indan-2-il].

Más particularmente R^2 se selecciona de *N*,*N*-dimetilcarbamoilo, *N*,*N*-dimetilsulfamoilamino, mesilaminocarbonilo, 2-metoxifenilo, fenoxi, 2-fenilciclopropilo, tien-2-ilo, 4-fluorofenilo, benzoilo, tiomorfolino, anilinocarbonilo, pirid-2- ilamino, tiazol-2-ilo, bencilsulfonilamino, 2,3-dihidro-1,5-benzotiazepin-4(5H)-on-3-ilo, 1-fenil-2,3-dimetil-5-oxo-3-pirazolin-4-ilo, 3-fenil-2-oxazolidinon-5-ilo, 5- hidroxi-1,3,4,5-tetrahidro-benzo[b]azepin-2-onilo, 3-fenil-5-oxo-2-isoxazolin-4-ilo, imidazo[1,2-a]piridin-2-ilo, benzotiazol-2-ilo, 2,5-dioxoimidazolidin-3-ilo, naft-2-ilaminocarbonilo, fenilo, 4-sulfamoilfenetilo, 4-(*N*,*N*-dimetilamino)fenilo,

4-sulfamoilfenilo, anilina, 4-hidroxifenilo, quinolin-3-ilo, 4-clorofenilo, 2-metoxipirid-5-ilo, 3-metilisotiazol-5-ilo, 3-trifluorometilpirid-2-ilo, tetrazol-5-ilo, benciloxicarbonilamino, benzimidazol-2-ilo, 2-trifluorometilpirid-5-ilo, piridazin-2-ilo, piridazin-3-iloxi, pirid-2-ilo, imidazol-5-ilo, 4-acetamidofenoxi, 2-ureidotiazol-4-ilo, benciltio, 2-fenil-1,3-dioxolan-2-ilo y 4-carbamoilmetilfenoxi.

Muy particularmente R^2 se selecciona de *N,N*-dimetilcarbamoilo, fenoxi, 2-fenilciclopropilo, tien-2-ilo, 4-fluorofenilo, benzoilo, tiomorfolino, anilinocarbonilo, pirid-2-ilamino o tiazol-2-ilo.

Preferiblemente R^3 es hidrógeno.

Preferiblemente n se selecciona de 0-3; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes.

Más preferiblemente n se selecciona de 0-2; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes.

En un aspecto de la invención preferiblemente n es 2; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes.

En un aspecto de la invención preferiblemente n es 1.

En un aspecto de la invención preferiblemente n es 0.

En otro aspecto de la invención, compuestos preferidos de la invención son uno cualquiera de los Ejemplos o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*.

En otro aspecto la presente invención provee un compuesto de fórmula (I) (como se describe más arriba en el texto) en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5- y -N=CR^4-S-;

R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo;

R^1 se selecciona de hidrógeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxicarbonilo, arilC_{1-6}alquilo y (grupo heterocíclico)C_{1-6}alquilo; en donde R^1 puede sustituirse opcionalmente por uno o más grupos seleccionados de P; y

P se selecciona de hidroxi y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

R^2 se selecciona de *N,N*-(C_{1-4}alquil)$_2$carbamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilaminocarbonilo y un grupo -E-F-G-H;

en donde E y G se seleccionan independientemente de un enlace directo, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- y -$NR^aC(O)O$-; en donde R^a es hidrógeno;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

S se selecciona de halo, hidroxi, trifluorometilo, sulfamoilo, ureido, C_{1-6}-alquilo, C_{1-6}alcoxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino y arilo; en donde S puede sustituirse opcionalmente por uno o más grupos seleccionados de V;

Q es hidroxi;

V es carbamoilo; y

T se selecciona independientemente deC_{1-4}alquilo o fenilo;

R^3 es hidrógeno;

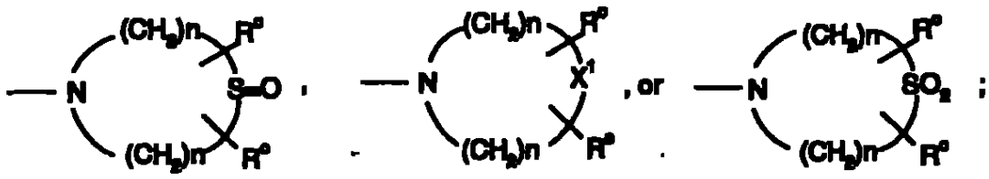
n se selecciona de 0-3; en donde los valores de R^1 pueden ser los mismos o diferentes; o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*; con las condiciones:

i) cuando -X-Y-Z- es -S-CH=CH-, R^2-(CR^1R^3)$_n$- no puede ser 1-fenil-5-metil-1H-1,5- benzodiazepin-2,4(3H,5H)dion-3-ilo, 1-metil-5-fenil-

2-oxo- 2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo, 2-(4-fenil-1,2,5,6-tetrahidropirid-1-il)etilo, 3-(4-fenil-1-2,5,6-tetrahidropirid-1-il)propilo, 2-(4-fenilpiperazin-1-il)etilo o 2- morfolinoetilo;

ii) cuando -X- Y-Z- es -CH=CH-S-, R^2-$(CR^1R^3)_n$- no puede ser 1-metil-5-fenil-2-oxo-2,3-dihidro-1H-benzo(E)(1,4)diazepin- 3-ilo; y

iii) cuando -X-Y-Z- es como se definió inicialmente, n es 1, R^1 es arilmetilo, arilmetilo sustituido, (grupo heterocíclico)metilo y (grupo heterocíclico)metilo sustituido y R^3 es hidrógeno entonces R^2 no es un grupo -C(=O)-A o un grupo -CH(OH)-C(=O)-A en el cual A es NR^dR^d, - $NR^aCH_2CH_2OR^a$, o



cada R^a y R^b es independientemente hidrógeno o -C_1-C_8alquilo;

cada R^d es independientemente hidrógeno, C_1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^c es independientemente hidrógeno, -C(=O)OR^a, -OR^a, -SR^a, o -NR^aR^a; y cada n es independientemente 1-3, y

X^1 es NR^a, -CH2-, O ó S.

En todavía otro aspecto la presente invención provee un compuesto de fórmula (I) (como se definió más arriba en el texto) en donde:

-X-Y-Z- se selecciona de -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH- y -N=C(Me)-S-;

R^1 se selecciona de hidrógeno, hidroxi, metilo, metoxicarbonilo, mesil-*N*-(metil)aminometilo e hidroximetilo;

R^2 se selecciona de *N,N*-dimetilcarbamoilo, *N,N*-dimetilsulfamoilamino, mesilaminocarbonilo, 2-metoxifenilo, fenoxi, 2-fenilciclopropilo, tien-2-ilo, 4-fluorofenilo, benzoilo, tiomorfolino, anilinocarbonilo, pirid-2-ilamino, tiazol-2-ilo, bencilsulfonilamino, 2,3-

dihidro-1,5-benzotiazepin-4(5H)-ona-3-ilo, 1-fenil-2,3-dimetil-5-oxo-3-pirazolin-4-ilo, 3-fenil-2-oxazolidinon-5-ilo, 5-hidroxi-1,3,4,5-tetrahidro-benzo[B]azepin-2-onilo, 3-fenil-5-oxo-2-isoxazolin-4-ilo, imidazo[1,2-a]piridin-2-ilo, benzotiazol-2-ilo, 2,5-dioxoimidazolidin-3-ilo, naft-2-ilaminocarbonilo, fenilo, 4-sulfamoilfenetilo, 4-(*N,N*-dimetilamino)fenilo, 4-sulfamoilfenilo, anilina, 4-hidroxifenilo, quinolin-3-ilo, 4-clorofenilo, 2-metoxipirid-5-ilo, 3-metilisotiazol-5-ilo, 3-trifluorometilpirid-2-ilo, tetrazol-5-ilo, benciloxicarbonilamino, benzimidazol-2-ilo, 2-trifluorometilpirid-5-ilo, piridazin-2-ilo, piridazin-3-iloxi, pirid-2-ilo, imidazol-5-ilo, 4-acetamidofenoxi, 2-ureidotiazol-4-ilo, benciltio, 2-fenil-1,3-dioxolan-2-ilo y 4- carbamoilmetilfenoxi;

R^3 es hidrógeno; y

n se selecciona de 0-3; en donde los valores de R^1 pueden ser los mismos o diferentes; o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*.

En un primer aspecto preferido la presente invención provee un compuesto de fórmula (I) (como se define más arriba en el texto) en donde:

-X-Y-Z- se selecciona de $-S-CR^4=CR^5-$ o $-CR^4=CR^5-S-$;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

n es 0;

R^2 es un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo;

H es un C_{3-12}cicloalquilo que se fusiona opcionalmente a un anillo benz en donde H puede sustituirse opcionalmente en carbono por uno o más grupos S que se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, grupos arilo y heterocíclico; en donde S puede sustituirse opcionalmente por uno o más grupos seleccionados de V;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonil, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo , *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica.

Valores preferidos de R^2, R^4, y R^5 son como siguen. Dichos valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba y más adelante en el texto.

En este primer aspecto preferido preferiblemente R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

En este primer aspecto preferido preferiblemente H es indanilo, 1,2,3,4-tetrahidronaftilo o ciclopropilo. Más preferiblemente H es indanilo o 1,2,3,4-tetrahidronaftilo. Muy preferiblemente H es indanilo.

En este primer aspecto preferido preferiblemente S se selecciona independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, C_{3-8}cicloalquilo y arilo. Más preferiblemente S se selecciona de hidroxi, amino, C_{1-6}alcoxi y C_{1-6}alcoxicarbonilamino.

En un segundo aspecto preferido la presente invención provee un compuesto de fórmula (I) (como se definió más arriba) en donde:

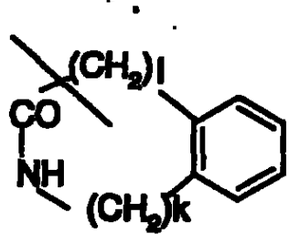
-X-Y-Z- se selecciona de -S-CR^4=CR^5- or -CR^4=CR^5-S-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)2amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

n es O;

R^2 es un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo; y H es una amida cíclica de fórmula



en la cual k es 0, 1, 2 ó 3 y 1 es 0, 1, 2 ó 3 tal que la suma de k y 1 es 2 ó 3 y en donde uno de los átomos de carbono gobernados por k ó 1 puede reemplazarse por azufre y en donde H se sustituye opcionalmente en carbono por uno o más grupos seleccionados de S y pueden independientemente sustituirse opcionalmente en nitrógeno por un grupo seleccionado de T;

S se selecciona de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, grupo arilo y heterocíclico; en donde S puede sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonilo, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo en donde T y U pueden sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo,

etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*.

Valores preferidos de R^4, R^5 y H son los siguientes. Dichos valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más adelante en el texto.

En este segundo aspecto preferido preferiblemente R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

En este segundo aspecto preferido preferiblemente H es 1,2,3,4-tetrahidroquinolilo, 2-oxo-1,2,3,4-tetrahidroquinolilo, 4-oxo-2,3,4,5-tetrahidrobenz[1,5]tiazepin-3-ilo, 2-oxo-2,3,4,5-tetrahidro-1H-benz[*b*]azepinilo, 2,3,4,5-tetrahidro-1H-benz[b]azepinilo o 3-oxo-2,3,4,5-tetrahidro-1H-benz[c]azepinilo cada uno opcionalmente sustituido en carbono por uno o más grupos seleccionados de S en donde S se selecciona de hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi, y cada uno independientemente opcionalmente sustituido en nitrógeno por un grupo seleccionado de T en donde T se selecciona de C_{1-4}alquilo o C_{1-4}alcanoilo.

Más preferiblemente H es 2-oxo-1,2,3,4-tetrahidroquinol-3-ilo, 1-metil-2-oxo-1,2,3,4-tetrahidroquinol-3-ilo, 4-oxo-2,3,4,5-tetrahidrobenz[1,5]tiazepin-3-ilo, 5-hidroxi-2-oxo-2,3,4,5-tetrahidro-1H-benz[b]azepin-4-ilo, 2-oxo-2,3,4,5-tetrahidro-1H-benz[b]azepin-3-ilo o 3-oxo-2,3,4,5-tetrahidro-1H -benz[c]azepin-4-ilo.

En un tercer aspecto preferido la presente invención provee un compuesto de fórmula (I) (como se definió más arriba) en donde:

-X-Y-Z- se selecciona de $-S-CR^4=CR^5-$ o $-CR^4=CR^5-S-$;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

n es 1;

R^1 es hidrógeno o arilC_{1-6}alquilo;

R^2 se selecciona de un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo;

H es un grupo heterocíclico de cinco miembros, insaturado, que contiene por lo menos un átomo de nitrógeno y uno o dos átomos de anillo seleccionados de oxígeno y azufre y en donde H puede sustituirse opcionalmente en carbono por uno o más grupos S que se seleccionan independientemente de halo, litro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo y grupos arilo;

R^3 es hidrógeno o C_{1-6}alquilo;

o su sal de aceptación farmacéutica.

Valores preferidos de R^1, R^3 y H son los siguientes. Dichos valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más adelante en el texto.

En este tercer aspecto preferido preferiblemente R^1 se selecciona de hidrógeno o bencilo y, más preferiblemente, bencilo.

En este tercer aspecto preferido preferiblemente R^3 es hidrógeno.

En este tercer aspecto preferido preferiblemente H es 1,3,4-oxadiazolilo, isoxazolilo, oxazolilo o 1,2,4-oxadiazolilo. Más preferiblemente H es 5-etoxicarbonil-1,3,4-oxadiazol-2-ilo, 4-fenilisoxazol-3-ilo, 3-fenil-1,2,4-oxadiazol-5-ilo, 4-metoxicarboniloxazol-5-ilo o 3-metilisoxazol-5-ilo.

En este tercer aspecto preferido preferiblemente H puede sustituirse opcionalmente en carbono por uno o más grupos S que se seleccionan

independientemente de halo, carboxi, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, C_{1-6}alcoxicarbonilo, C_{3-8}cicloalquilo y grupos arilo. Preferiblemente S es C_{1-6}alcoxi, C_{1-6}alcoxicarbonilo o fenilo.

En un cuarto aspecto preferido la presente invención provee un compuesto de fórmula (I) (como se definió más arriba) en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5- o -CR^4=CR^5-S-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

n es 0;

R^2 es un grupo -E-F-G-H;

en donde E es un enlace directo;

F es metileno;

en donde G es -C(O)NR^a-, en donde R^a se selecciona de hidrógeno o C_{1-6}alquilo que se sustituye opcionalmente por un grupo V ;

H es arilo que puede sustituirse opcionalmente por uno o más grupos seleccionados de S;

S se selecciona de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquilsulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, arilo y grupo heterocíclico; en donde S puede sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino,

dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonil, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica.

Valores preferidos de R^1, R^2, R^3, -X-Y-Z- n son los siguientes. Dichos valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más adelante en el texto.

En este cuarto aspecto preferido preferiblemente H es arilo.

En este cuarto aspecto preferido preferiblemente V es ciano o hidroxi.

Compuestos específicos de la presente invención son:

2,3-dicloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[N-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[(2-piridil)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-[*N* -(benzoilmetil)carbamoil]- 2.3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3.2-*b*]pirrol;

3-cloro-5-[*N*-(benzoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5- {*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]

pirrol;

3-cloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(1-fenilmetanesulfonamido)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-{*N*-[(4-oxo-2,3,4,5-tetrahidrobenz[1,5]tiazepin-3-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(benzoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-(*N*-{2-[(2-piridil)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[2-(N-metilmetanosulfonamido)-1-(tiazol-2-il)etil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2,3-dimetil-5-oxo-1-fenil-2,5-dihidro-1*H*-pirazol-4-il)carbamoil]-4*H*-tieno[3.2-*b*]pirrol;

2.3-dicloro-5-[*N*-(4-sulfamoilfenilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-hidroxi-1-fenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[(3-trifluorometilpirid-2-il)amino]etil) carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[3-(5-tetrazolil)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(5-oxo-3-fenil-4,5-dihidroisoxazol-4-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(5-hidroxi-2-oxo-2,3,4,5-tetrahidro-1*H*-benz[b]azepin-4-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-{*N*-[3-(benciloxicarbonilamino)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(4-dimetilaminofenil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(1-bencil-2-hidroxietil)carbamoil]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(fenilamino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(β-(*R*)-hidroxi-α-metilfenetil)carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(β-hidroxifenetil)carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-hidroxifenil)etil]carbamoil}4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(benzimidazol-2-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-clorofenil)-2-hidroxi-1-metoxicarbonil)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(imidazo[1,2-*a*]pirid-2-il)carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-{*N*-[(benztiazol-2-il)metil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(6-trifluorometilpirid-3-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[(2-piridazinil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxi-3-fenoxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-metilisotiazol-5-il)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(piridazin-3-iloxi)etil]carbamoil}-4*H*-tieno[3,2-]pirrol;

2-cloro-5-(*N*-{2-[(3-trifluorometilpirid-2-il)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-sulfamoilfenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-piridil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(1-hidroximetil-2-4-imidazolil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[(3-quinolil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-{*N*-[3-(4-acetamidofenoxi)-2-hidroxipropil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(3-[(*N*-metilsulfonilcarbamoil)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-{[2-(guanidino)tiazol-4-il]metiltio}etil)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-{2-(2,4-dioxoimidazolidin-1-il)etil]carbamoil}-4*H*-tieno [3,2-*b*]pirrol;

5-{*N*-[2-benciltio-1-(hidroximetil)etil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(dimetiaminosulfonilamino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(6-metoxipirid-3-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

(*S*)-2,3-dicloro-5-{*N*-[(2-oxo-3-fenil-2,3,4,5-tetrahidrooxazol-5-il) metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[3-(carbamoilmetil)fenoxi]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{[6-(benzo[1,3]dioxol-5-il)-4-metilmorfolin-2-il]metil} carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-bencilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-fenetilcarbamoil)-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(3-fenilpropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-hidroxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(α,α-dimetilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-fenilciclobutil)metil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(β-metilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(*N*-bencilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(*N*-bencil-*N*-metilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-metil-*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-[*N*-(2-cianoetil)-*N*- fenilcarbamoilmetil)carbamoil] -4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-metoxifenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-fluorofenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-nitrofenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,6-dimetilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-metil-*N*-(4-metilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-b]pirrol;

2,3-dicloro-5-{*N*-[*N*-metil-*N*-(3-metilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-clorofenil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-fenilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(1,1-dimetil-2-hidroxietil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-hidroxipropil)carbamoilmetil]carbamoil}-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroxibutil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-[bis(hidroximetil)metil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,3-dihidroxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroximetilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(5-isoquinoil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-hidroximetil)fenil]carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-[4-(2-hidroxietil)fenil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroxibutil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,4-difluorofenil)-*N*-metil-carbamoilmetil] carbamoil}-4*H*-tieno[3,2- *b*]pirrol;

2,3-dicloro-5-{*N*-[(1,2,3,4-tetrahidro-1-quinolil))carbamoilmetil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-cianoetil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroxipiperidino)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-ciclopentilcarbamoilmetil)carbamoil]-4H-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-isopropilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-isopropil-*N*-metilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(tiomorfolinocarbonilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(morfolinocarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1,1-dioxotiomorfolino)carbonilmetil]carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-oxotiomorfolino)carbonilmetil]carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2-cloro-5-[*N*-(2- indanil)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

5-[*N*-(benz[1,2]oxazol-3-ilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-{2-[2-(hidroximetil)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(4-fenilisoxazol-3-ilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-{2-[2-(2-morfolinoetoxi)fenil]etil}carbamoil)-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-{2-[2-(metoxicarbonilmetoxi)fenil]etil}carbamoil)-4*H*-tieno [3,2-*b*]pirrol;

5-[*N*-{2-[2-carboximetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(3-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(2-metoxietoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{2-[2-(carbamoilmetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(*N*-metilcarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(morfolinocarbonilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{2-[2-(*N*-bencilcarbamoilmetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(4-hidroxipiperidinocarbonilmetoxi)fenil]etil} carbamoil)-4*H*- tieno[3,2-*b*]pirrol;

(S)-2-cloro-5-{*N*-[α-(5-etoxicarbonil-1,3,4-oxadiazol-2-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-{*N*-[α-(3-piridil)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-{*N*-[α-(3-piridil)fenetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

(S)-2-cloro-5-{*N*-[α-(5-fenil-l,2,4-oxadiazol-5-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-hidroxilndan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-((*1S,2S*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-((*1R,2R*)-1-hidroxiindan-2-il)carbamoil]-4H-tieno[3,2-*b*]pirrol;

2-cloro- 5-[*N*-(l-hidroxiindan-2-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-hidroxi-1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(6-fluoro-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(7-metoxi-1-oxo-1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro- 5-[*N*-(2-indanil)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(3-metilisoxazol-5-il)metil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(4-hidroxi-1,1-dioxotetrahidrotiopen-3-il)carbamoil]-4*H*-tieno[3 ,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-metil-*N*-[(1-oxo-1,2,3,4-tetrahidronaft-2-il)metil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-[*N*-(1-metil-2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno [2,3-*b*]pirrol;

2-cloro-5-[*N*-(3-oxo-2,3,4,5-tetrahidro-1*H*-benz[2]azepin-4-il)carbamoil]-6*H*-tieno [2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-metoxiindan-2-il)carbamoil]-4*H*-tieno [3 ,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{1-[*N*-(l,l-dimetiletoxi)carbonilamino]indan-2-il} carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(1-aminoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(l-acetamidoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[1-(metanosulfonamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

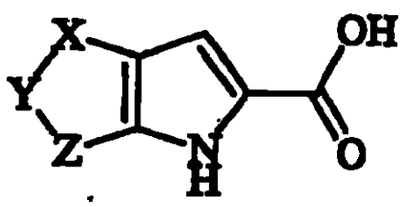
2,3-dicloro-5-{*N*-[1-(metilamino)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol; y

2,3-dicloro-5-{*N*-[1-(*N*-metilacetamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

Aspectos preferidos de la invención son aquellos que se relacionan con el compuesto de fórmula (I) o su sal de aceptación farmacéutica.

Otro aspecto de la presente invención provee un proceso para preparar un compuesto de fórmula (I) o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo* proceso que (en donde R^1, R^2, R^3, -X-Y-Z- y n son, a menos que se especifique otra cosa, como se define en fórmula (I)) comprende:

a) hacer reaccionar un ácido de la fórmula (II):



(II)

o su derivado activado; con una amina de fórmula (III):



(III)

y, a partir de entonces, si es necesario:

i) convertir un compuesto de la fórmula (I) en otro compuesto de la fórmula (I);

ii) retirar todos los grupos protectores;

iii) formar una sal de aceptación farmacéutica o un éster hidrolizable *in vivo*.

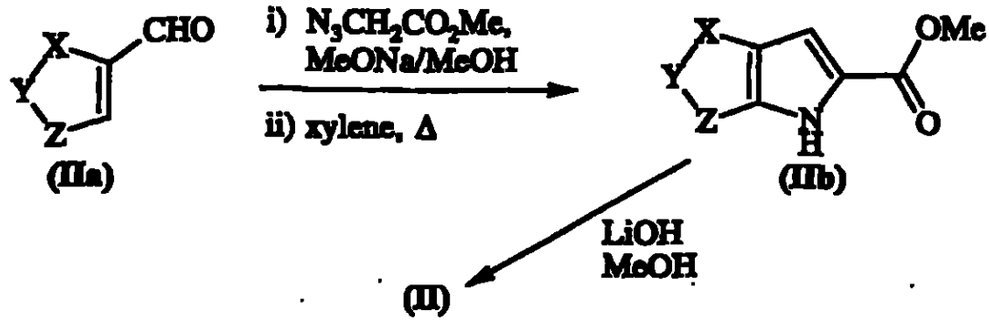
Condiciones específicas para la reacción anterior son las siguientes.

Proceso a) Ácidos de fórmula (II) y aminas de fórmula (III) pueden acoplarse en presencia de un agente de acoplamiento adecuado. Como reactivos de acoplamiento apropiados pueden emplearse reactivos estándar de acoplamiento de péptidos conocidos en el arte o, por ejemplo, carbonildiimidazol, clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida y diciclohexilcarbodiimida, opcionalmente en presencia de un catalizador tal como 1-hidroxibenzotriazol, dimetilaminopiridina o 4-pirrolidinopiridina, opcionalmente en presencia de una base por ejemplo trietilamina, di-isopropiletilamina, piridina, o 2,6-di-*alquil*-piridinas tales como 2,6-lutidina o 2,6-di-*tert*-butilpiridina. Solvente apropiados incluyen dimetilacetamida, diclorometano, benceno, tetrahidrofurano y dimetilformamida. La reacción de acoplamiento puede llevarse convenientemente a cabo a una temperatura en el rango de -40 a 40°C.

Derivados activados de ácido adecuados incluyen halogenuros de ácido, por ejemplo, cloruros de ácido y ésteres activos, por ejemplo, ésteres de pentafluorofenilo. La reacción de estos tipos de compuestos con aminas es bien conocida en el arte, por ejemplo, se los puede hacer reaccionar en

presencia de una base, tal como las descritas más arriba, y en un solvente adecuado, tal como los ya descritos. Convenientemente, la reacción puede llevarse a cabo a una temperatura en el rango de -40 a 40°C.

Los ácidos de fórmula (II) pueden prepararse de acuerdo con el *Esquema 1*:



Esquema 1

Compuestos de fórmula (IIa) y aminas de fórmula (III) se obtienen en el comercio o son compuestos conocidos o se preparan mediante procesos conocidos en el arte.

Se apreciará que ciertos de los diferentes sustituyentes de anillo en los compuestos de la presente invención pueden introducirse mediante reacciones estándar de sustitución aromática o generarse mediante modificaciones convencionales de grupo funcional sea antes o inmediatamente después de los procesos mencionados más arriba y, como tales, se incluyen en el aspecto de los procesos de la invención. Dichas reacciones y modificaciones incluyen, por ejemplo, introducción de un sustituyente por medio de una reacción de sustitución aromática, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes. Los reactivos y condiciones de reacción para dichos procedimientos son bien conocidos en el arte químico. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro usando ácido nítrico concentrado, la introducción de un grupo acilo usando, por ejemplo, un halogenuro acilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquilo usando un halogenuro alquilo y ácido de Lewis (tal como tricloruro

de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro en un grupo amino mediante, por ejemplo, hidrogenación catalítica con un catalizador de níquel o tratamiento con hierro en presencia de ácido clorhídrico con calentamiento; oxidación de alquiltio en alquilsulfinilo o alquilsulfonilo.

Se apreciará igualmente que en algunas de las reacciones mencionadas aquí puede ser necesario/deseable proteger grupos sensibles en los compuestos. Los casos en donde la protección es necesaria o deseable y métodos apropiados para protección son conocidos por aquellas personas con habilidades en el arte. Grupos protectores convencionales pueden usarse de acuerdo con la práctica estándar (para ilustración, véase T. W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). En consecuencia, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aquí.

Un grupo protector adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos protectores mencionados más arriba varían necesariamente con la elección del grupo protector. Por lo tanto, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo puede retirarse, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo, hidróxido de sodio o litio. Alternativamente, un grupo acilo tal como un grupo *t*-butoxicarbonilo puede retirarse, por ejemplo, mediante tratamiento con un ácido adecuado tal como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede retirarse, por ejemplo, mediante

hidrogenación sobre un catalizador tal como paladio-en-carbono, o mediante tratamiento con un ácido de Lewis, por ejemplo, tris(trifluoroacetato) de boro. Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo que puede retirarse mediante tratamiento con una alquilamina, por ejemplo, dimetilaminopropilamina, o con hidrazina.

Un grupo protector apropiado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo, un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos protectores mencionados arriba variarán necesariamente con la elección del grupo protector. Por consiguiente, por ejemplo, un grupo acilo tal como un grupo alcanoilo un grupo aroilo puede retirarse, por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de sodio o litio. Alternativamente, un grupo arilmetilo tal como un grupo bencilo puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio-en-carbono.

Un grupo protector apropiado para un grupo carboxi es, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o un grupo etilo que puede retirarse, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *t*-butilo que puede retirarse, por ejemplo, mediante tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo que puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio-en-carbono.

Los grupos protectores pueden retirarse en cualquier fase conveniente en la síntesis usando técnicas convencionales bien conocidas en el arte químico.

Tal como se indicó más arriba en el texto, los compuestos definidos en la presente invención poseen actividad inhibidora de glucógeno fosforilasa. Esta propiedad puede evaluarse, por ejemplo, usando el procedimiento expuesto a continuación.

Ensayo

La actividad de los compuestos se determina midiendo el efecto inhibidor de los compuestos en la dirección de síntesis de glucógeno, la conversión de glucosa-1-fosfato en glucógeno con la liberación de fosfato inorgánico, como se describe en EP 0 846 464 A2. Las reacciones tuvieron un formato microplate de 96 pozos en un volumen de 100µl. El cambio en la densidad óptica debida a la formación de fosfato inorgánico se midió a 620nM en un Labsystems iEMS Reader MF mediante el método general de (Nordlie R.C y Arion W.J, Methods of Enzymology, 1966,619-625). La reacción es en 50mM HEPES, 2.5mM $MgCl_2$, 2.25mM etilen glicol-bis(b-aminoetiléter) ácido *N,N,N',N'*-tetraacético, 100mM KCl, 2mM D-(+)-glucosa pH 7.2, que contenía 0.5mM ditiotreitol, la solución tampón de ensayo, con 0.1mg glucógeno tipo III, 0.15ug glucógeno fosforilasa *a* (GP*a*) de músculo de conejo y 0.5mM glucosa-1-fosfato. Gp*a* se pre-incuba en la solución tampón de ensayo con el glucógeno tipo III a 2.5 mg ml^{-1} durante 30 minutos. Se agregan 40µl de la solución enzimática a 25µl de solución tampón de ensayo y la reacción se inicia con la adición de 25µl 2mM glucosa-1-fosfato. Los compuestos a ensayarse se preparan en 10µl 10% DMSO en solución tampón de ensayo, con una concentración final de 1 % DMSO en el ensayo. La actividad no-inhibida de GP*a* se mide en presencia de 10µl 10% DMSO en solución tampón de ensayo y una inhibición máxima medida en presencia de 30µl CP320626 (Hoover y colaboradores (1998) J Med Chem 41, 2934-8; Martin y colaboradores (1998) PNAS 95, 1776-81). La reacción de detiene después de 30 minutos con la adición de 50µl de solución acídica de molibdato de amonio, 12ug ml^{-1} en 3.48% H_2SO_4 con 1% laurel sulfato de sodio y 10ug ml^{-1} ácido ascórbico. Luego de 30 minutos a temperatura ambiente se mide la absorción a 620nm.

El ensayo se lleva a cabo en una concentración de prueba del inhibidor de 10µM o 100µM. Compuestos que demuestran inhibición significativa en una o ambas de estas concentraciones pueden evaluarse además usando un rango de concentraciones de prueba de inhibidor para

determinar una IC_{50}, una concentración prevista para inhibir la reacción enzimática en 50%.

La actividad se calcula como sigue:-

% inhibición= (1 - (OD620 compuesto – totalmente inhibida OD620)/ (tasa no-inhibida OD620 – totalmente inhibida OD620)) * 100.

OD620= densidad óptica a 620nM.

Valores IC_{50} típicos para compuestos de la invención cuando se prueban en el ensayo ya mencionado se encuentran en el rango 100µM a 1nM.

Alternativamente, la actividad de los compuestos se determina midiendo el efecto inhibidor de los compuestos sobre la degradación de glucógeno, la producción de glucosa-1-fosfato de glucógeno se monitorea mediante el ensayo acoplado a multienzima, como se describe en EP 0 846 464 A2, método general de Pesce y colaboradores (Pesce, M A, Bodourian, S H, Harris, R C, y Nicholson, J F (1977) Clinical Chemistry 23, 1171-1717). Las reacciones se hicieron en formato microplate de 384 pozos en un volumen de 50µl. El cambio en fluorescencia debido a la conversión del co-factor NAD en NADH se mide a una excitación de 340nM, emisión de 465nm en un Tecan Ultra Multifunctional Microplate Reader. La reacción se produce en 50mM HEPES, 3.5mM KH_2PO_4, 2.5mM $MgCl_2$, 2.5mM etilen glicol-bis(b-aminoetiléter) ácido *N,N,N',N'*-tetraacético, 100mM KCl, 8mM D-(+)-glucosa pH 7.2, que contiene 0.5mM ditiotreitol, la solución tampón de ensayo. Glucógeno fosforilasa hepática recombinante humana *a* (hrl GP*a*) 20nM se pre-incuba en solución tampón de ensayo con 6.25mM NAD, 1.25mg glucógeno tipo III a 1.25 mg ml^{-1} tampón de reactivo, durante 30 minutos. Las enzimas de acoplamiento, fosfoglucomutasa y glucosa-6-fosfato dehidrogenasa (Sigma) se preparan en tampón de reactivo, concentración final 0.25Unidades por pozo. Se agregan 20µl de la solución hrl GPa a 10µl de solución del compuesto y la reacción se inicia con la adición de 20µl de solución de enzima de acoplamiento. Los compuestos a probarse se preparan en 10µl 5% DMSO

en solución tampón de ensayo, con una concentración final de 1% DMSO en el ensayo. La actividad no-inhibida de GP*a* se mide en presencia de 10µl 5% DMSO en solución tampón de ensayo e inhibición máxima mediada en presencia de 5mgs ml^{-1} N-etilmaleimida. Después de 6 horas a 30°C se miden Unidades de Fluorescencia Relativa (RFUs) a una excitación de 340nM, emisión de 465nm.

El ensayo se lleva a cabo en una concentración de prueba del inhibidor de 10µM o 100µM. Los compuestos que demuestran una inhibición significativa en una o ambas de estas concentraciones pueden evaluarse además usando un rango de concentraciones de prueba del inhibidor para determinar una IC_{50}, una concentración prevista para inhibir la reacción enzimática en 50%.

La actividad se calcula como sigue:-

% inhibición= (1 - (RFUs del compuesto – RFUs totalmente inhibidas)/ (tasa no-inhibida RFUs – RFUs totalmente inhibidas)) * 100.

Valores IC_{50} típicos para compuestos de la invención cuando se prueban en el ensayo ya mencionada se encuentran en el rango 100µM a 1nM.

La actividad inhibidora de los compuestos se probó adicionalmente en hepatocitos primarios de rata. Se aislaron hepatocitos de rata mediante la técnica de perfusión de colagenasa, método general de Seglen (P.O. Reglen, Methods Cell Biology (1976) 13 29-83). Se cultivaron células en placas de cultivo de seis pozos Nunclon en DMEM con alto nivel de glucosa que contenía 10% de suero de bobino fetal, NEAA, Glutamina, penicilina / estreptomicina ((100units/100ug)/ml) durante 4 a 6 horas. Los hepatocitos se cultivaron a continuación en la solución DMEM sin suero de bobino fetal y con 10nM insulina y 10nM dexametasona. Se iniciaron experimentos después de un cultivo de 18-20 horas lavando las células y agregando tampón de bicarbonato Krebs-Henseleit que contenía 2.5mM $CaCl_2$ y 1% gelatina. Se agregó el compuesto de prueba y 5 minutos después las células de expusieron con 25nM de glucagón. Se retiró la solución Krebs-Henseleit después de 60 minutos de incubación a 37°C,

95%O_2/5%CO_2 y se midió la concentración de glucosa de la solución Krebs-Henseleit.

De acuerdo con un aspecto más de la invención se provee una composición farmacéutica que comprende un compuesto de la fórmula (I), o su sal de aceptación farmacéutica o un éster hidrolizable *in vivo*, como se define más arriba en el texto en asociación con un diluyente o portador de aceptación farmacéutica.

La composición puede estar en una forma apropiada para administración oral, por ejemplo como un comprimido o cápsula, para inyección parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o infusión) como una solución estéril, suspensión o emulsión, para administración tópica como un ungüento o crema o para administración rectal como un supositorio.

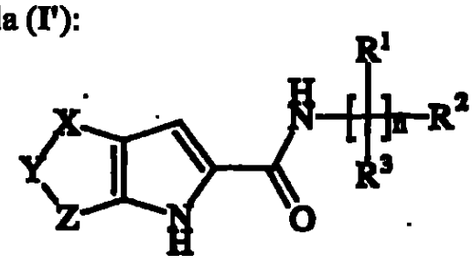
En general, las composiciones ya indicadas pueden prepararse en una manera convencional usando excipientes convencionales.

El compuesto de fórmula (I) se administrará normalmente a un animal de sangre caliente en una dosis unitaria en el rango 5-5.000 mg por área en m^2 del cuerpo del animal, i,e. aproximadamente 0.1-100 mg/kg, y esto provee una dosis de efecto terapéutico. Una dosis unitaria tal como un comprimido o cápsula contendrá usualmente, por ejemplo, 1-250 mg de ingrediente activo. Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg. No obstante, la dosis diaria se variará necesariamente dependiendo del anfitrión tratado, la vía particular de administración, y la gravedad de la enfermedad que se está tratando. En consecuencia, la dosificación óptima puede determinarse por el médico que está tratando a cualquier paciente particular.

De acuerdo con un aspecto más de la presente invención se provee un compuesto de la fórmula (I), o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto, para uso en un método de tratamientote un animal de sangre caliente tal como un hombre mediante terapia.

De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula (I), o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto, para uso como un medicamento.

De acuerdo con otro aspecto de la invención se provee el uso de un compuesto de la fórmula (I'):



(I')

en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-,-S-CR^4=N-,-NR^6-CR^4=CR^5- y -CR^4=CR^5-NR^6-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

R^6 es hidrógeno o C_{1-6}alquilo;

R^1 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alkil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-6}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}

$_6$alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, C_{3-8}cicloalquilC_{1-6}alquilo, arilo, arilC_{1-6}alquilo, grupo heterocíclico y (grupo heterocíclico)C_{1-6}alquilo; en donde R^1 puede sustituirse opcionalmente por uno o más grupos seleccionados de P y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R;

R^2 se selecciona de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alkil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, sulfamoilamino, *N*-(C_{1-6}alquil)sulfamoilamino, *N,N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonilaminocarbonilo, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino y un grupo -E-F-G-H;

en donde **E** y **G** se seleccionan independientemente de un enlace directo, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- y -C(O)NR^aSO_2-; en donde R^a y R^b se seleccionan independientemente de hidrógeno o C_{1-6}alquilo que se sustituye opcionalmente por un grupo V;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una

mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

R^3 es hidrógeno o C_{1-6}alquilo;

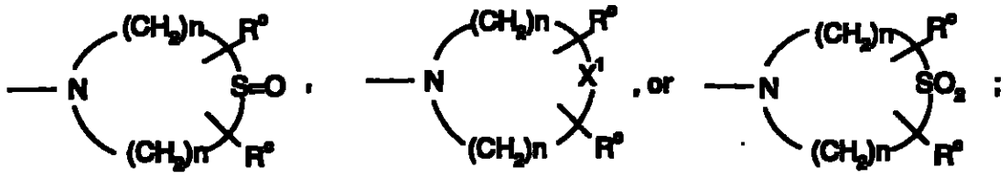
n se selecciona de 0-4; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes;

P, S y Q se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, arilo y grupo heterocíclico; en donde P, S y Q pueden sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*- bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

R, T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonilo, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; o su sal de aceptación farmacéutica o su éster hidrolizable *in vivo*; con la condición que

cuando -X-Y-Z- es como se define inicialmente, n es 1, R^1 es arilmetilo, arilmetilo sustituido, (grupo heterocíclico)metilo y (grupo heterocíclico)metilo sustituido y R^3 es hidrógeno entonces R^2 no es un grupo -C(=O)-A o un grupo -CH(OH)-C(=O)-A en el cual A es NR^dR^d,-$NR^aCH_2CH_2OR^a$, o



cada R^a y R^b son independientemente hidrógeno o -C_1-C_8alquilo;

cada R^d es independientemente hidrógeno, C_1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^c es independientemente hidrógeno, -C(=O)OR^a, -OR^a, -SR^a, o -NR^aR^a; y cada n es independientemente 1-3, y

X^1 es NR^a, -CH_2-, O ó S;

o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de glucógeno fosforilasa en un animal de sangre caliente como el hombre.

De acuerdo con otro aspecto de la invención se provee el uso de un compuesto de la fórmula (I'), o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto en la manufactura de un medicamento para uso en el tratamiento de diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca u obesidad en un animal de sangre caliente como el hombre.

De acuerdo con este otro aspecto de la invención se provee el uso de un compuesto de la fórmula (I'), o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto en la manufactura de un medicamento para uso en el tratamiento de diabetes tipo 2 en un animal de sangre caliente como el hombre.

De acuerdo con una característica más de este aspecto de la invención se provee un método de producir un efecto inhibidor de glucógeno fosforilasa en un animal de sangre caliente tal como un hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I').

De acuerdo con esta característica adicional de este aspecto de la invención se provee un método de tratar diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca u obesidad en un animal de sangre caliente, tal como un hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I').

De acuerdo con esta característica adicional de este aspecto de la invención se provee un método de tratar diabetes tipo 2 en un animal de sangre caliente, tal como un hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I').

Como se indicó más arriba el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de una enfermedad de proliferación celular particular variará necesariamente dependiendo del anfitrión tratado, la vía de administración y la gravedad de la afección que se está tratando. Se contempla una dosis unitaria en el rango, por ejemplo, 1-100 mg/kg, preferiblemente 1-50 mg/kg:

Además de su uso en medicina terapéutica, los compuestos de fórmula (I) y sus sales de aceptación farmacéutica son igualmente útiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de prueba *in vitro* e *in vivo* para la evaluación de los efectos de

inhibidores de actividad del ciclo celular en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapéuticos.

En las demás características indicadas de la composición farmacéutica, proceso, método, uso y manufactura de un medicamento, se aplican también las incorporaciones alternativas y preferidas de los compuestos de la invención descritos aquí.

Ejemplos

La invención se ilustrará ahora por los siguientes ejemplos no limitantes en los cuales, a menos que se indique lo contrario:

(i) las temperaturas se dan en grados Celsius (°C); las operaciones se llevaron a cabo a temperatura del cuarto o a temperatura ambiente, es decir, a una temperatura en el rango de 18-25°C y bajo una atmósfera de un gas inerte tal como argón;

(ii) las soluciones orgánicas se secaron sobre sulfato de magnesio anhidro; la evaporación de solvente se llevó a cabo usando un evaporador rotatorio bajo presión reducida (600-4.000 Pascals; 4.5-30 mmHg) con una temperatura de baño de hasta 60°C;

(iii) cromatografía significa cromatografía de destello en gel de sílice; la cromatografía de capa delgada (TLC) se realizó en placas de gel de sílice; donde se menciona una columna Bond Elut, esto significa una columna que contiene10 g ó 20 g ó 50 g de sílice de tamaño de partícula de 40 micrones, estando contenido el sílice en una jeringa desechable de 60 ml y soportada por un disco poroso, obtenido de Varian, Harbor City, California, USA bajo el nombre "Mega Bond Elut SI"; "Mega Bond Elut" es una marca comercial; donde se menciona un cartucho Biotage esto significa uncartucho que contiene sílice KP-SIL™, 60 angstroms, tamaño de partícula 32-63mM, suministrado por Biotage, una división de Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) en general, la secuencia de las reacciones se siguió mediante TLC y los tiempos de reacción se dan con fines de ilustración únicamente;

(v) los rendimientos se dan con fines de ilustración únicamente y no son necesariamente aquellos que pueden obtenerse mediante el desarrollo de procesos minuciosos; las preparaciones se repetían si se requería más material;

(vi) donde se incluyen, los datos de la NMR se dan en forma de valores delta para protones esenciales de diagnóstico, en partes por millón (ppm) relativas a tetrametilsilano (TMS) como un estándar interno, determinadas a 300 MHz usando sulfóxido de dimetilo perdeuterio (DMSO-δ_6) como solvente a menos que se indica que lo contrario, otros solventes (donde se indica en el texto) incluyen cloroformo deuterado $CDCl_3$;

(vii) los símbolos químicos tienen sus significados usuales; se utilizan unidades y símbolos del Sistema Internacional (SI);

(viii) las presiones reducidas se dan como presiones absolutas en Pascals (pa); las presiones elevadas se dan como presiones manométricas en bars;

(ix) las proporciones de los solventes se dan en términos volumen: volumen (v/v);

(x) los espectros de masas (MS) se ejecutaron con una energía de electrón de 70 voltios de electrón en el modo de Ionización Química (CI) usando una sonda de exposición directa; en donde la ionización indicada se efectuó mediante impacto de electrón (EI), bombardeo de átomos rápidos (FAB) o electrorrociado (ESP); se dan valores para m/z; generalmente, sólo se reportan iones que indican la masa original y, a menos que se especifique otra cosa, el valor citado es (M-H)-;

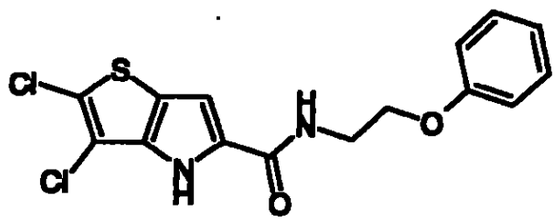
(xi) se utilizaron las siguientes abreviaturas:

SM	material inicial;
EtOAc	acetato de etilo;
MeOH	metanol;
DCM	diclorometano
HOBT	1-hidroxibenzotriazol

DIAD	diisopropil azodicarboxilato
HATU	*O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N'*,*N'*, tetrametiluronio hexafluorofosfato
TFA	ácido trifluoroacético
DIPEA	di-isopropiletilamina; y
EDAC	clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida

Ejemplo #1

2 3-Dicloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno [3,2-*b*] pirrol



5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 47 mg, 0.2 mmol) se disolvió en DCM (10 ml) que contenía 2-fenoxietilamina (27 mg, 0.2 mmol), HOBT (27 mg, 0.2 mmol) y DIPEA (70 ml, 0.4 mmol). La mezcla se agitó durante 1 minuto antes de la adición de EDAC (50 mg, 0.26 mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 18 horas antes de lavarse con agua. La fracción orgánica se concentró y se purificó en una columna Bond Elut (eluyente 1:1 EtOAc/isohexano) para proporcionar el compuesto del título como un sólido blancuzco (32 mg). NMR: 12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, d), 7.1 (1H, s), 6.9 (2H, m), 3.5 (2H, m), 3.0 (2H, t); m/z 353.2.

Ejemplos #2 - #9

Los siguientes compuestos se elaboraron por el proceso de Ejemplo #1 usando 5-carboxi- 2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9) y la amina apropiada:

Ejemplo #2: 2,3-Dicloro-5-{*N*-[2-(2-tienil)etil)carbamoil}4*H*-tieno[3,2-*b*]pirrol

Ejemplo #3: 2,3-Dicloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #4: 2,3-Dicloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

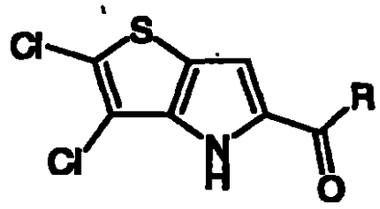
Ejemplo #5: 2,3-Dicloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

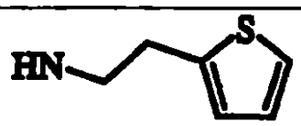
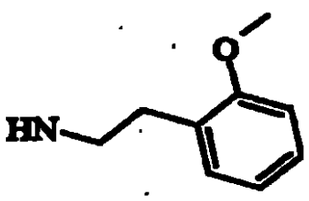
Ejemplo #6: 2,3-Dicloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

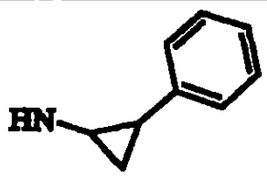
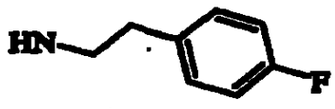
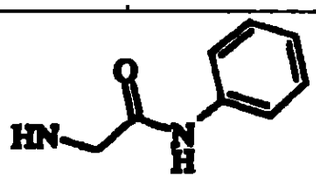
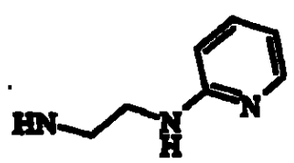
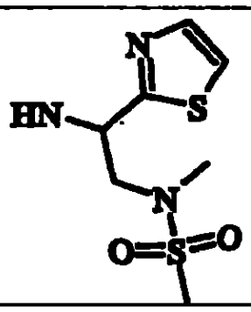
Ejemplo #7: 2,3-Dicloro-5-(*N*-{2-[(2-piridil)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #8: 2,3-Dicloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-il)etil]carbamoil}-4*H*-tieno[3.2-*b*] pirrol

Ejemplo #9: 2,3-Dicloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	M/z
#2		12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, d), 7.1 (1H, s), 6.9 (2H,m), 3.5 (2H, m), 3.0 (2H, t)	343.1
#3		12.3 (1H, s), 8.3 (1H, t), 6.8-7.2 (5H, m), 3.8 (3H, s), 3.4 (2H, m), 2.8 (2H, t)	367.3

#4		12.4 (1H, s), 8.5 (1H, d), 7.2 (5H, m), 7.1 (1H, s), 3.0 (1H, m), 2.1 (1H, m), 1.3 (2H, m)	349.3
#5		12.3 (1H, s), 8.4 (1H, t), 7.3 (2H, m), 7.1 (3H, m), 3.4 (2H, m), 2.8 (2H, t)	355.3
#6[1]		12.4 (1H, s), 10.0 (1H, s), 8.7 (1H, br), 7.1-7.6 (5H, m), 7.2 (1H, s), 4.1 (2H, d)	366.2
#7[1, 2]		12.4 (1H, s), 8.4 (1H, s), 6.5-8.0 (5R, m), 6.6 (1H, s), 3.3 (4H, m)	353.3
#8[3]		($CDCl_3$) 9.6 (1H, br), 7.8 (1H, m), 7.7 (1H, m), 7.3 (1H, m), 7.0 (1H, s), 5.6 (1H, m), 3.9 (1H, m), 3.7 (1H, m), 2.9 (3H, s), 2.8 (3H, s)	451.2
#9		($CDCl_3$) 9.8 (1H, br), 6.9 (1H, br), 6.7 (1H, s), 4.1 (2H, m), 3.6 (2H, m), 2.8 (8H, m)	362.2

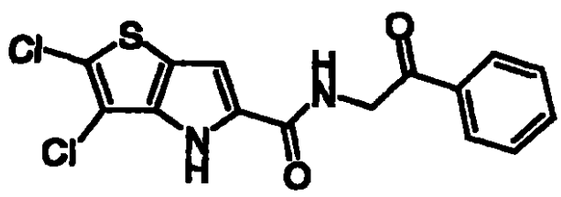
[1] Se agregó agua y se precipitó el compuesto del título como un sólido amarillo que se filtró, se lavó con agua, se secó bajo presión reducida y no se purificó más..

[2] Amina: Eur J Méd Chem, 1987, 22, 91.

[3] Amina: Método #15

Ejemplo #10

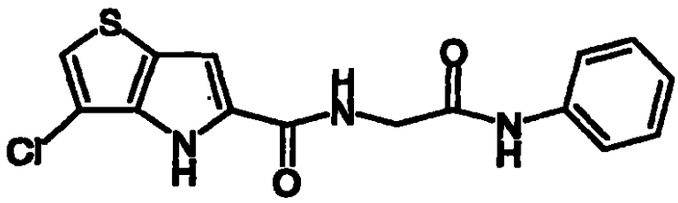
5-[*N*-(Benzoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



2,3-Dicloro-5-{*N*-[(2-fenil-1,3-dioxolan-2-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol (Método #17; 80 mg, 0.2 mmol) se disolvió en acetona (15 ml) que contenía ácido clorhídrico acuoso (2.0 M, 1 ml). La mezcla se calentó bajo reflujo durante 90 minutos. El precipitado blanco formado se filtró y se lavó con acetona. El filtrado se concentró y el residuo se trituró con agua. El sólido formado se filtró y se secó bajo presión reducida para proporcionar el compuesto del título como un sólido blanco (20 mg). NMR: 12.4 (1H, s), 8.6 (1H, t), 7.6-8.0 (5H, m), 7.2 (1H, s), 4.8 (2H, d); m/z 351.1.

Ejemplo #11

3-Cloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-3-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #7; 100 mg, 0.5 mmol) se disolvió en DCM (6 ml) que contenía HOBT (68 mg, 0.5 mmol), DIPEA (176 ml, 1.0 mmol) y *N*-glicilanilina (75 mg, 0.5 mmol). La mezcla se dejó reposar durante un minuto antes de la adición de EDAC (150 mg, 0.7 mmol). La solución se dejó reposar durante aproximadamente 18 horas antes de lavarse con agua. La capa orgánica se secó, se filtró y se concentró bajo presión reducida para proporcionar el compuesto del título (112 mg, 67%). NMR ($CDCl_3$) 9.7 (1H, br), 8.6 (1H, br), 7.0-8.0 (8H, m), 4.3 (2H, d); m/z 332.1.

Ejemplos #12 - #21

Los siguientes compuestos se elaboraron por el proceso de Ejemplo #11 usando 5-carboxi-3-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #7) y la amina apropiada:

Ejemplo #12: 3-Cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno [3,2-*b*]pirrol

Ejemplo #13: 3-Cloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-il)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #14: 3-Cloro-5-{*N*-(benzoilmetil)carbamoil]-4H-tieno[3,2-*b*]-pirrol

Ejemplo #15: 3-Cloro-5-{*N*-[2-(2-metoxifenil)etilcarbamoil-4H-tieno[3.2-*b*]-pirrol

Ejemplo #16: 3-Cloro-5-{*N*-[2-(2-tienil)etilcarbamoil-4H-tieno[3.2-*b*]-pirrol

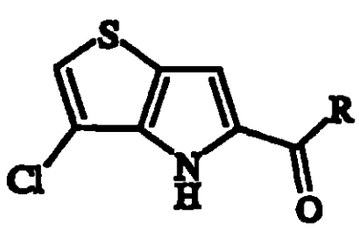
Ejemplo #17: 3-Cloro-5-{*N*-(2-fenil-1-ciclopropil)carbamoil}-4*H*-tieno [3,2,*b*]pirrol

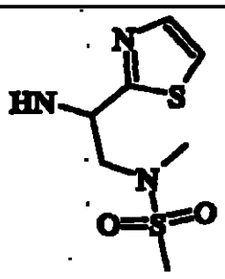
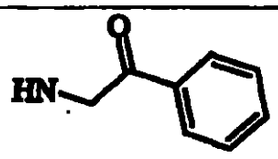
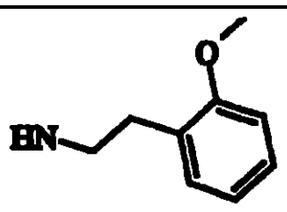
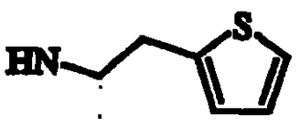
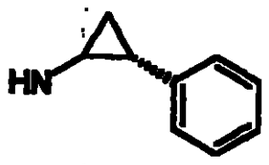
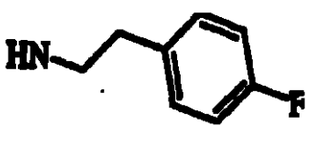
Ejemplo #18: 3-Cloro-5-{*N*-[2-(4fluorofenil)etil]carbamoil-4H-tieno[3.2-*b*]pirrol

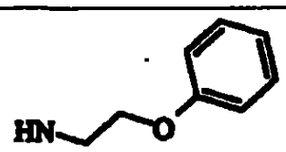
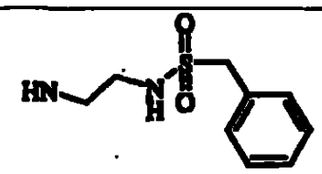
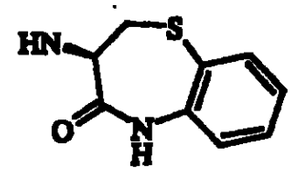
Ejemplo #19: 3-Cloro-5-[*N*-(2-fenoxietil)carbamoil]-4H-tieno[3,2-*b*]pirrol

Ejemplo #20: 3-Cloro-5-[*N*-(2-(1-fenilmetanosulfonamido)etil]carbamoil]-4H-tieno[3,2-*b*]-pirrol

Ejemplo #21: 3-Cloro-5-[*N*-(4-oxo-2,3,4,5-tetrahidrobenzo[1,5]tiazepin-3-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	M/z
#12		($CDCl_3$) 9.6 (1H, br), 7.0 (1H, s), 6.7 (1H, s), 6.6 (1H, br), 4.1 (2H, m), 3.5 (2H, m), 2.7 (8H, m)	328.3
#13[1]		($CDCl_3$) 9.5 (1H, br), 7.8 (1H, m), 7.6 (1H, m), 7.3 (1H m), 7.0 (2H, 2 x s), 5.6 (1H, m), 3.9 (1H, m), 3.7 (1H, m), 2.9 (6H, 2 x s)	419.0 $(M+H)^+$
# 14		($CDCl_3$) 9.6 (1H, s), 7.0-8.0 (8H, m), 5.0 (2H, m)	317.1
#15		($CDCl_3$) 9.6 (1H, br), 7.2 (2H, m), 7.0 (1H, s), 6.9 (2H, m), 6.6 (1H, s), 6.3 (1H, br), 3.9 (3H, s), 3.7 (2H, m), 2.9 (2H, t)	333.1
#16		($CDCl_3$) 9.8 (1H, br), 6.9-7.2 (4H, m), 6.7 (1H, s), 6.2 (1H, br), 3.8 (2H, m), 3.2 (2H, t)	309.1
# 17		($CDCl_3$) 9.6 (1H, br), 7.0-7.3 (6H, m), 6.8 (1H, s), 6.3 (1H, br), 3.1 (1H, m), 2.2 (1H, m), 1.3 (2H, m)	315.1
#18		($CDCl_3$) 9.5 (1H, br), 7.0-7.2 (5H, m), 6.6 (1H, s), 5.9 (1H, br), 3.7 (2H, m), 2.9 (2H, t)	321.1

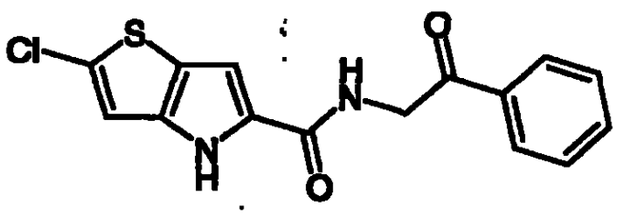
# 19		($CDCl_3$) 9.6 (1H, br), 6.9-7.3 (6H, m), 6.8 (1H, s), 6.5 (1H, m), 4.2 (2H, t), 3.8 (2H, m)	319.1
# 20		($CDCl_3$) 9.6 (1H, s), 6.8-7.4 (9H, m), 4.3 (2H, s), 3.4 (2H, m), 3.1 (2H, m).	396.1
# 21[2]		($CDCl_3$) 9.7 (1H, s), 8.0 (1H, s), 7.7 (1H, d), 7.1-7.4 (4H, m), 7.0 (1H, s), 6.9 (1H, s), 4.9 (1H, m), 4.0 (1H, m), 3.0 (1H, m)	378.1 (M+H)$^+$

[1] Amina: Método #15

[2] Amina: J Med Chem, 1985,28,1517

Ejemplo #22

2-Cloro-5-[*N*-(benzoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #8; 50 mg, 0.25 mmol) se disolvió en DCM (7 ml) que contenía HOBT (34 mg, 0.25 mmol), DJPEA (49 ml, 0.28 mmol) y 2-amino-1-feniletanona (43 mg, 0.25 mmol). La mezcla se agitó durante un minuto y se agregó EDAC (63 mg, 0.33 mmol). La mezcla se agitó a la temperatura del cuarto durante aproximadamente 18 horas. Se agregó agua a la solución y se precipitó un sólido. El sólido se filtró y se lavó con agua y DCM antes de secarse bajo presión reducida para proporcionar el compuesto del título como un sólido

blanco (45 mg, 61 %). NMR: 11.9 (1H, s), 8.6 (1H, t), 7.1-8.1 (7H, m), 4.8 (2H, d); m/z 317.3.

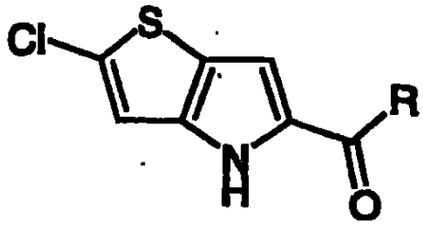
Ejemplos #23 - #25

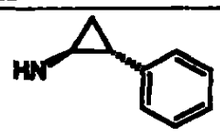
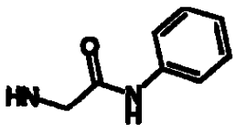
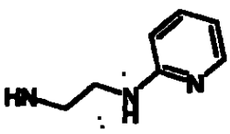
Los siguientes compuestos se elaboraron por el proceso de Ejemplo #22 usando 5-carboxi-2-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #8) y la amina apropiada:

Ejemplo #23: 2-Cloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #24: 2-Cloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #25: 2-Cloro-5-{*N*-{2-[(2-piridil)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol

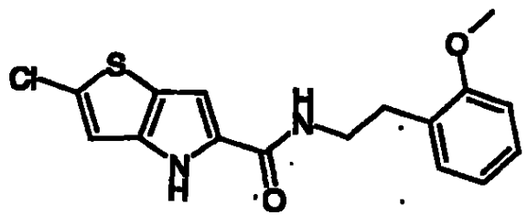


Ej.	R	NMR	M/z
#23		11.8 (1H,s), 8.5 (1H, d), 7.0-7.3 (7H,m), 3.0 (1H, m), 2.1 (1H, m), 1.3 (2H, m)	315.3
#24		11.8 (1H, s), 10.0 (1H, br), 8.6 (1H, br), 7.0-7.6 (7H, m), 4.0 (2H, d)	332,3
#25[1]		11.8 (1H, s), 8.4 (1H, s), 6.4-8.0 (6H, m), 6.6 (1H, br), 3.4 (4H, m)	319.3

[1] Amina: Eur J Med Chem, 1987, 22, 91.

Ejemplo #26

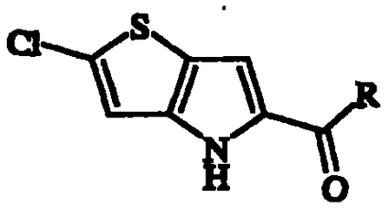
2-Cloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #8; 50 mg, 0.25 mmol) se disolvió en DCM (7 ml) que contenía HOBT (34 mg, 0.25 mmol), DIPEA (49 ml, 0.28 mmol) y 2-(2-metoxifenil)etilamina (43 mg, 0.25 mmol). La mezcla se agitó durante un minuto y se agregó EDAC (63 mg, 0.33 mmol). La mezcla se agitó a temperatura del recinto durante aproximadamente 18 horas. La mezcla de reacción se lavó con agua, la fase orgánica se secó, se filtró y se concentró para proporcionar el compuesto del título como un sólido blancuzco (84 mg, 100%). NMR (CDCI3): 9.7 (1H, br), 6.9-7.2 (5H, m), 6.5 (1H, s), 6.3 (1H, br), 3.9 (3H, s), 3.7 (2H, m), 3.0 (2H, t); m/z 333.4.

Ejemplos #27 - #31

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #26 usando 5-carboxi-2-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #8) y la amina apropiada.



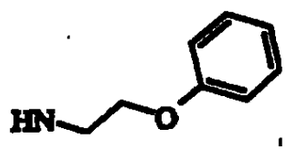
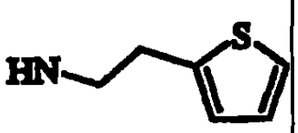
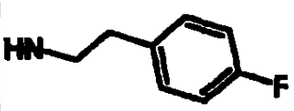
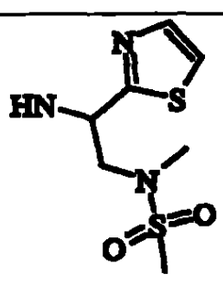
Ejemplo #27: 2-Cloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #28: 2-Cloro-5-{*N*-[2-(2-tienil)etil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #29: 2-Cloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil]-4*H*-tieno[3 2-*b*]pirrol

Ejemplo #30: 2-Cloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-il)etil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #31: 2-Cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ej.	R	NMR	M/z
#27		($CDCl_3$) 9.5 (1H, s), 6.9-7.3 (6H, m), 6.7 (1H, s), 6.4 (1H, br), 4.2 (2H, m), 3.9 (2H, m)	319.3
#28		($CDCl_3$) 9.4 (1H, br), 6.6-7.2 (5H, m), 6.0 (1H, br), 3.7(2H, m), 3.1 (2H, m)	309.3
#29		($CDCl_3$) 9.4 (1H, s), 7.0-7.2 (4H, m), 6.9 (1H, s), 6.6 (1H, s), 5.9 (1H, br), 3.7 (2H, m), 2.9 (2H, t)	321.3
#30		11.9 (1H, br), 9.0 (1H, d), 7.8 (1H, m), 7.7 (1H), 7.2 (1H, s), 7.0 (1H, s), 5.6 (1H, m), 3.9 (1H, m), 3.6 (1H, m), 2.9 (3H, s), 2.8 (3H, s)	417.2
#31		11.8 (1H, s), 8.1 (1H, t), 6.8-7.4 (2H, m), 2.5-4.0 (12H, m)	328.3

[1] Amina: Método #15

Ejemplos #32 - #69

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #1 usando 5-carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9) o Ejemplo #22 usando 5-carboxi-2-cloro-4*H*-tieno[3,2-*b*]pirrol (Método #8) y la amina apropiada:

Ejemplo #32: 2,3-Dicloro-5-[*N*-(2,3-dimetil-5-oxo-1-fenil-2,5-dihidro-1*H*-pirazol-4-il)carbamoil]4*H*-tieno[3,2-*b*]pirrol

Ejemplo #33: 2,3-Dicloro-5-[*N*-(4sulfamoilfenilmetil)carbamoil] 4*H*-tieno[3,2-*b*]pirrol

Ejemplo #34: 2,3-Dicloro-5-[*N*-(2-hidroxi-1-fenil)carbamoil]4*H*-tieno[3,2-*b*]pirrol

Ejemplo #35: 2,3-Dicloro-5-{*N*-(2-[(3-trifluorometilpirid-2-il)amino]etil)carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #36: 2,3-Dicloro-5-{*N*-[3-(5-tetrazolil)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #37: 2,3-Dicloro-5-[*N*-(5-oxo-3-fenil-4,5-dihidroisoxazol-4-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #38: 2,3-Dicloro-5-[*N*-(5-hidroxi-2-oxo-2,3,4,5-tetrahidro-1H-benz[*b*]azepin-4-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #39: 2-Cloro-5-{*N*-[3-(benciloxicarbonilamino)propil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #40: 2,3-Dicloro-5-{*N*-[(4-dimetilaminofenil)metil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #41: 5-[*N*-(1-Bencil-2-hidroxietil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #42: 2,3-Dicloro-5-{*N*-[2-(fenilamino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #43: 2,3-Dicloro-5-[*N*-(β-(*R*)-hidroxi-α-metilfenetil) carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #44: 2,3-Dicloro-5-[*N*-(β-hidroxifenetil) carbamoil)-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #45: 2,3-Dicloro-5-{*N*-[2-(4-hidroxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #46: 2,3-Dicloro-5-{*N*-[(bencimidazol-2-il)metil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #47: 2,3-Dicloro-5-{*N*-[2-(4-clorofenil)-2-hidroxi-1-(metoxicarbonil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #48: 2,3-Dicloro-5-{*N*-(imidazo[1,2-*a*]pirid-2-il) carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #49: 5-{*N*-[(Benztiazol-2-il)metil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #50: 2,3-Dicloro-5-{*N*-[(6-trifluorometilpirid-3-il)metil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #51: 2,3-Dicloro-5-{*N*-(2-[(2-piridazinil)metil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #52: 2,3-Dicloro-5-{*N*-[*N*-(2-hidroxi-3-fenoxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #53: 2,3-Dicloro-5-{*N*-[*N*-(3-metilisotiazol-5-il)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #54: 2,3-Dicloro-5-{*N*-[2-(piridazin-3-iloxi)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #55: 2-Cloro-5-(*N*-{2-[(3-trifluorometilpirid-2-il)amino]etil}carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #56: 2,3-Dicloro-5-{*N*-[2-(4-sulfamoilfenil)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #57: 2,3-Dicloro-5-{*N*-[2-(2-piridil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #58: 2,3-Dicloro-5-{*N*-(2-[1-hidroximetil-2-(4-imidazolil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #59: 2,3-Dicloro-5-{*N*-(2-[(3-quinolil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #60: 5-{*N*-[3-(4-Acetamidofenoxi)-2-hidroxipropil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #61: 2,3-Dicloro-5-{*N*-[3-(*N*-metilsulfonilcarbamoil) propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #62: 2,3-Dicloro-5-{*N*-(2-{[2-(guanidino)tiazol-4-il]metilito}etil)-carbamoil}-4*H*- tieno[3,2-*b*]pirrol

Ejemplo #63: 2,3-Dicloro-5-{*N*-[2-(2,4-dioxoimidazolidin-1-il)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #64: 5-{*N*-[2-Benciltio-1(hidroximetil)etil]carbamoil-2,3-dicloro-4*H*- tieno[3,2-*b*]pirrol

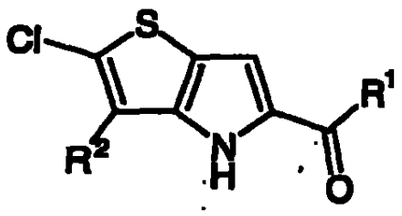
Ejemplo #65: 2,3-Dicloro-5-{*N*-[2-(dimetilaminosulfonilamino)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

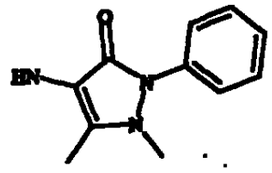
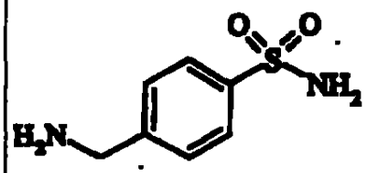
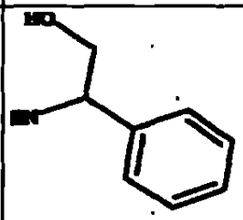
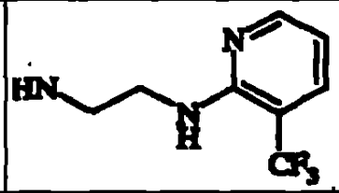
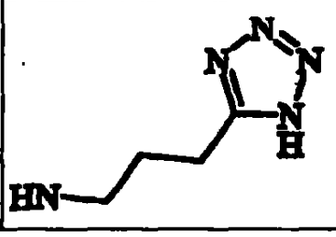
Ejemplo #66: 2,3-Dicloro-5-{*N*-[(6-metoxipirid-3-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

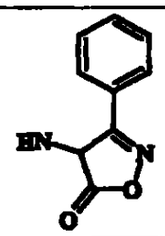
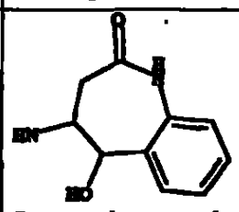
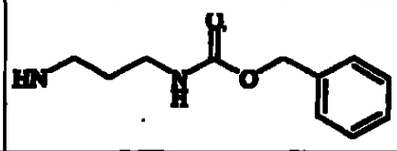
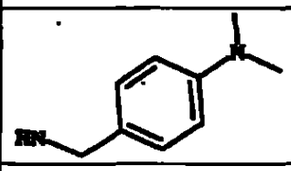
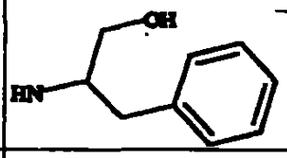
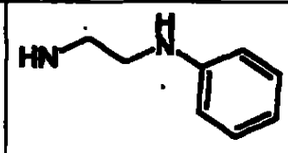
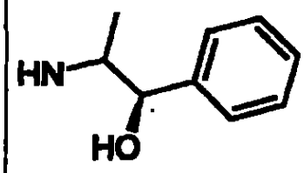
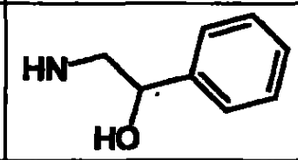
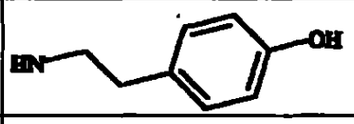
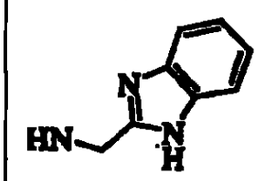
Ejemplo #67: (*S*)-2,3-Dicloro-5-{*N*-[(2-oxo-3-fenil-2,3,4,5-tetrahidrooxazol-5-il)-metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

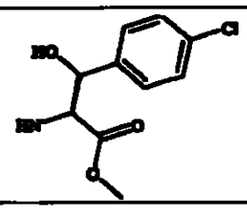
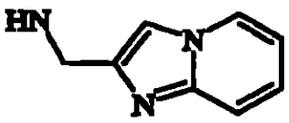
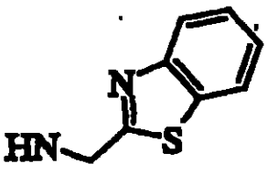
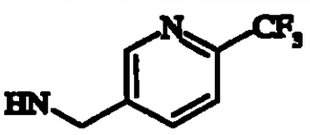
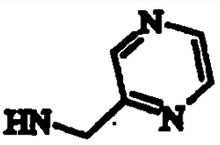
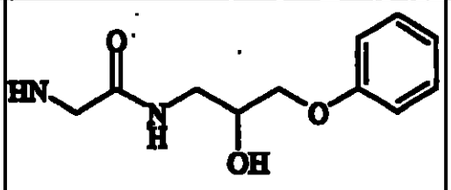
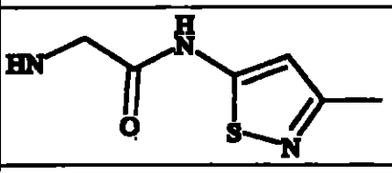
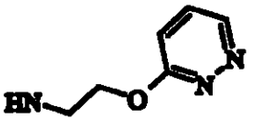
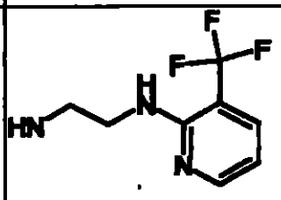
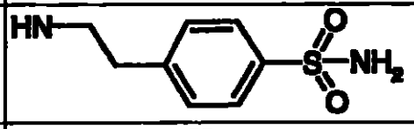
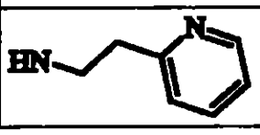
Ejemplo #68: 2,3-Dicloro-5-(*N*-{2-[3-(carbamoilmetil)fenoxi]etil} carbamoil}-4*H*-tieno[3,2-*b*]pirrol

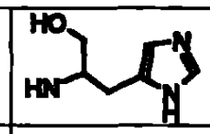
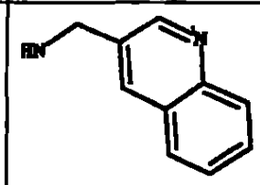
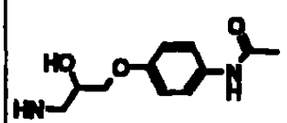
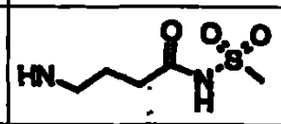
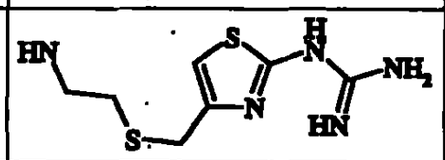
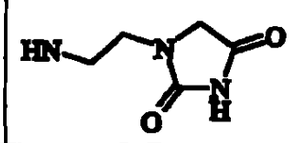
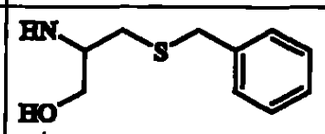
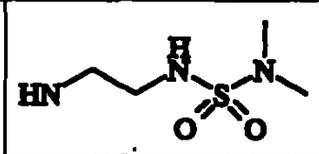
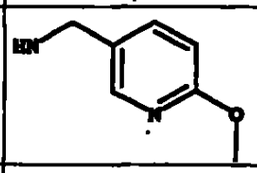
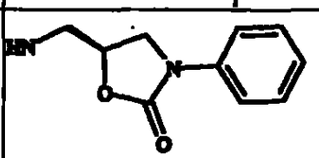
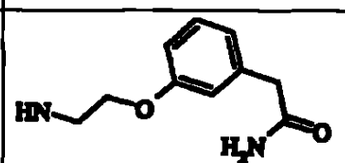
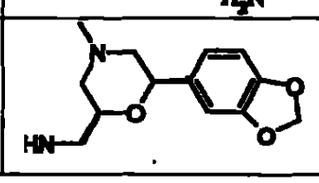
Ejemplo #69: 5-(*N*-{[6-(Benzo[1,3]dioxol-5-il)-4-metilmorfolin-2-il]metil}-carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



Ej.	R^1	R^2	M/z $(M+H)^+$	Amina
32		Cl	421	Obtenible en el comercio
33		Cl	404	Obtenible en el comercio
34		Cl	355	Obtenible en el comercio
35		Cl	423	Obtenible en el comercio
36		Cl	245	Mét. # 19

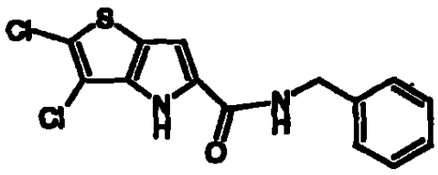
37		CI	394	Gazz. Chim. Ital., 1981, 111, 167
38	 La amina y el grupo hidroxi son trans uno con respecto al otro	CI	410	Mét. # 26
39		H	393	Obtenible en el comercio
40		CI	368	Obtenible en el comercio
41		CI	369	Obtenible en el comercio
42		CI	354	Obtenible en el comercio
43		CI	369	Obtenible en el comercio
44		CI	355	Obtenible en el comercio
45		CI	355	Obtenible en el comercio
46		CI	365	Obtenible en el comercio

47		CI	448	Obtenible en el comercio
48		CI	365	Obtenible en el comercio
49		CI	382	Obtenible en el comercio
50		CI	394	Obtenible en el comercio
51		CI	327	Obtenible en el comercio
52		CI	442	Método # 20
53		CI	389	Método # 21
54		CI	357	Método # 22
55		H	388	Obtenible en el comercio
56		CI	418	Obtenible en el comercio
57		CI	340	Obtenible en el comercio

58		CI	359	Obtenible en el comercio
59		CI	376	Obtenible en el comercio
60		CI	442	Obtenible en el comercio
61		CI	398	Método # 24
62		CI	449	Eur. J.Med. Chem., 1993, 28, 601
63		CI	361	Método # 23
64		CI	415	Obtenible en el comercio
65		CI	385	Obtenible en el comercio
66		CI	356	WO 9518097
67		CI	410	J. Med. Chem., 1989, 32, 1673
68		CI	412	Método # 25
69		CI	468	Método # 27

Ejemplo #70

5-*(N*-Bencilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método # 9, 118mg, 0.5mmol) se disolvió en diclorometano (10ml) que contenía bencilanmina (55 mg, 0.5 mmol), 1-HOBT (68mg, 0.5mmol) y DIPEA (258µl, 2mmol). La mezcla se agitó durante un minuto durante la adición de EDAC (125mg, 0.65mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 16 horas antes de lavarla con agua. La fracción orgánica se concentró y se purificó usando cromatografía de columna de sílice Bond-Elut (eluyente: diclorometano-diclorometano/metanol 5% gradiente) para proporcionar el *compuesto del título* como un sólido blanco (121mg, 75%). NMR: 12.4 (1H, br), 8.8 (1H, t), 7.3 (5H, m), 7.1 (1H, s), 4.5 (2H, d); m/z 323,27

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #70 usando 5-carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9) y la amina apropiada:

Ejemplo #71: 2,3-Dicloro-5-(*N*-fenetilcarbamoil)-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #72: 2,3-Dicloro-5-[*N*-(3-fenilpropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #73: 2,3-Dicloro-5-{*N*-[2-(2-hidroxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #74: 2,3-Dicloro-5-[*N*-(α,α-dimetilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #75: 2,3-Dicloro-5-[*N*-((1-fenilciclobutil)metil) carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #76: 2,3-Dicloro-5-[*N*-(β-metilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

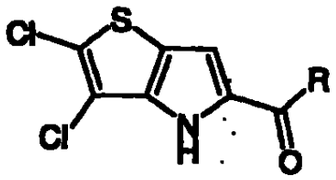
Ejemplo #77: 2,3-Dicloro-5-[*N*-(1,2,3,4-tetrahidronaft-2-il) carbamoil]-4*H*-tieno[3,2-*b*]pirrol

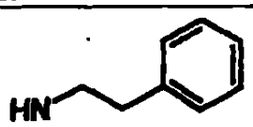
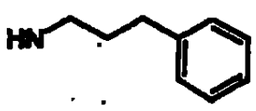
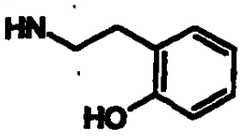
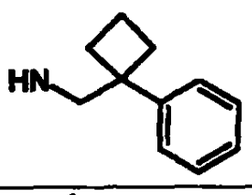
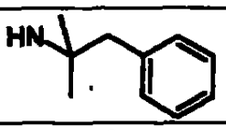
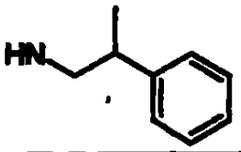
Ejemplo #78: 5-[*N*-(*N*-Bencilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

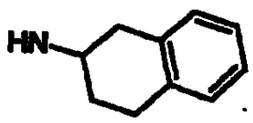
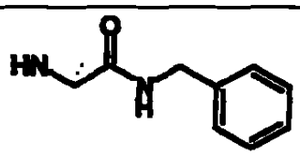
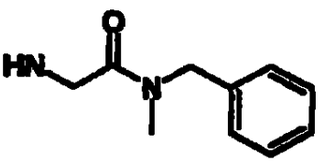
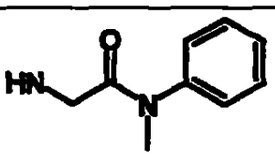
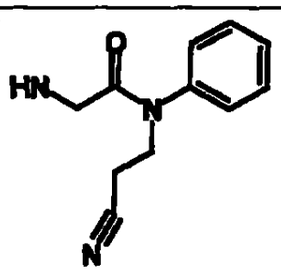
Ejemplo #79: 5-[*N*-(*N*-Bencil-*N*-metilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #80: 2,3-dicloro-5-[*N*-(*N*-metil-*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #81: 2,3-dicloro-5-{*N*-[*N*-(2-cianoetil)-*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	M/z
#71		12,33 (1H, br), 8.4 (1H, t), 7.3 (5H, m), 7.1 (1H, s), 3.5 (2H, dd), 2.8 (2H, t).	337.38
#72		12,35 (1H, br), 8.3 (1H, t), 7.2 (5H, m), 7.1 (1H, s), 3.3 (2H, q), 2.6 (2H, t), 1.8 (2H, m).	351.40
#73		12,3 (1H, br), 8.3 (1H, t), 7.0 (3H, m), 6.8 (1H, d), 6.7 (1H, t), 3.4 (2H, q), 2.8 (2H, t)	353.39
#74[1]		12,3 (1H, br), 8.1 (1H, t), 7.3 (2H, t), 7.15 (3H, m), 7.05 (1H, s), 3.6 (2H, d), 2.4 (2H, m), 2.2 (2H, m), 2.0 (1H, m), 1.8 (1H, m).	377.44
#75[2]		12.25 (1H, br), 7.4 (1H, s), 7.1 (6H, m), 3.1 (2H, s), 1.3 (6H, s)	365.41
#76[3]		12,3 (1H, br), 8.3 (1h, t), 7.2 (5H, m), 7.0 (1H, s), 3.4 (2H, m), 3.0 (1H, q), 1.2 (3H, d).	Sin ión de masa
#77		12,35 (1H, br), 8.2 (1H,	363.35

		d), 7.1 (1H, s), 7.05 (4H, s), 4.2 (1H, br), 3.1 (1H, dd), 2.8 (3H, m), 2.0 (1H, m), 1.8 (1H, m).	
#78[4]		12.4 (1H, br), 8.6 (1H, t), 8.4 (1H, t), 7.3 (5H, m), 4.3 (2H, d), 3.9 (2H, d).	380.41
#79[5]		12.45 (1h, br), 8.4(1H, m), 7.3 (5H, m), 7.2(1H, m), 4.6 (0.6, s), 4.5 (1.4H, s), 4.2(2H, m), 3.0 (2H, s), 2.8 (1H, s)	394.44
#80[6]		12.4 (1H, br), 8.4(1H, t), 7.4 (5H, m), 7.1 (1H, s), 3.8(2H, br), 3,2(3H, s)	380.41
#81[7]		12.4 (1H, br), 8.4 (1H, t), 7.5 (5H, m), 7.1 (1H, s), 3.9 (2H, t), 3.7 (2H, br), 2.7 (2H, t)	419.41

[1] Amina: J. Org. Chem.; 1976, 41(14), 2502-2503

[2] Amina: J. Med. Chem.; 1993, 36(22), 3300-3307

[3] Amina: J. Am. Chem. Soc.; 1960, 82, 2577

[4] Amina: Método #6

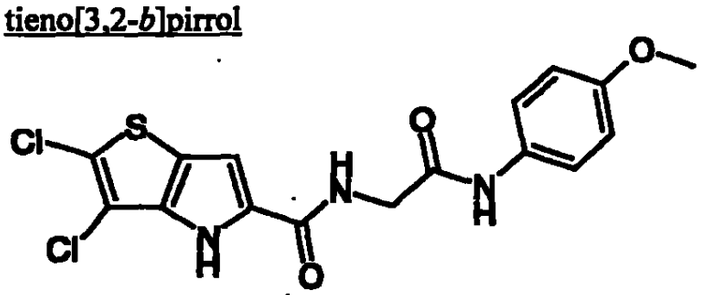
[5] Amina: Método #31

[6] Amina: Método #30

[7] Amina: Método #14

Ejemplo #82

2,3-dicloro-5-{*N*-[*N*-(4-metoxifenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



Una solución de 5-(*N*-carboximetilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-b]pirrol (Método #12, 150mg, 0.51mmol) y 4-metoxianilina (69mg, 0.56mmol) en tetrahidrofurano (THF) (6ml) se agitó a temperatura ambiente durante 30 minutos. Se agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio (DMTMM) (142mg, 0.51mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche, se vertió en agua (15ml) y se extrajo con acetato de etilo (3x15ml). Los extractos orgánicos se combinaron y lavaron con solución 1N de ácido cítrico (15ml), solución de bicarbonato de sodio (15ml), se secó sobre sulfato de magnesio, se filtró y se concentró para producir el *producto del título* como un sólido blanco. NMR: 12.4 (1H, s). 9.9 (1H. s). 8.6 (1H, t). 7.5 (2H. d). 7.2 (1H. s), 6.85 (2H. d), 4.0 (2H. d), 3.7 (3H, s); m/z 396.38

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #82 usando 2,3-dicloro-5-[*N*-carboximetilcarbamoil]-4*H*-tieno[3,2-*b*]pirrol (Método #12) y la amina apropiada obtenible en el comercio:

Ejemplo #83: 2,3-dicloro-5-{*N*-[*N*-(4-fluorofenil)-carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #84: 2,3-dicloro-5-{*N*-[*N*-(4-nitrofenil)-carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #85: 2,3-dicloro-5-{*N*-[*N*-(2,6-dimetilfenil)-carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #86: 2,3-dicloro-5-{*N*-[*N*-metil-*N*-(4-metilfenil) carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #87: 2,3-dicloro-5-{*N*-[*N*-metil-*N*-(3-metilfenil) carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #88: 2,3-dicloro-5-{*N*-[*N*-(3-clorofenil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #89: 2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-fenilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #90: 2,3-dicloro-5-{*N*-[*N*-(1,1-dimetil-2-hidroxietil) carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #91: 2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

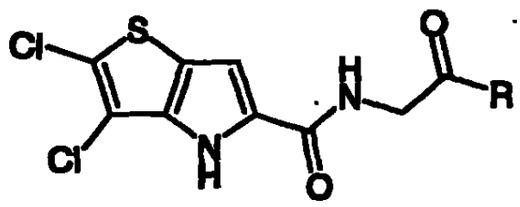
Ejemplo #92: 2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

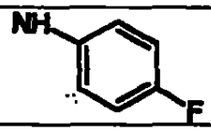
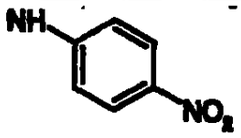
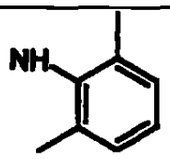
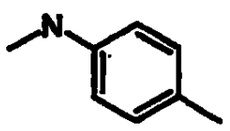
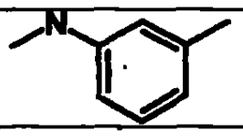
Ejemplo #93: 2,3-dicloro-5-{*N*-[*N*-(3-hidroxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

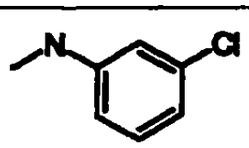
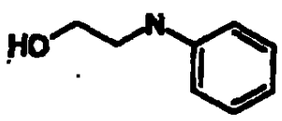
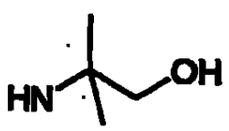
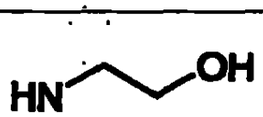
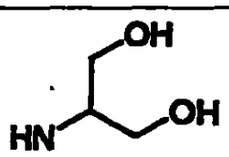
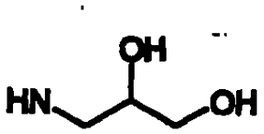
Ejemplo #94: 2,3-dicloro-5-{*N*-[*N*-(4-hidroxibutil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #95: 2,3-dicloro-5-(*N*-{*N*-[bis(hidroximetil)metil]carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #96: 2,3-dicloro-5-{*N*-[*N*-(2,3-dihidroxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

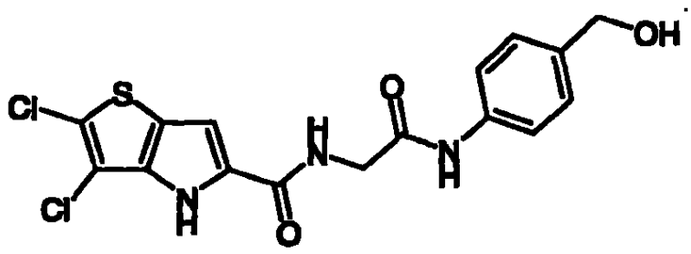


Ej.	R	NMR	m/z
#83		12.42 (1H, br), 10.08 (1H, br), 8.6 (1H, t), 7.6 (2H, m), 7.1 (3H, m), 4.0 (2H, d)	384.20
#84		12.5 (1H, br), 10.74 (1H, br), 8.8 (1H, t), 8.3 (2H, d), 7.9 (2H, d), 7.2 (1H, s), 4.2 (2H, d).	411.36
#85		12.45 (1H, br), 9.3 (1H, br), 8.7 (1H, t), 7.2 (1H, s), 7.1 (3H, s), 4.1 (2H, d), 2.1 (6H, s).	394.39
#86		12.4 (1H, br), 8.4 (1H, t), 7.3 (4H, s), 7.1 (1H, s), 3.7 (2H, br), 3,2 (3H, s), 2,3 (3H, s)	394.17
#87		12.4 (1H, br), 8.4 (1H, t), 7.4 (1H, t), 7.2 (3H, m), 7.1 (1H, s), 3.8 (2H, br), 3.3	394.28

		(3H, s), 2,3 (3H, s)	
#88		12.4 (1H, br), 8.4 (1H, t), 7.5 (4H, m), 7.1 (1H, s), (3.9, br), 3,2 (3H, s).	Sin ión de masa
#89		12.4 (1H, br), 8.4 (1H, t), 7.4 (5H, m), 7.1 (1H, s), 4.7 (1H, br), 3.7 (4H, m), 3.5 (2H, d).	410.54
#90		12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, br), 7.1 (1H, s), 4.8 (1H, t), 3.8 (2H, d), 3.4 (1.3H, d), 3.1 (0.7H, d), 1.2 (6H, s)	362,33
#91		12.44 (1H, br), 8.3 (1H, br), 7.1 (1H, s), 4.9 (0.5H, t), 4.6 (0.5H, t), 4.1 (2R, dd), 3.4 (4H, m), 3.0 (1.5H, s), 2.8 (0.5H, s).	348.30
#92		12.42 (1H, br), 8.5 (1H, t), 7.8 (1H, t), 7.1 (1H, s), 4.6 (1H, br), 3.8 (2H, d), 3.4 (2H, br), 3.1 (2H, q).	334.34
#93		12.41 (1H, br), 8.5 (1H, t), 7.8 (1H, t), 7.1 (1H, s), 4.4 (1H, t, br), 3.8 (2H, d), 3.4 (2H, q, br), 3.1 (2H, q), 1.5 (2H, m).	348.38
#94		12.4 (1H, br), 8.5 (1H, t), 7.9 (1H, t), 7.1 (1H, s), 4.3 (1H, t), 3.8 (2H, d), 3.4 (2H, d), 3.1 (2H, q, br), 1.4 (4H, m).	362,36
#95		12.42 (1H, br), 8.5 (1H, t), 7.6 (1H, d), 7.1 (1H, s), 4.6 (2H, br), 3.9 (2H, d), 3.7 (1H, m), 3.4 (4H, br).	364.36
#96		12.4 (1H, br), 8.5 (1H, br), 7.8 (1H, t), 7.1 (1H, s), 4.7 (1H, br) 4.5 (1H, br), 3.8 (2H, d), 3.5 (1H, m), 3,2 (3H, m), 3.0 (1H, m).	364.35

Ejemplo #97

2,3-dicloro-5-{*N*-[*N*-(4-hidroximetilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



Una solución de 5-(*N*-carboximetilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #12) (150mg, 0.51mmol), y alcohol 4-aminobencílico (70.5mg, 0.56mmol) en THF (6ml) se agitó a temperatura ambiente durante 30 minutos. Se agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio (DMTMM) (142mg, 0.51mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua (15ml). El precipitado resultante se aisló mediante filtración, se lavó con agua, éter y se secó *in vacuo* para generar el *producto del título* como un sólido blanco (149mg, 73%)

NMR: 12.42 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.5 (2H, d), 7.2 (2H, d), 7.1 (1H, s), 5.0 (1H, br), 4.4 (2H, s), 4.0 (2H, d); m/z 396.21

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #97 usando 5-(*N*-carboximetilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #12) y la amina apropiada obtenible en el comercio:

Ejemplo #98: 2,3-dicloro-5-{*N*-[*N*-(5-isoquinolil)carbamoilmetil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #99: 2,3-dicloro-5-{*N*-[*N*-(3-hidroximetil)fenil] carbamoilmetil]-carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #100: 2,3-dicloro-5-(*N*-{*N*-[4-(2-hidroxietil)fenil] carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*] pirrol

Ejemplo #101: 2,3-dicloro-5-(*N*-{*N*-[2,4-difluorofenil)-*N*-metil-carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*] pirrol

Ejempl #102: 2,3-dicloro-5-{*N*-[(1,2,3,4-tetrahidro-1-quinolil) carbonilmetil]-carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #103: 2,3-dicloro-5-{*N*-[*N*-(2-cianoetil)-*N*-metilcarbamoilmetil]-carbamoil}-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #104: 2,3-dicloro-5-{*N*-[*N*-(4-hidroxipiperidino) carbamoilmetil]-carbamoil}-4*H*-tieno[3,2-*b*]pirrol

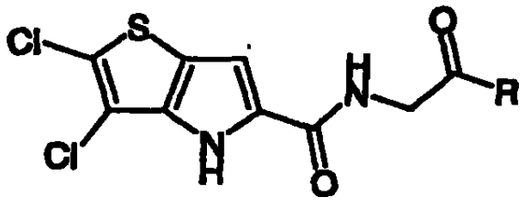
Ejemplo #105: 2,3-dicloro-5-[*N*-(*N*-ciclopentilcarbamoilmetil]-carbamoil]-4*H*-tieno[3,2-*b*]pirrol

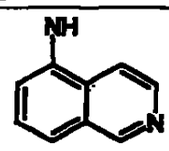
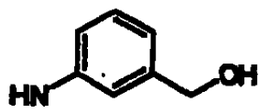
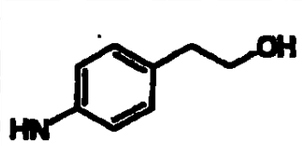
Ejemplo #106: 2,3-dicloro-5-[*N*-(*N*-isopropilcarbamoilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol

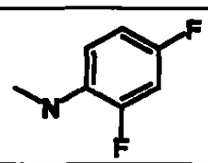
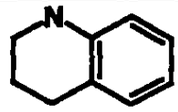
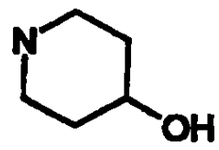
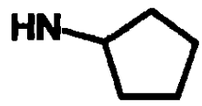
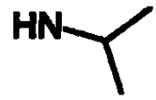
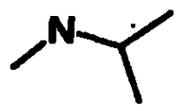
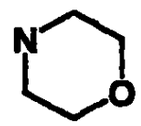
Ejemplo #107: 2,3-dicloro-5-[*N*-(*N*-isopropil-*N*-metilcarbamoilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #108: 2,3-dicloro-5-{*N*-(tiomorfolinocarbonilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #109: 2,3-dicloro-5-{*N*-(morfolinocarbonilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	m/z
#98		12.5 (1H, s), 8.7 (1H, t), 8.5 (1H, d), 8.0 (3H, m), 7.7 (1H, t), 7.1 (1H, s), 4.2 (2H, d).	
#99		12.42 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.55 (1H, s), 7.45 (1H, d), 7.2 (1H, t), 7.1 (1H, s), 7.0 (1H, d), 5.1 (1H, br), 4.4 (2H, s), 4.0 (2H, d)	396.19
#100		12.41 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.5 (1H, m), 7.1 (3H, m), 4.6 (1H, br), 4.0 (2H, d), 3.6 (2H, br), 2.6 (2H, t)	410.16
#101		12.4 (1H, br), 8.5 (1H, t), 7.7 (1H, q), 7.5 (1H, dt), 7.2 (1H,	Sin ión de masa

		t, br), 7.1 (1H, s), 3.8 (1H, m), 3.6 (1H, m), 3.1 (3H, s).	
#102		12.41 (1H, br), 8.5 (1H, t), 7.6 (1H, d), 7.1 (5H, m), 4.2 (2H, d), 3.7 (2H, t), 2.7 (2H, t), 1.9 (2H, m).	406.18
#103		12.42 (1H, br), 8.4 (1H, m), 7.1 (1H, s), 4.1(2H, m), 3.7 (0.5H, t); 3.6 (1.5H, t), 3.1 (2H, s), 2.9 (1.5H, m), 2.7 (1.5H, t).	357.27
#104		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.7 (1H, br), 4.1 (2H, d), 3.9 (1H, m), 3.7 (2H, m), 3,2 (1H, m), 3.0 (1H, m), 1.7 (2H, m), 1.3 (2H, m).	376.26
#105		12.4 (1H, br), 8.45 (1H, t), 7.8 (1H, d), 7.1 (1H, s), 4.0 (1H, m), 3.8 (2H, d), 1.8 (2H, m), 1.6 (2H, m), 1.5 (2H, m), 1.4 (2H, m).	358.35
#106		12.4 (1H, br), 8.5 (1H, t), 7.7 (1H, d), 7.1 (1H, s), 3.9 (1H, m), 3.8 (2H, d), 1.1 (6H, d).	335.34
#107		12.42 (1H, br), 8.3 (1H, m), 7.1 (1H, s), 4.6 (0.66H, m), 4.1 (2,33H, m), 2.8 (2H, s), 2.7 (1H, s), 1.15 (2.4H, d), 1.05 (3.6H, d).	346.34
#108		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (1H, d), 3.7 (4H, m), 2.7 (2H, br), 2.5 (2H, br).	No mass ion
#109		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (2H, d), 3.6 (4H, br), 3.5 (4H, br).	360.30

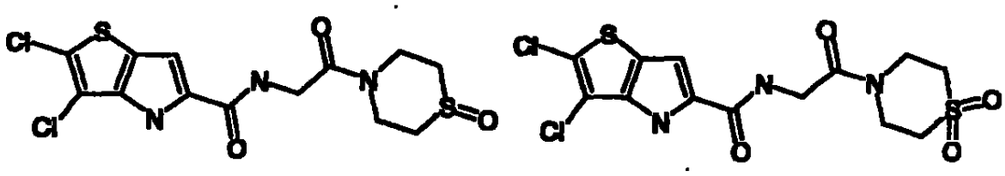
Ejemplo #110

2,3-dicloro-5-{*N*-[1,1-dioxotiomorfolino)carbonilmetil]-carbamoil}-4*H*-tieno[3,2-*b*]pirrol

y

Ejemplo #111

2,3-dicloro-5-{*N*-[(1-oxotiomorfolino)carbonilmetil)-carbamoil]-4*H*-tieno[3,2-*b*]pirrol



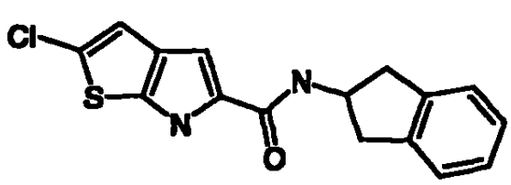
Una solución de ácido *m*-cloroperbenzoico (mCPBA) (14mg, 0.85mmol) en diclorometano (5ml) se añadió gota a gota a una suspensión de 2,3-dicloro-5-[*N*-(tiomorfolinocarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol (Ejemplo # 108) en diclorometano y la mezcla de la reacción se agitó a temperatura ambiente durante una hora. Se agregó solución de metabisulfito de sodio al 5% (5ml) y la mezcla se agitó durante varios minutos. La capa acuosa se extrajo con acetato de etilo (2x15ml) y los extractos orgánicos combinados se lavaron con solución de bicarbonato de sodio (2x15ml) y se concentraron. La mezcla de los dos componentes se separó usando cromatografía de columna de sílice bond-elute (eluyente: diclorometano-diclorometano/metanol 5% gradiente) para proporcionar el producto menos polar (sulfona) como un polvo blanco (57mg 33%) y el producto más polar (sulfóxido) como un sólido blanco (62mg, 37%).

NMR: (sulfona) 12.43 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (2H, d), 3.9 (4H, br), 3.3 (2H, br), 3.1 (2H, br); m/z 408.33

NMR: (sulfóxido) 12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (3H, m), 3.9 (2H, d), 3.6 (1H, m), 2.9 (4H, m).

Ejemplo #112

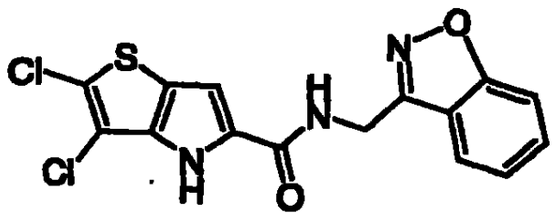
2-Cloro-5-[*N*-(2-indanil)carbamoil]-6*H*-tieno{2,3-*b*}pirrol



5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 101mg, 0.5mmol) se disolvió en diclorometano (6ml) que contenía 2-aminoindano (68mg, 0.5mmol), 1-hidroxibenotriazol (HOBT) (68mg, 0.5mmol) y DIPEA (355µl, 2.0mmol). La mezcla se agitó durante un minuto antes de la adición de EDAC (125mg, 0.65mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 16 horas antes de lavarla con agua. La fracción orgánica se concentró y se purificó usando cromatografía de columna de sílice bond-elute (eluyente: diclorometano-diclorometano/metanol 2.5% gradiente) para proporcionar el compuesto del título como un sólido color crema (96mg, 61%).
NMR: 11.80 (1H, br), 8.3 (1H, t), 7.2 (5H, m), 7.0 (1H, s), 4.6 (1H, m), 4.7 (1H, d), 3,2 (2H, m), 2.9 (2H, m); m/z 315.46

Ejemplo #113

5-[*N*-(Benz[1,2]oxazol-3-ilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 118 mg, 0.5 mmol) se disolvió en DMF (5 ml) que contenía HOBT (83 mg, 0.55 mmo1), DIPEA (52 ul, 0.30 mmol) y 1,2-bencisoxazol-3-metilamina (Eur.J .Med.Chem-Chimica Therapeutica, Jan.-Feb.-10, No. 1 p 32) (89 mg, 0.6 mmol). La mezcla se agitó durante un minuto y se agregó EDAC (106 mg, 0.55 mmol). La mezcla se agitó a temperatura del recinto durante aproximadamente 18 horas. Se agregó agua a la solución y se precipitó un sólido. Este sólido se filtró y se lavó con agua antes de secarse bajo presión reducida para proporcionar el compuesto del título como un sólido blanco (174mg). 1H NMR: 4.9 (2H, s), 7.1 (1H, s), 7.4 (1H, t), 7.6 (1H, t), 7.8 (1H, d), 8.0 (1H, d), 9.2 (1H, s), 12.5 (1H, s); m/z 366 (M+H);

Columna HPLC Hichrome C18 acetonitrilo/agua/0.1 %TFA 5-95% durante 7.5 min Rt 4.9 min m/z 366 (M+H)

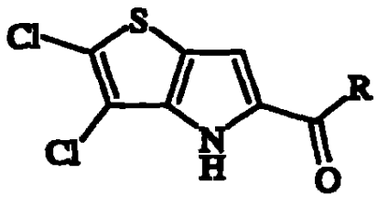
Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #113 usando 5-carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9) y la amina apropiada:

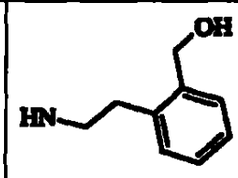
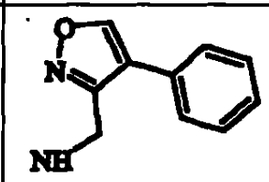
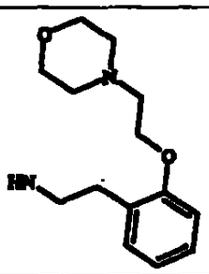
Ejemplo #114: 2,3-Dicloro-5-(*N*-{2-[2-(hidroximetil)fenil]etil} carbamoil)-4*H*-tieno[3,2-*b*]pirrol

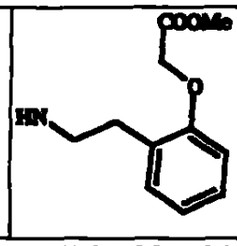
Ejemplo #115: 2,3-Dicloro-5-[*N*-(4-fenilisoxasol-3-ilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #116: 2,3-Dicloro-5-(*N*-{2-[2-(2-morfolinoetoxi)fenil] etil}carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #117: 2,3-Dicloro-5-(*N*-{2-[2-(metoxicarbonilmetoxi) fenil]etil}-carbamoil]-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	Rt	M/z
#114[1]		1H NMR: 2.9 (2H, q), 3.4 (2H, q), 4.6 (2H, d), 5.1 (1H, t), 7.1 (1H, s), 7.2 (3H, m), 7.4 (1H, m), 8.4(1H, m)	4.55	369
#115[2]		1H MR: 4.7 (2H, s), 7.1 (1H, s), 7.4 (3H, m), 7.6 (2H, m), 8.8 (1H, t), 9.2 (1H, s)	5.01	392
#116[3]		1H NMR ($CDCl_3$): 2.6 (4H, m), 2.8 (2H, t), 3.0 (2H, t), 3.7 (6H, m), 4.1 (2H, t), 6.3 (1H, m), 6.6 (1H, s), 6.9 (2H, m), 7.2 (2H, m), 9.8 (1H, b)	4.26	468
#117[4]		($CDCl_3$): 3.0 (2H, q), 3.8 (2H, q), 3.9 (3H, s), 4.7	4.47	413

		(2H, s), 6.6 (1H, s), 6.7 (1H, s), 6.8 (1H, d), 7.0 (1H, t), 7.2 (2H, m)		

[1] Amina: EP86-300884

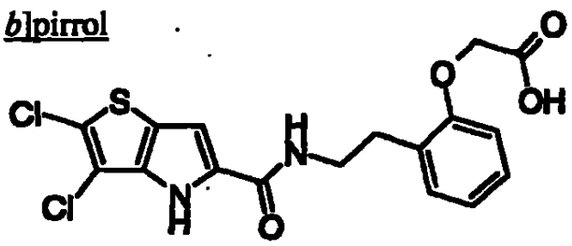
[2] Amina: Método #33

[3] Amina: Método #34

[4] Amina: Método #35

Ejemplo #118

5-(*N*-{2-[2-(Carboximetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



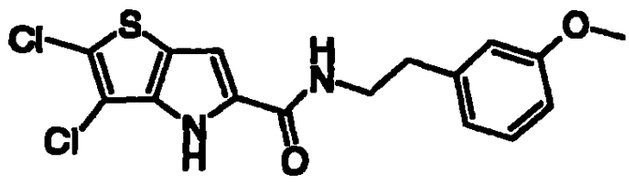
2,3-Dicloro-5-(*N*-{2-[2-(metoxicarbonilmetoxi)fenil] etil} carbamoil)-4*H*-tieno[3,2-*b*]pirrol (Ejemplo #117, 100mg, 0.25mmol) disuelto en 2:1 THF : metanol (2ml) se trató con solución 1N de hidróxido de litio (0.25ml, 0.25mmol), seguida por la adición de agua hasta que la solución adquirió una apariencia un poco opalescente y luego se agitó durante 2 horas a la temperatura del recinto. Los solventes orgánicos se retiraron mediante evaporación bajo presión reducida, la solución se filtró y luego se acidificó con 2N HCl para producir un precipitado espeso blanco que se aisló mediante filtración, se lavó con agua y se secó bajo presión reducida sobre pentóxido de fósforo para producir el compuesto del título (83mg).

1H NMR : 2.9 (2H,q), 3.5 (2H,q), 4.7 (2H,s), 6.8 (2H,m), 7.1 (1H,s), 7.2 (2H,m), 8.4 (1H,m), 12.4 (1H;s)

Columna HPLC Hichrome C18 acetonitrilo/agua/0.1 % TFA 5-95% durante 7.5 min Rt 4.47min m/z 413 (M+H)

Ejemplo #119

2,3-Dicloro-5-{*N*-[2-(3-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

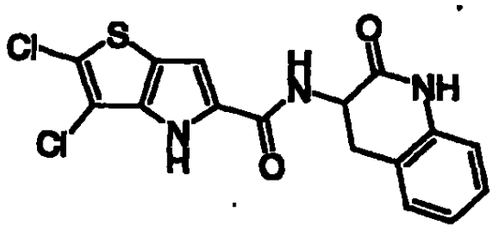


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 100mg, 0.42mmol) se suspendió en DCM 10ml; se agregó gota a gota una solución 2M de cloruro de oxalilo en DCM (750ul, 1.5mmol) seguido por una gota de DMF y la mezcla resultante se agitó durante la noche a la temperatura del recinto. La suspensión se filtró, el residuo se lavó con DCM y le filtrado se evaporó a sequedad bajo presión reducida y a continuación se destiló azeotrópicamente con tolueno para producir un sólido amarillo que se disolvió en DCM (6.9ml) bajo nitrógeno. Se agregó carbonato de calcio (60mg, 0.6mmol) seguido por una solución de 3-metoxifenetilamina; 90mg, 0.4mmol) y la mezcla se agitó a la temperatura del recinto durante la noche. La mezcla se filtró, el residuo se lavó con DCM seguido por 0.1 M HCl, seguidamente agua para producir el compuesto del título como un sólido blanco (98mg). 1H NMR ($CDCl_3$): 2.9 (2H, t), 3.7 (2B, t), 3.9 (3H, s), 6.0 (1H, m), 6.6 (1H, s), 6.8 (3H, m), 7.2 (2H, m), 9.9 (1H,s)

m/z 369 (M+H)

Ejemplo #120

23-Dicloro-5-[*N*-(2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



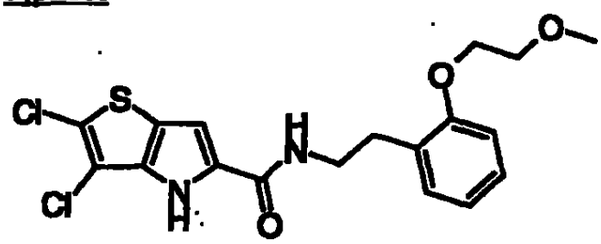
Éste se preparó siguiendo el procedimiento descrito en Ejemplo #97 usando 3-aminohidrocarbostirilo (Arch.Biochem&Biophys. 1963 109 48) que se empleó en lugar de alcohol 4-aminobencílico y 5-carboxi-2,3-

dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9) se empleó en lugar de 5-(*N*-carboximetilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol para producir el compuesto del título: 1H NMR : 3.0 (2H, d), 4.7 (1H, q), 6.9 (3H, m), 7.2 (2H, m), 8.5 (1H, d), 10.35 (1H, s)

Columna HPLC Hichrome C18 acetonitrilo/agua/0.1 % TFA 5-95% durante 7.5 min Rt 4.44min m/z 380 (M+H)

Ejemplo #121

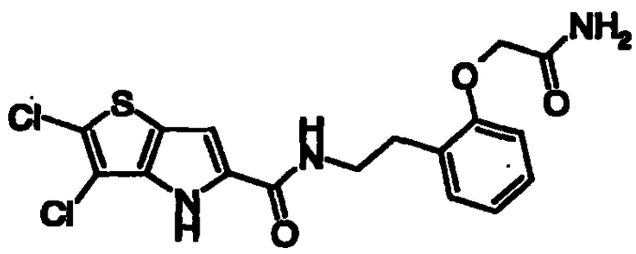
23-Dicloro-5-(*N*-{2-[2-(2-metoxietoxi)fenil]etil}carbamoil]-4*H*-tieno[3,2-*b*]pirrol



2,3-Dicloro-5-{*N*-[2-(2-hidroxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol (Ejemplo 73, 177.5 mg, 0.5mmol) se disolvió en THF 3ml bajo nitrógeno junto con metoxietanol (38µl, 0.5mmol) y trifenilfosfina (131mg, 0.5mmol), la solución agitada resultante se enfrió a 0°C y se trató con DIAD (98µl, 0.5mmol) gota a gota durante 30 minutos, luego se dejó calentar a temperatura del recinto durante la noche. Una vez evaporada a sequedad, la mezcla se purificó por cromatografía en una columna de sílice Bond Elute 20g eluyendo con DCM. El producto se tomó en éter dietílico 20ml, se lavó con 2N NaOH (3x5ml), agua (5ml) y salmuera saturada (5ml), seguidamente se secó sobre sulfato de magnesio y se evaporó bajo presión reducida para producir el compuesto del título (45mg). 1H NMR ($CDCl_3$) : 3.0 (2H, t), 3.5 (3H, s), 3.7 (2H, m), 3.9 (2H, m), 4.2 (2H, m), 6.6 (1H, m), 6.8 (1H, s), 6.9 (2H, m), 7.2 (2H, m), 9.9 (1H, s). Columna HPLC Hichrome C18 acetonitrilo/agua/0.1 %TFA 5-95% durante 7.5 min Rt 5.02min m/z 411 (M-H)

Ejemplo #122

5-[*N*-{2-[2-(carbamoilmetoxi)fenil]etil}carbamoil]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol



5-[*N*-{2-[2-(carbamoilmetoxi)fenil]etil}carbamoil]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol (Ejemplo #118,124 mg, 0.3 mmol) se disolvió en DMF (3 ml) que contenía HOBT (50 mg, 0.33 mmol), DIPEA (140µl, 0.69 mmol) y cloruro de amonio (18mg, 0.36 mmol). La mezcla se agitó durante un minuto y se agregó EDAC (64mg, 0.33 mmol). La mezcla se agitó a temperatura del recinto durante aproximadamente 18 horas. Se agregó agua a la solución y se precipitó un sólido. Este sólido se filtró y se lavó con agua antes de secarse bajo presión reducida para proporcionar el compuesto del título como un sólido blanco (111mg). 1H NMR: 2.9 (2H, q), 3.5 (2H, q), 4.5 (2H, s), 6.8 (2H, m), 7.0 (1H, s), 7.2 (2H, m), 7.5 (1H, s), 7.6 (1H, s), 8.4 (1H, m), 12.4 (1H, s)
Columna HPLC Hichrome C18 acetonitrilo/aguar/0.1 %TFA 5-95% durante 7.5 min Rt 4.37min m/z 412 (M+H)

Los siguientes compuestos se elaboraron mediante el proceso de Ejemplo #122 usando 5-(*N*-{2-[2-(Carboximetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Ejemplo #118) y la amina apropiada:

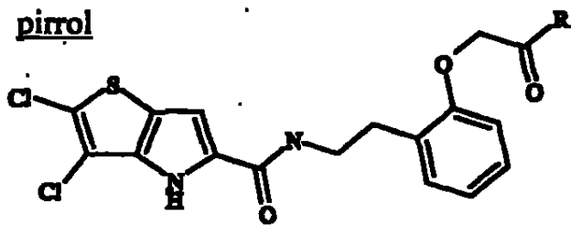
Ejemplo #123: 2,3-Dicloro-5-(*N*-{2-[2-(*N*-metilcarbamoilmetoxi) fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*] pirrol

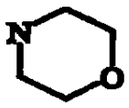
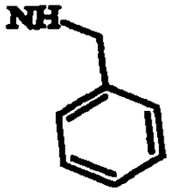
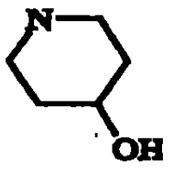
Ejemplo #124: 2,3-Dicloro-5-(*N*-{2-[2-(*N*,*N*-dimetilcarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*] pirrol

Ejemplo #125: 2,3-Dicloro-5-(*N*-{2-[2-(morfolinocarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno [3,2-*b*]pirrol

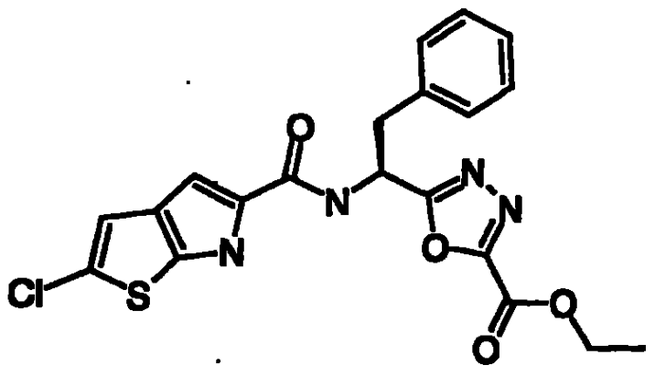
Ejemplo #126: 5-(*N*-{2-[2-(*N*-Bencilcarbamoilmetoxi)fenil]etil} carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol

Ejemplo #127: 2,3-Dicloro-5-(*N*-{2-[2-(4-hidroxipiperidinocarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol



Ej.	R	NMR	Rt	M/z
#123		1H NMR: 2.8 (3H, d), 2.9 (2H, q), 3.5 (2H, q), 4.5 (2H, s), 6.8 (2H, m), 7.1 (1H, s), 7.2 (2H, m), 8.0 (1H, m), 8.5 (1H, m), 12.2 (1H, s)	4.65	426
#124		1H NMR : 2.9 (5H, m), 3.0 (3H, s), 3.5 (2H, q), 4.8 (2H, s), 6.8 (2H, m), 7.0 (1H ,s), 7.1 (2H, m), 8.4 (1H, m), 12.4 (1H, s)	4.57	440
#125		1H NMR : 2.9 (2H, q), 3.4-3.7 (10H, m), 4.8 (2H, s), 6.8 (2H, m), 7.0 (1H, s), 7.1 (2H, m), 8.3 (1H, m), 12.4 (1H, s)	4.5	484
#126		1H NMR : 2.9 (2H, q), 3.5 (2H, q), 4.4 (2H, d), 4.6 (2H, s), 6.9 (2H, m), 7.0 (1H, s), 7.2-7.4 (7H, m), 8.4 (1H, m), 8.6(1H,m), 12.4 (1H, s)	5.26	502
#127		1H NMR: 1.2-1.5 (2H,m), 1.6-1.8 (2H, m), 2.9 (2H, q), 3.1 (1H,q), 3,2(1H, q), 3.5 (2H, q), 3.7 (2H, q), 3.9 (1H, m), 4.7 (1H, d), 4.8 (2H, s), 6.9(2H,m), 7.1 (1H, s), 7.2 (2H, m), 8.0 (1H, s), 8.4 (1H, m), 12.4 (1H, s).	4.2	496

Ejemplo #128
(*S*)-2-Cloro-5-{N-[α-(5-etoxicarbonil-1,3,4-oxadiazol-2-il)fenetil] carbamoil}-6*H*-tieno[2,3-*b*]pirrol



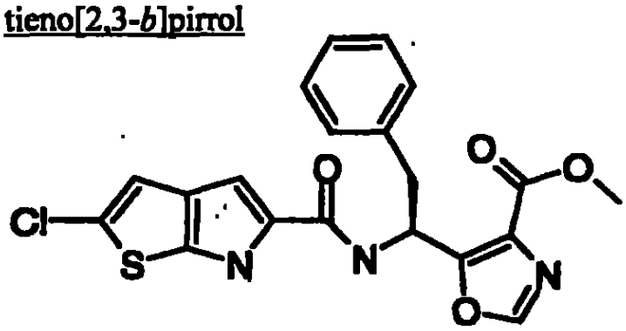
5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10 172mg, 0.86mmol) se disolvió en DCM (10ml) que contenía HOBT (115mg, 0.86mmol), DWEA (331mg, 2.57mmol) y etil (*S*)-5-(α-aminofenetil)-1,3,4-oxadiazol-2-carboxilato trifluoroacetato (Método #16; 322mg, 0.86mmol). Se agregó EDAC (205mg, 1.07mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se filtró y el filtrado se lavó con ácido clorhídrico diluido y agua. Luego de secar sobre sulfato de magnesio y concentración del material crudo se purificó por cromatografía de columna de sílice bond elute (eluyente - DCM/acetato de etilo gradiente 0-20%) para producir el compuesto del título (104mg, 21%)

MR 1.3 (3H, t); 3.3-3.5 (2H, m); 4.4 (2H, q); 5.5-5.6 (1H, m); 7.05 (1H, s); 7.15 (1H, s); 7.2-7.35 (5H, m); 8.95 (1H, d); 11.84 (1H, s)

m/z 444.9

Ejemplo #129

(*S*)-2-Cloro-5-{*N*-[α-(4-metoxicarboniloxazol-5-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol

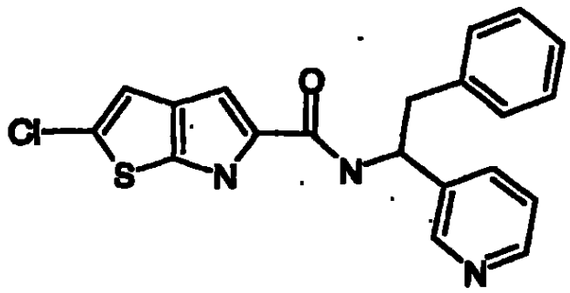


5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10, 100mg, 0.5mmol) se disolvió en DCM (10ml) que contenía HOBT (68mg, 0.5mmol), DIPEA

(193mg, 1.5mmol) y metil (*S*)-5-(α-aminofenetil)oxazole-4-carboxilato trifluoroacetato (Método #32, 230mg, 0.5mmol). Se agregó EDAC (143mg, 0.15mmol) y la mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo (75ml), se lavó con ácido cítrico diluido, agua y salmuera, se secó sobre sulfato de magnesio y se concentró. El material crudo se purificó mediante cromatografía de columna de sílice bond elute (eluyente - DCM/acetato de etilo gradiente 0-50%) para producir el compuesto del título (147mg, 34%). NMR 3.05-3.15 (1H, m); 3,2-3,25 (1H, m); 3.8 (3H, s); 5.85-5.95 (1H, m); 7.1 (1H, s); 7.15 (1H, s); 7.15-7.25 (5H, m); 7.75 (1H, d) 8.4 (1H, s); 11.74 (1H, s); m/z 429

Ejemplo #130

2-Cloro-5-{*N*-[α-(3-piridil)fenetil]carbamoil}-6*H*-tieno[2,3-*b*] pirrol

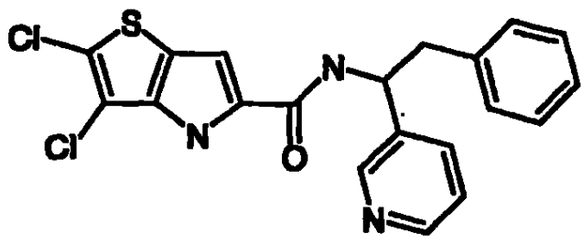


5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10, 100mg, 0.5mmol) se disolvió en DCM (10ml) que contenía HOBT (68mg, 0.5mmol), DIPEA (193mg, 1.5mmol) y diclorhidrato de α-(3-piridil)fenetilamina (J. Am. Chem. Soc., 1950, 72, 1988; 135mg, 0.5mmol). Se agregó EDAC (143mg, 0.75mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (50ml), se agregó agua (20ml) y el pH se ajustó a 7 con ácido clorhídrico diluido. La fracción orgánica se separó, se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se concentró. El material crudo se purificó mediante cromatografía de columna de sílice bond elute (eluyente – acetato de etilo) para producir el compuesto del título como un sólido (128mg, 67%).

NMR 3.0-3,2 (2H, m); 5.2-5.3 (1H, m); 7.05 (1H, s); 7.1-7.2 (2H, m); 7.2-7.4 (5H, m); 7.8 (1H, d); 8.4 (1H, d); 8.55-8.65 (2H, m); 11.71 (1H, s); m/z 381

Ejemplo #131

2,3-dicloro-5-{*N*-[α-(3-piridil)fenetil)]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



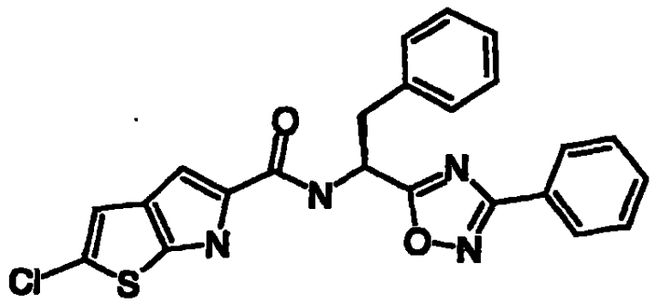
5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 118mg, 0.5mmol) se disolvió en DCM (10ml) que contenía HOBT (68mg, 0.5mmol), DIPEA (193mg,1.5mmol), diclorhidrato de α-(3-piridil)fenetil)amina (J. Am. Chem. Soc., 1950, 72, 1988; 135mg, 0.5mmol). Se agregó EDAC (143mg, 0.75mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (100ml), se agregó aguar (20ml) y se ajustó el pH a 7 con ácido clorhídrico diluido. La fracción orgánica se separó se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se concentró.

El material crudo se purificó mediante cromatografía de columna de sílice bond elute (eluyente – acetato de etilo) para producir el compuesto del título como un sólido (72mg, 34%)

NMR 3.0-3.3 (2H, m); 5.2-5.3 (1H, m); 7.1-7.2 (2H, m); 7.2-7.4 (5H, m); 7.85 (1H, dt); 8.4 (1H, dd); 8.6 (1H, s); 8.75 (1H, d); 12.28 (1H, s); m/z 417

Ejemplo #132

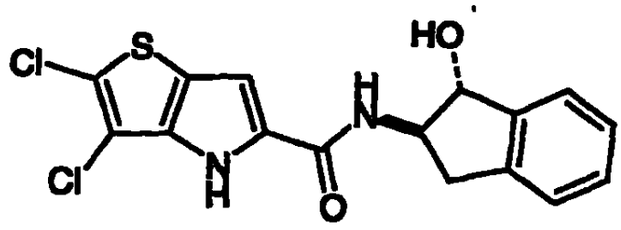
(*S*)-2-Cloro-5-{*N*-[α-(3-fenil-1,2,4-oxadiazol-5-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol



5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10, 201mg, 1mmol) se disolvió en DCM (15ml) que contenía HOBT (148mg, 1.1mmol), DIPEA (387mg, 3mmol) y (*S*)-5(α-aminofenetil)-3-fenil-1,2,4-oxadiazol trifluoroacetato (Método #18, 379mg, 1mmol). Se agregó EDAC (238mg, 1.25mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se filtró y el filtrado se diluyó con DCM (50ml), se lavó con ácido clorhídrico diluido y agua. Luego de secar sobre sulfato de magnesio y concentración, el material crudo se purificó mediante cromatografía de columna de sílice bond elute (eluyente - DCM/acetato de etilo gradiente 0-20%) para producir el compuesto del título (120mg, 26%); NMR 3.3-3.6 (2H, m); 5.5-5.7 (1H, m); 7.1 (1H, s); 7.15-7.4 (6H, m); 7.55-7.65 (3H, m); 8.05 (2H, d); 9.05 (1H, d); 11.9 (1H, s); m/z 449

Ejemplo #133

2,3-Dicloro-5-{*N*-(1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

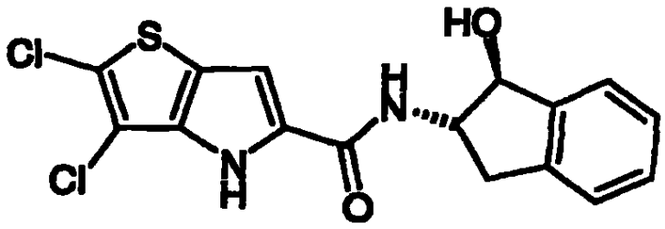


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 329 mg, 1.4 mmol) se disolvió en DCM (20 ml) que contenía HOBT (189 mg, 1.4 mmol), DIPEA (0.5 ml, 2.8 mmol) y 2-aminoindan-1-ol (Método #36, 250 mg, 1.4 mmol). La mezcla de reacción se agitó durante un minuto y se agregó EDAC (306 mg, 1.6 mmol). La mezcla de reacción se agitó a temperatura del recinto durante aproximadamente 18 horas. La solución

resultante se lavó con agua (20 ml) y la capa acuosa se extrajo con DCM (2 x 20 ml). Se combinaron los extractos orgánicos, se secaron sobre sulfato de magnesio y se concentraron bajo presión reducida para producir el compuesto del título como un sólido blanco (70 mg, 14%).
NMR: 2.8 (1H, dd), 3,2 (1H, dd), 4.4 (1H, quin), 5.1 (1H, d), 7.1 (1H, s), 7.2-7.4 (4H, m), 8.7 (1H, d), 12.4 (1H, s); m/z 366 (M-H)

Ejemplo #134

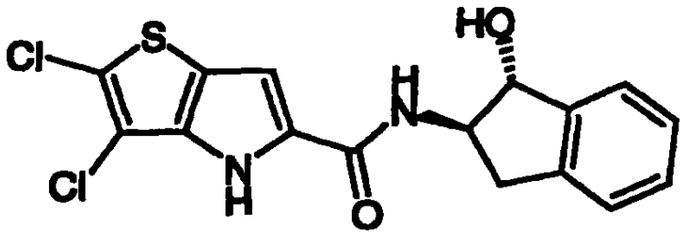
2,3-Dicloro-5-[*N*-((*1S,2S*)-1-hidroxiindan-2-il)carbamoil-4*H*-tieno[3,2-*b*]pirrol



y

Ejemplo #135

2,3-Dicloro-5-[*N*-((*1R,2R*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol

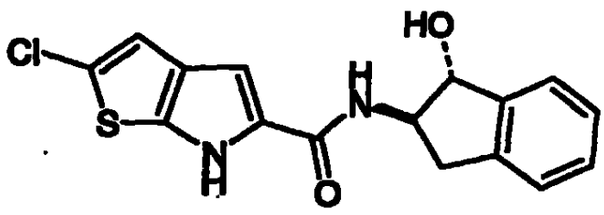


2,3-Dicloro-5-[*N*-(1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol (Ejemplo #133) se sometió a HPLC preparativa bajo las siguientes condiciones para producir 2,3-dicloro-5-[*N*-((*1S,2S*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol como un sólido blanco (9 mg) y 2,3-dicloro-5-[*N*-((*1R,2R*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol como un sólido blanco (12 mg).

Instrumento	Sistema 1 P.E Series 200
Columna	Chiralpak AD (250mm x 4.6 mm) No. ADOOCE-AJ052
Eluyente	MeOH
Temperatura del Horno	Ambiente
Flujo	1ml/min
Longitud de Onda	254 nm
Concentración de la muestra	1 mg/ml en EtOH + sonicación

Ejemplo #136

2-Cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol

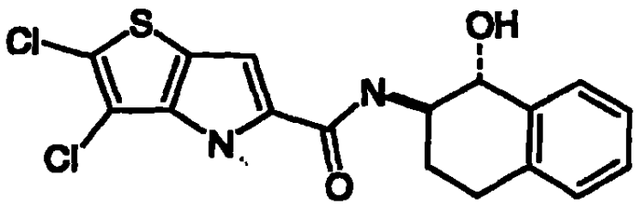


5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 280 mg, 1.4 mmol) se disolvió en DCM (20 ml) que contenía HOBT (189 mg, 1.4 mmol), DIPEA (0.5 ml, 2.8 mmol) y 2-aminoindan-1-ol (Método #36, 250 mg, 1.4 mmol). La mezcla de reacción se agitó durante un minuto y se agregó EDAC (306 mg, 1.6 mmol). La mezcla de reacción se agitó a temperatura del recinto durante aproximadamente 18 horas. La solución resultante se lavó con agua (20 ml) y se extrajo la capa acuosa con DCM (2 x 20 ml). Se combinaron los extractos orgánicos, se secaron sobre sulfato de magnesio y se concentraron bajo presión reducida para producir el compuesto del título como un sólido blanco (78 mg, 17%).

NMR: 2.8 (1H, dd), 3,2 (1H, dd), 4.4 (1H, quin), 5.1 (1H, t), 5.6 (1H, d), 7.1 (1H, s), 7.2-7.4 (5H, m), 8.4 (1H, d), 11.8 (1H, s); m/z 331 (M-H)

Ejemplo #137

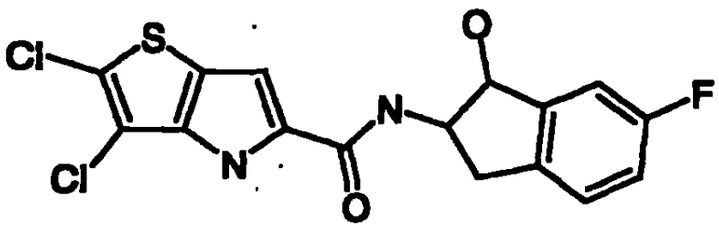
2,3-Dicloro-5-{*N*-(1-hidroxi-1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 216 mg, 0.9 mmol) se disolvió en DCM (15 ml) que contenía HOBT (122 mg, 0.9 momol), DIPEA (0.3 ml, 1.8 mmol) y 2-amino-1,2,3,4-tetrahidronaft-1-ol (Método #39, 150 mg, 0.9 mmol). La mezcla de reacción se agitó durante un minuto y se agregó EDAC (206 mg, 1.1 mmol). La mezcla de reacción se agitó a temperatura del recinto durante aproximadamente 18 horas. La solución resultante se lavó con agua (20 ml) y la capa acuosa se extrajo con DCM (2x20 ml). Las fracciones orgánicas se combinaron y se concentraron bajo presión reducida para producir el compuesto del título como un sólido blanco (70 mg, 14%). NMR 1.8 (1H, m), 2.0 (1H, qd), 2.9 (1H, m), 3.3 (1H, qd), 4.4 (1H, quin), 4.9 (1H, m), 5.2 (1H, s), 5.8 (1H, brs), 6.8 (1H, s), 7.0 (1H, dd), 7.1 (1H, d), 7.2 (1H, s), 7.5 (1H, d) 10.1 (1H, brs). m/Z 380 (M-H).

Ejemplo #138

2,3-Dicloro-5-[*N*-(6-fluoro-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

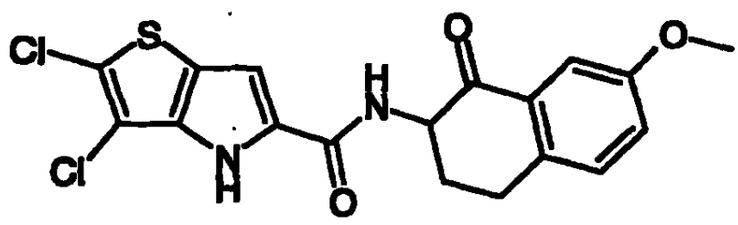


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 141 mg, 0.6 mmol) se disolvió en DCM (10 ml) que contenía HOBT (81 mg, 0.6 mmol), DIPEA (0.2 ml, 1.2 mmol) y 2-amino-6-fluoro-1-indanol (Método #38, 100 mg, 0.6 mmol). La mezcla de reacción se agitó durante un minuto y se agregó EDAC (138 mg, 0.7 mmol). La mezcla de reacción se agitó a

temperatura del recinto durante aproximadamente 18 horas. La solución resultante se lavó con agua (20 ml) y la capa acuosa se extrajo con DCM (2x20 ml). Las fracciones orgánicas se combinaron y se concentraron bajo presión reducida para producir un sólido blanco. La purificación mediante cromatografía de columna de destello (isohexano:acetato de etilo 1: 1) produjo el compuesto del título como un sólido blanco (70 mg, 14%). NMR 3.0 (1H, dd), 3.3 (1H, m),4.6 (1H, q), 4.9 (1H, t), 5.5 (1H, d), 4.9 (1H, m), 6.9-7.2 (4H, m), 8.1 (1H, d), 12.4 (1H, brs); m/Z 383 (M-H)

Ejemplo #139

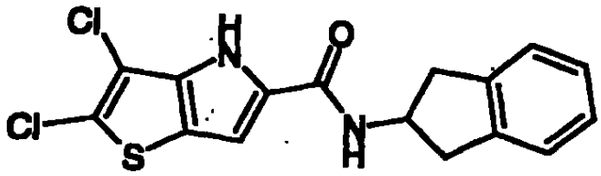
2,3-Dicloro-5-[*N*-(7-metoxi-1-oxo-1,2,3,4-tetrahidronaft-2-il) carbamoil]-4*H*-tieno[3,2-*b*]pirrol



5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 216 mg, 0.9 mmol) se disolvió en DCM (20 ml) que contenía HOBT (122 mg, 0.9 mmol), DIPEA (0.3 ml, 1.8 mmol) y 2-amino-7-metoxi-1-oxo-1,2,3,4-tetrahidronaftaleno (Farmaco, Ed. Sci. (1985), 40(6) , 422-428), 204 mg, 0.9 mmol). La mezcla de reacción se agitó durante un minuto y se agregó EDAC (206 mg, 1.0 mmol). La mezcla de reacción se agitó a temperatura del recinto durante aproximadamente 18 horas. La solución resultante se lavó con agua (20 ml) y la capa acuosa se extrajo con DCM (2x20 ml). Las fracciones orgánicas se combinaron y se concentraron bajo presión reducida para producir el compuesto del título como un sólido de color café (100 mg, 27%). NMR 3.0 (1H, dd), 3.1 (1H, dd), 3.3 (2H, m), 4.8 (1H, q), 5.8 (1H, s), 6.9-7.2 (4H, m), 8.6 (1H, d), 12.2 (1H, brs); m/z 408 (M-H).

Ejemplo #140

2,3-Dicloro-5-[*N*-(2-indanil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol



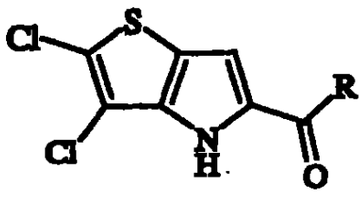
5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 45 mg, 0.19 mmol) se disolvió en DMF (10 ml) con 2-aminoindano (28 mg, 0.21 mmol), di-isopropiletilamina (0.1 ml, 0.57 mmol) y HATU (80 mg, 0.21 mmol). Las mezclas se agitaron a temperatura ambiente durante aproximadamente 16 horas. La mezcla se porcionó entre agua y acetato de etilo y se lavó con agua (x 5). La fase acuosa se secó, se filtró y se concentró, y el residuo se purificó mediante cromatografía bond-elut de sílice usando una gradiente de acetato de etilo en isohexano (0-50%) como eluyente para producir el compuesto del título, m/z 351.

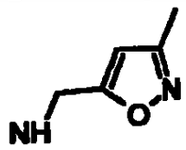
Siguiendo un procedimiento similar al proceso de Ejemplo #140 se prepararon los siguientes Ejemplos:

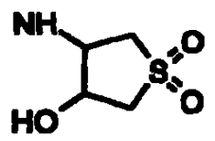
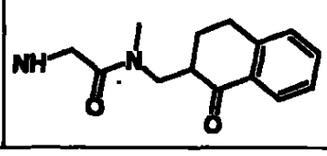
Ejemplo #141: 2,3-Dicloro-5-[*N*-(3-metilisoxazol-5-il)metil] carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #142: 2,3-Dicloro-5-[*N*-(4-hidroxi-1,1-dioxotetrahidrotiofen-3-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

Ejemplo #143: 2,3-Dicloro-5-(*N*-{*N*-metil-*N*-[(1-oxo-1,2,3,4-tetrahidronaft-2-il)metil]carbamoilmetil}carbamoil-4*H*-tieno[3,2-*b*]pirrol



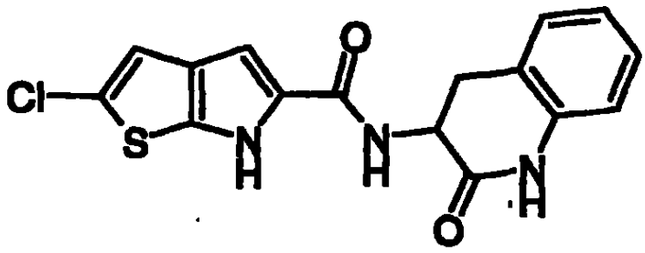
Ejemplo	R	M/z
#141		329

#142		365
#143[1]		491

[1] Amina: Método #37

Ejemplo #144

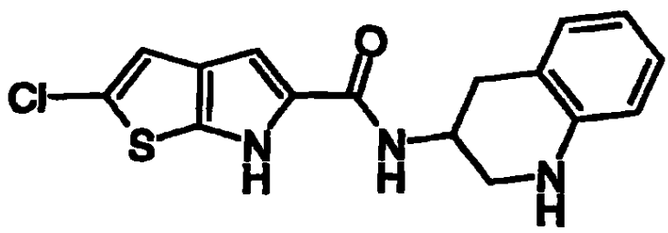
2-Cloro-5-[*N*-(2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol



5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 101 mg, 0.5 mmol) se disolvió en DMF (2.5 ml) que contenía 3-amino-3,4-dihidro-2(1*H*)-quinolinona [J Med Chem (1986) 29 (12) 2427-32] (99 mg, 0.5 mmol), HOBT (68 mg. 0.5 mmol) y Et_3N (55 mg, 0.5 mmol). La mezcla se agitó durante 1 minuto antes de la adición de EDAC (96 mg, 0.5 mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 18 horas antes de verterse en agua (50 ml), se agitó vigorosamente y se filtró. El sólido recuperado se lavó con agua, éter y se secó para producir el compuesto del título como un sólido amorfo (161 mg). NMR ($DMSOd_6$): 11.96 (1H, s), 10.36 (1H, s), 8.50 (1H, d), 7.20 (2H, m), 7.19 (1H, s), 7.09 (1H, s), 6.96 (1H, m), 6.91 (1H,m), 4.72 (1H, m), 3.08 (2H, m); MH^+ 346.14.

Ejemplo #145

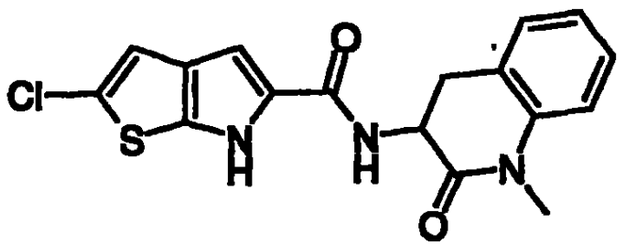
2-Cloro-5-[*N*-(1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol



5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 157 mg, 0.78 mmol) se disolvió en DMF (4 ml) que contenía 3-amino-1,2,3,4-tetrahidroquinolina [J Med Chem (1982) 25 (1) 68-70] (115 mg, 0.78 mmol) y HOBT (105 mg, 0.78 mmol). La mezcla se agitó durante 1 minuto antes de la adición de EDAC (149 mg, 0.78 mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 64 horas antes de porcionarse entre agua y EtOAc. Los orgánicos se lavaron con agua, $NaHCO_3$ acuoso saturado, agua, salmuera saturada t se secaron. Los orgánicos se filtraron, se concentraron y se cromatografiaron en sílice Fluorochem 40-63µl 60A (eluyente 40:60 EtOAc/isohexano) para proporcionar el compuesto del título como un sólido amorfo (44 mg). NMR ($DMSOd_6$): 11.94 (1H, s), 8.04 (1H, d), 7.16 (1H, s), 7.06 (1H, s), 6.90 (2H, m), 6.48 (2H, m), 5.8 (1H, br), 4.18 (1H, m), 3.05 (1H, t), 2.85 (2H, m); MH^+ 332.17.

Ejemplo #146

2-Cloro-5-[*N*-(1-metil-2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol

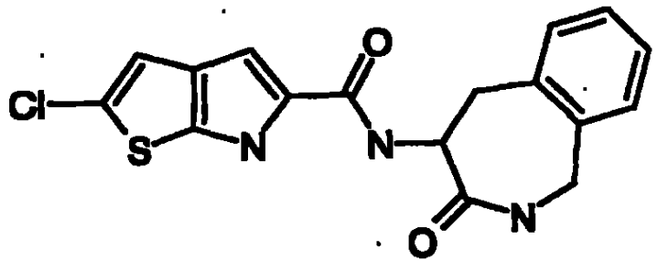


5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 80 mg, 0.4 mmol) se disolvió en DMF (2 ml) que contenía 3-amino-3,4-dihidro-1-carbostirilo [JCS 1965 1080-1087] (71 mg, 0.4 mmol) y HOBT (54 mg, 0.4 mmol). La mezcla se agitó durante 1 minuto antes de la adición de EDAC

(77 mg, 0.4 mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 18 horas antes de porcionarse entre agua y EtOAc. Los orgánicos se lavaron con agua, $NaHCO_3$ acuoso saturado, agua, salmuera saturada y se secaron. Los orgánicos se filtraron, se concentraron y se re-cristalizaron de EtOAc para proporcionar el compuesto del título como un sólido amorfo (66 mg). NMR 11.96 (1H, s), 8.54 (1H, d), 7.30 (2H, m), 7.17 (2H, m), 7.08 (2H, m), 4.68 (1H, m), 3.32 (3H, s), 3.14 (1H, m), 3.04 (1H, m); m/z (MH^+) 360.14

Ejemplo #147

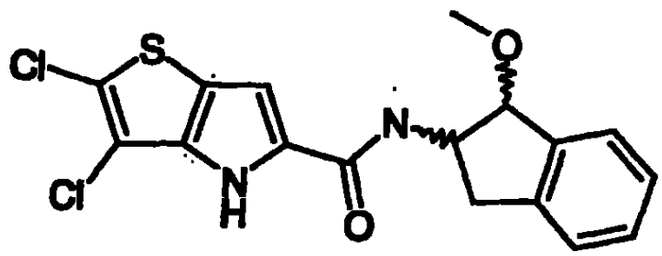
2-Cloro-5-[*N*-(3-oxo-2,3,4,5-tetrahidro-1*H*-benz[2]azepin-4-il) carbamoil]-6*H*-tieno[2,3-*b*]pirrol



5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol (Método #10; 101 mg, 0.5 mmol) se disolvió en DMF (2.5 ml) que contenía clorhidrato 4-amino-1,2,4,5-tetrahidro-3*H*-2-benzazepin-3-ona [CAS Reg No. 148842-85-7] (107 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol) y Et_3N (101 mg, 1.0 mmol). La mezcla se agitó durante 1 minuto antes de la adición de EDAC (96 mg, 0.5 mmol), luego a temperatura ambiente durante aproximadamente 18 horas antes de porcionarla entre agua y EtOAc. Los orgánicos se lavaron con agua, $NaHCO_3$ acuoso saturado, agua, salmuera saturada y se secaron; se filtraron y se evaporaron para proporcionar el compuesto del título como un sólido amorfo (26 mg). NMR: 11.92 (1H, s), 8.33 (1H, t), 8.29 (1H, d), 7.2 (6H, m), 5.30 (1H, m), 4.83 (1H, dd), 3.98 (1H, dd), 3,20 (2H, m); m/z (MH^+) 360.19.

Ejemplo #148

2,3-Dicloro-5-[*N*-(1-metoxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

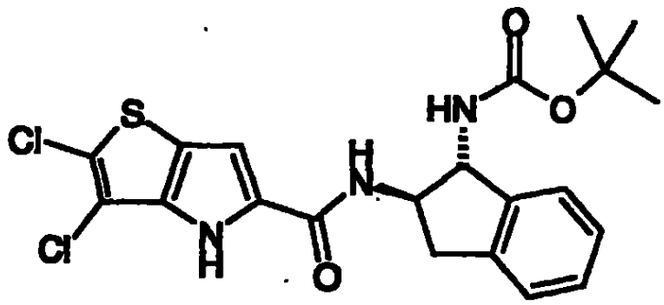


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 145mg, 0.613mmol), trans-2-amino-1-metoxiindano (Método #40, 100mg, 0.163mmol), DIPEA (0.105ml, 0.613mmol), y HOBT (83mg, 0.613mmol) se agitaron en diclorometano (5ml) durante un minuto. Se agregó EDAC (147mg, 0.766mmol) y la mezcla se agitó a la temperatura del recinto durante 20 horas. La mezcla de reacción se evaporó, se agregó acetato de etilo (25ml) y, a continuación, se lavó con agua. La solución orgánica se secó sobre sulfato de magnesio y se evaporó para producir el compuesto del título como un polvo blanco (180mg, 77%).

NMR 2.8 (1H, dd), 3.3 (1H, dd), 3.35 (3H, s), 4.1-4.2 (1H, m), 5.35-5.45 (1H, m), 7.1-7.3 (4H, m), 7.15 (1H, s), 8.7 (1H, d); m/z 380.9/382.9 (M+H).

Ejemplo #149

2,3-Dicloro-5-(*N*-{1-[N-(1,1-dimetiletoxi)carbonilamino]indan-2-il}carbamoil]-4*H*-tieno[3,2-*b*]pirrol

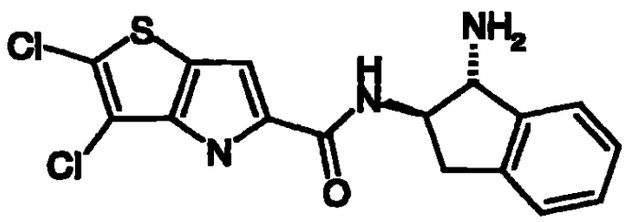


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 1.18g, 5.0mmol), (1*R*, 2*R*)-2-amino-l-[(1,1-dimetiletoxi)carbonilamino]indano (Método #43, 1.25g, 5.0mol), DIPEA (0.855ml, 5.0mmol), y HOBT (675mg, 5.0mmol) se agitaron en diclorometano (50ml) durante un minuto. Se agregó EDAC (1.2g, 6.25mmol) y la mezcla se agitó a la temperatura del

recinto durante 20 horas. La mezcla de reacción se diluyó con diclorometano (50ml), se filtró y se secó para producir el compuesto del título como un polvo de color verde pálido (1.95g, 85%). NMR 1.4 (9H, s), 2.8 (1H, dd), 3,2 (1H, dd), 4.5-4.7 (1H, m), 5.1-5.2 (1H, m), 7.05-7.3 (5H, m), 7.4 (1H, d), 8.6 (1H, d), 12.4 (1H, s).

Ejemplo #150

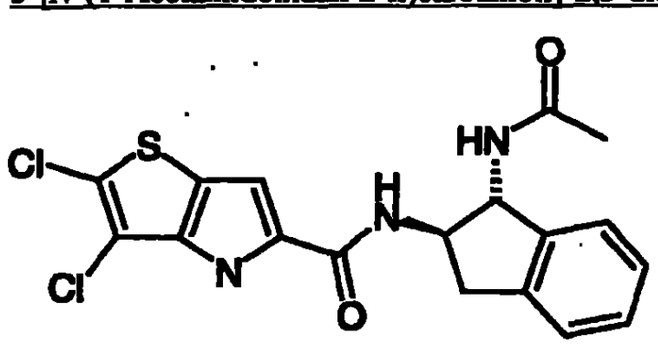
5-[*N*-(1-Aminoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol



2,3-Dicloro-5-(*N*-{1-[(1,1-dimetiletoxi)carbonilamino]indan-2-il}carbamoil)-4*H*-tieno[3,2-*b*]pirrol (Ejemplo #149, 1.0g, 2.15mmol) se disolvió en diclorometano (20ml). Se agregó ácido trifluoroacético (2ml) y la mezcla se agitó a la temperatura del recinto durante 24 horas. La reacción se filtró y el sólido aislado se lavó con diclorometano para producir la sal de ácido trifluoroacético del compuesto del título como un polvo de color verde pálido (800mg, 78%). NMR 3.05 (1H, dd), 3.4 (1H, dd), 4.6-4.85 (2H, m), 7.2 (1H, d), 7.3-7.45 (3H, m), 7.55 (1H, d), 8.6 (3H, s amplia), 8.8 (1H, d), 12.5 (1H, s)

Ejemplo #151

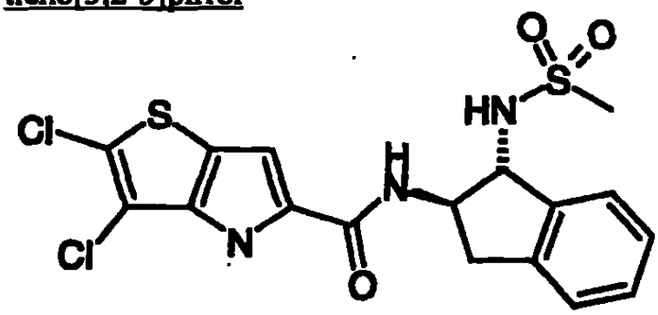
5-[*N*-(1-Acetamidoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



Se agregó trietilamina (101mg, 1.0mmol) a una suspensión de sal de ácido 5-[*N*-(1-aminoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-b]pirrol trifluoroacético (Ejemplo #150, 240mg, 0.5mmol) en diclorometano (4ml), seguida por cloruro de acetilo (47mg, 0.6mmol) disuelto en diclorometano (1ml) y la reacción se agitó a la temperatura del recinto durante 6 horas durante las cuales se precipitó un sólido blanco. La reacción se filtró y el material crudo se purificó mediante cromatografía de sílice con hexano: acetato de etilo para producir el compuesto del título como un sólido blanco (50mg, 25%). NMR 1.87 (3H, s), 2.82 (1H, dd), 3,22 (1H, dd), 4.45-4.62 (1H, m), 5.38-5.5 (1H, m), 7.02-7.27 (4H, m), 7.1 (1H, s), 8.35 (1H, d), 8.59 (1H, d), 12,36 (1H, s amplia); m/z 406.13/408.8 (M-H).

Ejemplo #152

2,3-Dicloro-5-{*N*-[1-(metanosulfonamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol

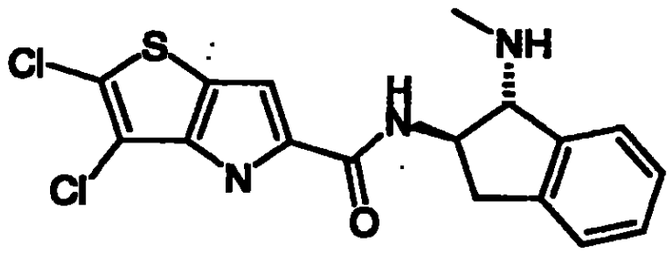


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 236mg, 1.0mmol), (1*R*,2*R*)-2-amino-1-metanosulfonamidoindano (Método #42, 226mg, 1.0mol), DWEA (0.174ml, 1.0mmol), y HOBT (135mg, 1.0mmol) se agitaron en diclorometano (10ml) durante un minuto. Se agregó EDAC (240mg, 1.25mmol) y la mezcla se agitó a la temperatura del recinto durante 20 horas. La mezcla se diluyó con acetato de etilo, se lavó con agua (2 x 25ml), se secó sobre sulfato de magnesio y se evaporó para producir el compuesto del título como una espuma (400mg, 90%). NMR 2.84 (1H, dd), 2.99 (3H, s), 3.22 (1H, dd), 4.44-4.64 (1H, m), 4.89-5.0 (1H, m), 7.14 (1H, s), 7.16-7.36 (4H, m), 7.84 (1H, d), 8.64 (1H, d), 12.43 (1H, s amplia); m/z 442.2/444.0 (M-H).

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Ejemplo #153

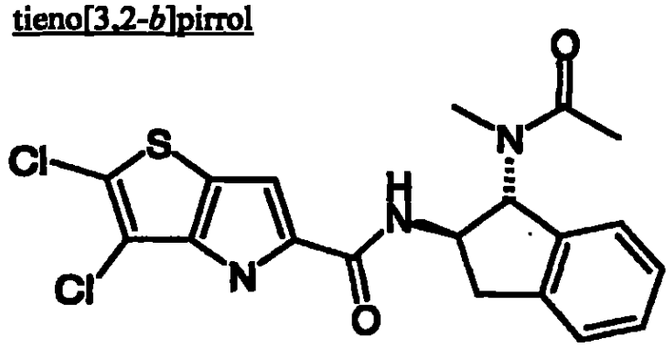
2,3-Dicloro-5-{*N*-[1-(metilamino)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



2,3-Dicloro-5-[*N*-(1-{*N*-[(1,1-dimetiletoxi)carbonil]-*N*-metilamino}indan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol (Método #44, 900mg, 1.87mmol) en diclorometano (20ml) se trató con ácido trifluoroacético (2ml) a temperatura del recinto durante 1 hora. Evaporación seguida por co-evaporación con cloroformo y secamiento produjo la sal de ácido trifluoroacético del compuesto del título como una espuma de color café claro (850mg, 92%). NMR 2.75 (3H, s), 3.02 (1H, dd), 3.5 (1H, dd), 4.7-4.95 (2H, m), 7.15 (1H, s), 7.28-7.48 (3H, m), 7.6 (1H, d), 8.68 (1H, d), 9.1 (2H, s amplia); m/z 380.4/382.4 (M+H).

Ejemplo #154

2,3-Dicloro-5-{*N*-[1-(N-metilacetamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



Sal de ácido 2,3-dicloro-5-{*N*-[1-(metilamino)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol trifluoroacético (Ejemplo #153, 390mg, 0.79mmol) en diclorometano (5ml) a 5°C se trató con trietilamina (0.33ml, 2,37mmol) y

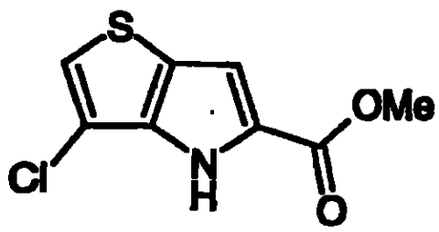
cloruro de acetilo (68mg, 0.86mmol). Luego de agitar a 5°C durante 15 minutos, la reacción se dejó calentar a la temperatura del recinto y se agitó durante 2 horas más. La mezcla se diluyó con acetato de etilo (25ml) y se lavó con bicarbonato de sodio saturado y agua. El secamiento sobre sulfato de magnesio seguido por evaporación produjo el compuesto del título como una espuma de color café claro (270mg, 80%). NMR: indica una proporción aproximada 1:1 de rotámeros del compuesto del título; 2.05 (1.5H, s), 2.1 (1.5H, s), 2.6 (1.5H, s), 2.8 (1.5H, s), 2.9-3.08 (1H, m), 3.12-3.3 (1H, m), 4.7-4.9 (1H, m), 5.24 (0.5H, d), 6.14 (0.5H, d), 6.94-7.35 (5H, m), 8.6 (0.5H, d), 8.68 (0.5H, d), 12,38 (0.5H, s amplia), 12.46 (0.5H, s amplia); m/z 421.9/423.9 (M+H)

Preparación de Materiales Iniciales

Los materiales iniciales para los Ejemplos ya indicados se obtienen en el comercio o se preparan fácilmente por métodos estándar a partir de materiales conocidos. Por ejemplo, las siguientes reacciones son ilustraciones pero no limitaciones de la preparación de algunos de los materiales iniciales utilizados en las reacciones anteriores.

Método #1

3-Cloro-5-metoxicarbonil-4*H*-tieno[3,2-*b*]pirrol

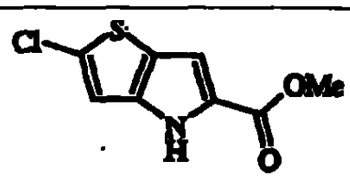
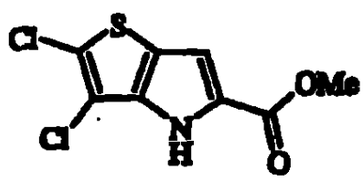
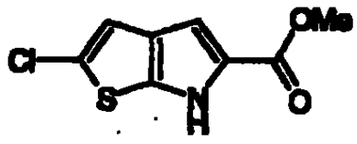


Solución de metóxido de sodio metanólico (28%) (5 ml, 25.9 mmol) se diluyó con MeOH (5 ml) y se enfrió a -25°C bajo nitrógeno. Una solución de 4-cloro-2-tiofenecarboxaldehído (J Heterocyclic Chem, 1976, 13, 393; 1.1 g, 7.5 mmol) y azidoacetato de metilo (3.0 g, 26.1 mmol) en MeOH (20 ml) se agregó gota a gota, manteniendo la temperatura a -25°C. Una vez concluida la adición, la solución se dejó calentar a 5°C durante un

período de aproximadamente 16 horas. La solución se agregó a cloruro de amonio acuoso saturado (250 ml) y la mezcla se extrajo usando DCM. Las capas orgánicas combinadas se concentraron a 0°C. El residuo se tomó en xileno (30 ml) y esta solución se agregó gota a gota a xileno (120 ml) bajo reflujo. La solución se calentó bajo reflujo durante 30 minutos antes de enfriarse y concentrarse. El compuesto del título se purificó mediante una mezcla de cristalización (EtOAc/isohexano) y cromatografía en una columna Bond Elut eluyendo con un solvente graduado de 5-50% EtOAc en isohexano (640 mg, 40%). NMR ($CDCl_3$) 9.1 (1H, br), 7.1 (2H, s), 3.9 (3H, s); m/z 214.3.

Métodos #2 - #4

Los siguientes compuestos se elaboraron mediante el proceso de Método #1 usando los materiales iniciales apropiados.

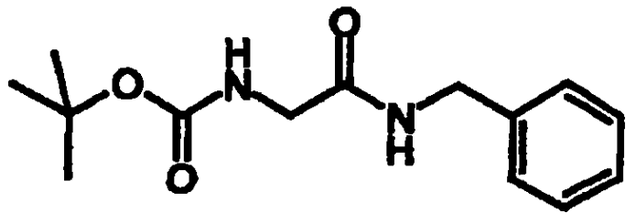
Mét.	Compuesto	NMR ($CDCl_3$)	M/z
#2		9.1 (1H, br), 7.0 (1H, s), 6.9 (1H, s), 3.9 (3H, s)	214.2
#3[1]		9.2 (1H, br), 7.0 (1H, s), 3.9 (3H, s)	248.2
#4[2]		9.4-9.2 (1H, br), 7.0 (1H, s), 6.9(1H, s), 3.9 (3H, s)	214

[1] Aldehído: DE 2814798

[2] Aldehído: Aldehído ref. Gronowitz *y colaboradores*. Tetrahedron Vol. 32 1976 página 1403

Método #5

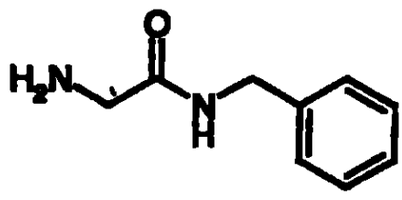
N- Bencil-2-(*tert*-butoxicarbonilamino)acetamida



N-(*tert*-Butoxicarbonil)glicina (875mg, 5mmol) se disolvió en DMF (7ml) que contenía DIPEA (3.5ml, 20mmol) y bencilamina (536mg, 5mmol). La mezcla de dejó reposar durante un minuto antes de la adición de hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (HATU) (2.09g, 5.5mmol). La solución se dejó reposar durante aproximadamente 18 horas antes de porcionarse entre acetato de etilo (50ml) y agua (50ml). Las capas se separaron y se secó la fase orgánica usando sulfato de magnesio, se filtró, se concentró y se purificó usando cromatografía de columna de sílice bond-elute (eluyente: diclorometano-diclorometano/metanol 5% gradiente) para proporcionar el compuesto del título como un aceite (1.32g, quantitativos).
NMR: ($CDCl_3$): 7.2 (5H, m), 6.3 (1H, br), 5.0 (1H, br), 4.4 (2H, d), 3.8 (2H, d), 1.4 (9H, s); m/z 265.4

Método #6

2-Amino-*N*-bencilacetamida

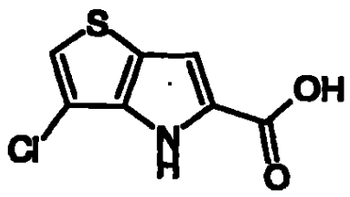


A una solución de *N*-bencil-2-(*tert*-butoxicarbonilamino)acetamida (Método #5, 1.18g, 4.47mmol) en diclorometano (6ml) a 0°C se agregó gota a gota ácido trifluoroacético (2.4ml) y la solución resultante se dejó agitar calentando a temperatura ambiente durante la noche. La mezcla de reacción se neutralizó mediante adición de una solución saturado de bicarbonato de sodio y se extrajo con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, se

concentraron y se purificaron mediante cromatografía de columna SCX bond-elute (eluyente: metanol/diclorometano (1:1), luego metanol/diclorometano (1:1)/amoníaco 5%) para proporcionar el *compuesto del título* como un aceite (215mg, 29%).
NMR: ($CDCl_3$): 7.2 (6H, m), 4.4 (1.4H, d), 4.3 (0.6H, d), 3.4 (2H, br); m/z 165.17

Método #7

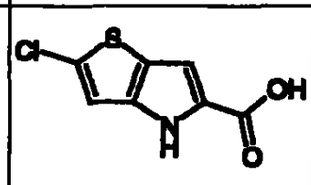
5-Carboxi-3-cloro-4*H*-tieno[3,2-*b*]pirrol

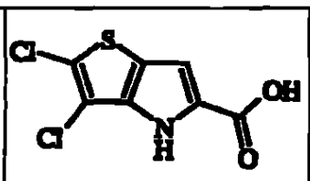
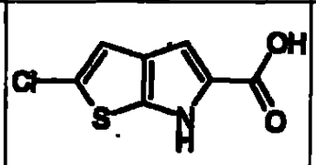


3-Cloro-5-metoxicarbonil-4*H*-tieno[3,2-*b*]pirrol (Método #1; 0.61 g, 2.83 mmol) se tomó en MeOH (10 ml) y se calentó bajo reflujo. Se agregó hidróxido de litio acuoso (2.0 M, 3.0 ml, 6.0 mmol) en porciones durante 45 minutos. La mezcla se calentó bajo reflujo durante 30 minutos antes de enfriarse y concentrarse. Se agregó agua (20 ml) y la solución se neutralizó usando ácido clorhídrico acuoso (2.0 M, 3.0 ml). La solución se extrajo usando EtOAc, y las capas orgánicas combinadas se concentraron para proporcionar el compuesto del título como un sólido amarillo (0.57 g, 100%). NMR: 12.4 (1H, br), 7.4 (1H, s), 7.0 (1H, s); m/z 200.3.

Métodos #8 - #10

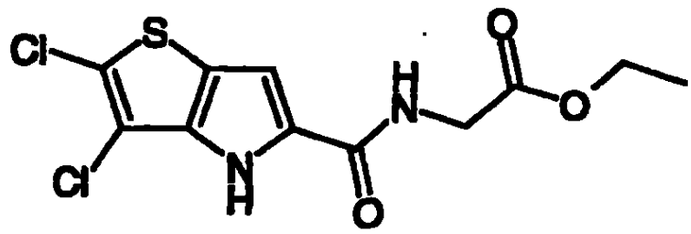
Los siguientes compuestos se elaboraron mediante el proceso de Método #7 usando los materiales iniciales apropiados.

Mét.	Compuesto	NMR	M/z	SM
#8		11.9 (1H, br), 7.0 (1H, s), 6.9 (1H, s)	200.1	Método #2

#9		7.0 (1H, s)	234.2	Método #3
#10		NMR 12.6-12.7 (1H, b), 12.0-12.1 (1H, b), 7.15(1H, s), 6.9(1H, s)	183	Método #4

Método #11

2,3-Dicloro-5-[*N*-(etoxicarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol

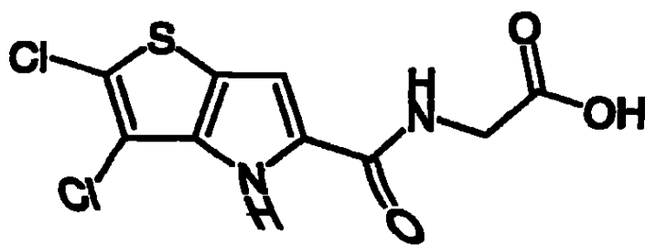


5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9, 4.0g 16.95mmol) se agregó a una solución de clorhidrato de éster etílico de glicina (2.60g, 18.64mmol) y DIPEA en diclorometano (200ml) seguido por HOBT (2.29g, 16.95mmol). La solución se agitó bajo nitrógeno durante 15 minutos antes de la adición de EDAC (3.89g, 22.03mmol). La mezcla se agitó a temperatura ambiente durante aproximadamente 16 horas. El precipitado blanco resultante se aisló mediante filtración, se lavó con agua y éter y se secó. (4.79g, 88%).

NMR: 12.45 (1H, br), 8.75 (1H, t), 7.1 (1H, s), 4.1 (2H, q), 4.0 (2H, d), 1.2 (3H, t); m/z 321.2

Método #12

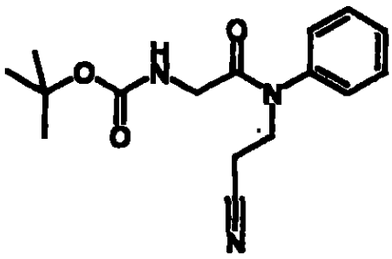
5-(*N*-Carboximetilcarbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol



Solución 2N de hidróxido de sodio (14.3ml, 28.7mmol) se agregó a una suspensión de 2,3-dicloro-5-[*N*-(etoxicarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol (Método #11, 4.60g, 14.33mmol) en tetrahidrofurano (THF) (100ml). La solución resultante se agitó a temperatura del recinto durante una hora. La mezcla de reacción se concentró *'in vacuo'*, el residuo se diluyó con agua (250ml), la solución se ajustó a pH 2 mediante adición de 2N ácido clorhídrico y, a continuación, se extrajo con acetato de etilo (3x150ml). Se combinaron los extractos orgánicos, se secaron sobre sulfato de sodio luego se filtraron y se concentraron para producir un polvo blanco (3.34g, 80%); NMR: 12.6 (1H,br), 12.4 (1H, br), 8.6 (1H, t), 7.1 (1H, s), 3.9 (2H, d); m/z 291.17

Método #13

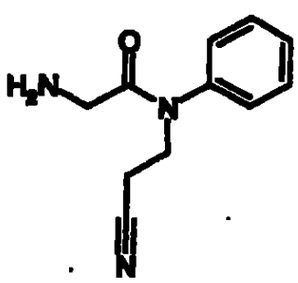
N-(2-Cianoetil)-*N*-fenil- 2-(*tert*-butoxicarbonilamino)acetamida



Por un procedimiento similar a Método #5 se preparó el *compuesto del título* usando anilinopropionitrilo para producir un aceite claro (598mg, 39%); NMR: ($CDCl_3$): 7.4 (3H, m), 7.2 (2H, m), 5.2 (1H, br), 3.9 (2H, t), 3.6 (2H, d), 2.6 (2H, t), 1.3 (9H, s); m/z 304.51

Método #14

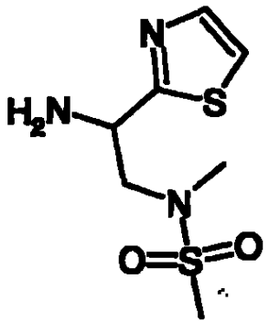
2- Amino-*N*-(2-cianoetil)-*N*-fenilacetamida



Por un procedimiento similar al Método #6 el *compuesto del título* se preparó usando *N*-(2-cianoetil)-*N*-fenil-2-(*tert*-butoxicarbonilamino)acetamida (Método #13) para producir un aceite claro (222mg, 60%); NMR: ($CDCl_3$): 7.4 (3H, m), 7.2 (1H, d), 7.1 (1H, d), 3.9 (2H, t), 3.1 (1.33H, s), 3.0 (0.67H, s), 2.65 (1.33H, t), (0.67H, t); m/z 204.31

Método #15

N-[(2-Amino-2-(2-tiazolil)etil-*N*-metilmetanosulfonamida

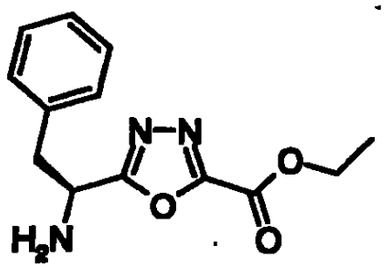


2-Bromotiazol (6.9 g, 42.0 mmol) se disolvió en éter dietílico seco (15 ml) y se agregó gota a gota a butil litio (1.6 M, 29.7 ml, 47.5 mmol) en éter dietílico (40 ml) a -70°C. La mezcla se agitó a -70°C durante 30 minutos antes de la adición de una solución fría de 2-(*N*-metilmetanosulfonamido)acetato de etiloe (Ger Offen, 1976, 27pp; 7.6 g, 39.0 mmol) en THF seco (70 ml). La solución se agitó durante 30 minutos más a -70°C antes de dejarse calentar a temperatura ambiente. Se agregó cloruro de amonio acuoso (10%, 200 ml) y la solución se extrajo usando éter dietílico. La capa acuosa se acidificó y se re-extrajo usando éter dietílico. Las capas orgánicas de combinaron, se secaron, se filtraron y se concentraron bajo presión reducida. El residuo (5.30 g, 22.6 mmol) se disolvió en etanol (100 ml) que contenía piridina (18 ml) y clorhidrato de hidroxilamina (1.88 g, 27.1 mmol). La mezcla se calentó bajo reflujo en una atmósfera inerte durante 2.5 horas antes de enfriarse y concentrarse bajo presión reducida. El residuo se suspendió en agua y se enfrió a 0°C. La mezcla se acidificó a pH 4 usando ácido clorhídrico acuoso (2.0 M). Se precipitó un sólido de una solución y se filtró y se lavó con agua. El

producto se secó bajo presión reducida en presencia de pentóxido de fósforo. El sólido seco (4.34 g, 17.4 mmol) se disolvió en ácido acético y se agregó 5% rodio en carbono (40% *p/p*, 1.7 g). La solución se agitó bajo una atmósfera de hidrógeno a 5 bar durante 48 horas. El recipiente de reacción se enjuagó libre de hidrógeno usando gas inerte y la solución se filtró a través de celita. El filtrado se concentró bajo presión reducida. El residuo se suspendió en etanol y se enfrió a 0 °C. Se agregó ácido clorhídrico acuoso (5.0 M) y etanol (50 ml, 1: 1) y la mezcla se agitó durante 30 minutos. Se filtró un precipitado blanco para proporcionar el compuesto del título (3.16 g) como una sal de clorhidrato.

Método #16

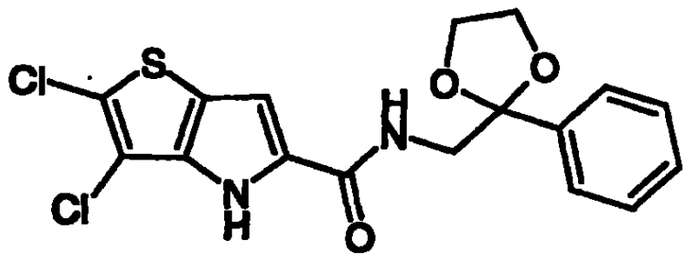
(*S*)-5-(□-aminofenetil)-1,3,4-oxadiazol-2-carboxilato trifluoroacetato de etilo



(*S*)-5-[□-[(*tert*-butoxicarbonilamino)fenetil]-1,3,4-oxadiazol-2-carboxilato de etilo (Borg y colaboradores. J. Org. Chem. 1995, 60, 3112; 350mg) se disolvió en ácido trifluoroacético (5ml) y se dejó reposar a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró y se secó bajo vacío para producir un sólido opaco (322mg). NMR 1.75 (3H, t); 3,2-3.4 (2H, m); 4.4 (2H, q); 5.2 (1H, t); 7.1-7.4 (5H, m); 8.8-9.2 (3H, bs)

Método #17

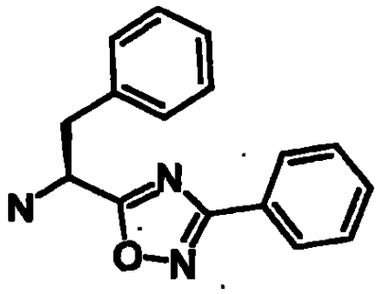
2,3-Dicloro-5-{*N*-[(2-fenil-1,3-dioxolan-2-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol



Clorhidrato de 2-fenil-1,3-dioxolan-2-ilmetilamina (65 mg, 0.3 mmol) y 5-carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (Método #9; 71 mg, 0.3 mmol) se disolvieron en DCM (10 ml) que contenía DIPEA (175 ml, 1.0 mmol) y HOBT (40 mg, 0.3 mmol). La mezcla se agitó durante un minuto antes de la adición de EDAC (75 mg, 0.39 mmol). La solución se agitó a temperatura del recinto durante aproximadamente 18 horas. La mezcla se concentró y cromatografó en una columna Bond Elut eluyendo con 20% - 40% EtOAc en isohexano. El compuesto del título se aisló como un sólido blanco (100 mg). NMR: 12.4 (1H, s), 8.2 (1H, s), 7.2 (1H, s), 4.0 (2H, m), 3.7 (2H, m), 3.6 (2H, d); m/z 395.2.

Método #18

(*S*)-5-(□ -Aminofenetil)-3-fenil-1,2,4-oxadiazol trifluoroacetato



BOC-Fenilalanina (614mg, 2,32mmol) se disolvió en DCM (20ml) enfriado con hielo/agua y se agregó diciclohexil carbodiimida (239mg, 1.16mmol). Luego de agitar a 0-5°C durante 1 hora la mezcla de reacción se filtró y concentró in vacuo. Se agregaron fenilamidoxima (104mg, 0.77mmol) y piridina (10ml) y la mezcla se calentó a reflujo durante 2 horas. La mezcla de reacción se evaporó luego a un volumen pequeño, se disolvió en acetato de etilo, se lavó con ácido cítrico diluido, bicarbonato de sodio saturado, agua y salmuera, se secó con sulfato de magnesio y se

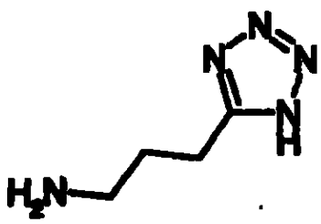
119

evaporó para producir un producto crudo que se purificó por cromatografía en gel de sílice (eluido con hexano/acetato de etilo 4:1) en (*S*)-5-[□-(*tert*-butoxicarbonilamino)fenetil]-3-fenil-1,2,4-oxadiazol (274mg).
NMR 1.2-1.4 (9H, s), 3.1-3.3 (2H, m); 5.1-5.2 (1H, m); 7.2-7.3 (5H, m); 7.5-7.6 (3H, m); 7.8 (1H, d); 7.95-8.05 (2H, m); m/z 364

(*S*)-5-[□-(*tert*-Butoxicarbonilamino)fenetil]-3-fenil-1,2,4-oxadiazol (274mg) se disolvió en ácido trifluoroacético (5ml) y se agitó a temperatura ambiente durante 2 horas. Luego de la evaporación y secamiento bajo vacío el compuesto del título se obtuvo como un sólido de color amarillo pálido (232mg). NMR 3,2-3.5 (2H, m); 5.15 (1H, t); 7.1-7.3 (5H, m); 7.4-7.6 (3H, m); 7.9 (2H, d); 9.0 (3H, s); m/z 266

Método #19

3-(1*H*-Tetrazol-5-il)propilamina

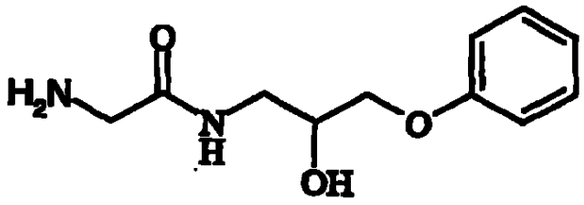


4-{[(Fenilacetil)oxi]amino}butanamida (*J. Biol. Chem.*, 1971, **246**, 6683) (16 g) se disolvió en piridina seca (150 ml) y la solución se enfrió a -10°C. Se agregó gota a gota una solución de $POCl_3$ (8.1 ml) en DCM (16.5 ml) durante 30 minutos. La mezcla se agitó a temperatura ambiente durante 1 hora antes de diluirse con agua hasta que el pH llegó a 5. La solución se extrajo usando EtOAc. Las capas orgánicas combinadas se lavaron con ácido clorhídrico acuoso y agua antes de secarse, se filtraron y se concentraron. El sólido resultante (9.2 g, 42.8 mmol) se disolvió en DMF seco (30 ml) y la solución se calentó en un baño de vapor durante 2 horas. Se agregó cloruro de amonio (2.22 g, 41.5 mmol) y la solución caliente junto con azida de sodio (2.68 g, 56.3 mmol). La mezcla se enfrió y se dejó agitar durante más de 48 horas. La solución se filtró y basificó a

pH 8 usando bicarbonato de sodio acuoso. La capa acuosa se lavó usando EtOAc antes de acidificarse usando ácido clorhídrico acuoso diluido. Se filtró un sólido blanco. Este sólido (3.0 g, 11.5 mmol) se disolvió en ácido acético (50 ml) y agua 5 ml. Se agregó paladio sobre carbón vegetal (5%, 400 mg) y la solución se agitó bajo una atmósfera de hidrógeno durante 6.5 horas. La suspensión se filtró y se lavó con ácido acético. El filtrado se concentró y se secó. El residuo se trató con iso-propanol y el compuesto del título se filtró como un sólido blanco (1.37 g, 94%).

Método #20

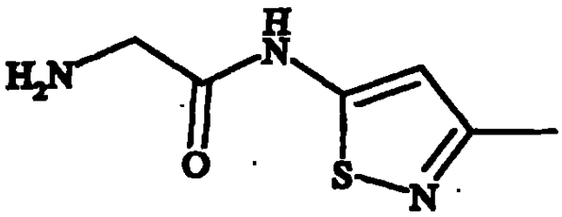
2-Amino-*N*-(2-hidroxi-3-fenoxipropil)acetamida



N-Benciloxicarbonilglicina (2.09 g) se disolvió en tolueno (40 ml) y DMF (5 gotas). Se agregó cloruro de oxalilo (1.3 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución se diluyó con éter dietílico (25 ml) y se agregó gota a gota a una solución de 1-amino-3-fenoxi-2-propanol (1.67 g) en éter dietílico (25 ml). Hidróxido de sodio (0.4 g) se disolvió en agua (1.5 ml) y se agregó a la mezcla. La solución se agitó durante más de 48 horas antes de filtrarse. El sólido pegajoso aislado se agregó a bicarbonato de sodio acuoso (100 ml) y se agitó durante 15 minutos antes de filtrarse. El sólido se re-cristalizó de una mezcla de EtOAc/petróleo. Este compuesto resultante (650 mg) se disolvió en MeOH (10 ml) y se agregó paladio en carbón vegetal (5%, 50 mg) junto con ácido acético (1 ml). La solución se agitó bajo una atmósfera de hidrógeno durante 4 horas antes de filtrarse. El filtrado se concentró para proporcionar un residuo oleoso. El residuo se re-cristalizó de una mezcla de EtOH/éter dietílico para proporcionar el compuesto del título (200 mg).

Método #21

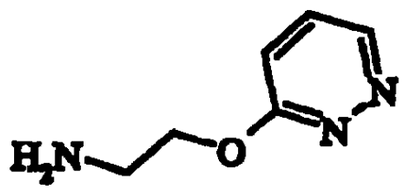
2-Amino-*N*-(3-metilisotiazol-5-il)acetamida



N-*t*-Butoxicarboilglicina (1.92 g, 1.1 mmol) se disolvió en EtOAc seco (20 ml) y la solución se enfrió a -25°C. Se agregó *N*-metil morfolina (1.1 g, 1.1 mmol) y la mezcla se agitó durante 2 minutos antes de la adición de cloroformato de etilo (1.08 g, 1.0 mmol). Se precipitó un sólido blanco de la solución. Se agregó una suspensión de clorhidrato de 5-amino-3-metilisotiazol (1.5 g, 1.0 mmol) en trietilamina (1.01 g, 1.0 mmol) y EtOAc seco (10 ml). La mezcla se agitó a temperatura ambiente durante 17 horas antes de filtrarse. El filtrado se concentró y el residuo se purificó por cromatografía de columna de destello, usando éter dietílico como eluyente. El residuo (271 mg, 0.1 mmol) se disolvió en EtOAc (3 ml). Se agregó HCl etanólico (1 ml) y la mezcla se agitó a temperatura ambiente durante 2.5 horas. El compuesto del título se precipitó como un sólido blanco y se aisló mediante filtración (220 mg, 92%).

Método #22

2-(Piridazin-3-iloxi)etilamina

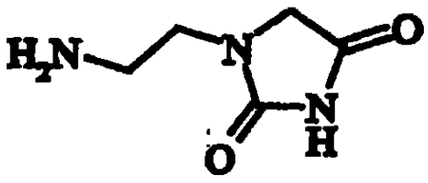


Etanolamina (6.0 ml) se suspendió en xileno seco (100 ml) y la mezcla se agitó a temperatura ambiente con hidruro de sodio (3 g). Luego de 20 minutos la solución se enfrió a 0°C. Se agregó 3,6-dicloropiridazina (15.0 g). La solución se calentó a temperatura ambiente y se agitó durante 15 horas antes de extraerse con cloroformo. El cloroformo se concentró y el

residuo se tomó en EtOAc antes de filtrarse. Se agregó HCl etanólico y se filtró un sólido blanco. Este compuesto (550 mg) se disolvió en MeOH (130 ml) y se agregó paladio sobre carbón vegetal (5%, 200 mg). La suspensión se agitó bajo una atmósfera de hidrógeno durante 6 horas antes de filtrarse. El filtrado se concentró y el residuo se trituró usando éter dietílico. El compuesto del título se aisló como un sólido blanco (340 mg).

Método #23

1-(2-Aminoetil)imidazolidina-2.4-diona

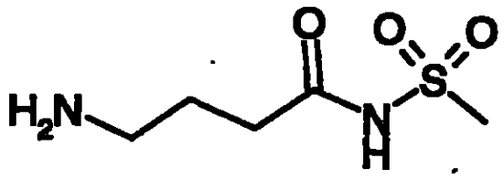


Etilen diamina (30 ml) se disolvió en DCM (130 ml) con dicarbonato di-*t*-butílico (13.5 g). La mezcla se agitó a temperatura ambiente durante 30 minutos antes de que el solvente se decantara. El residuo se lavó con agua y se secó. El producto (6.1 g) se disolvió en etanol (15 ml). Se agregó gota a gota una solución de ácido cloroacético (5.77 g) en hidróxido de sodio acuoso (1 M, 61 ml), seguida por más hidróxido de sodio acuoso (1 M, 31 ml). La mezcla se agitó durante 17 horas antes de lavarse con éter dietílico. Se agregó cloroformato de bencilo (5 g) a la fase acuosa y la mezcla se agitó a temperatura ambiente durante 4 horas. La solución se lavó con éter dietílico y la capa acuosa se acidificó usando ácido cítrico acuoso (30%). La solución se extrajo usando EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, luego con agua antes de secarse, se filtraron y se concentraron. El residuo se trituró usando una mezcla de éter dietílico/petróleo y el intermedio requerido se aisló como un sólido blanco. Siguiendo el procedimiento repetido a mayor escala, este sólido (28 g) se disolvió en etanol (250 ml) que contenía paladio sobre carbón vegetal (10%, 4.6 g). La suspensión se agitó bajo una atmósfera de hidrógeno hasta concluir la reacción. La mezcla se filtró y el filtrado se concentró. El residuo (3g, se trató con cianato de potasio (1.3 g) en agua (30 ml) y la

mezcla se calentó bajo reflujo durante 2 horas. Se agregó un exceso de ácido clorhídrico concentrado y la mezcla se calentó durante un corto tiempo antes de concentrarse. El residuo se tomó en agua (50 ml) y se cargó en resina básica Amberlite® IRA. La resina se lavó con agua hasta que el eluyente se encontró neutral. Se usó ácido clorhídrico acuoso diluido para eluir el producto crudo de la resina. Las fracciones acídicas se concentraron y el residuo se trituró con etanol. El compuesto del título se aisló como cristales color anaranjado (950 mg).

Método #24

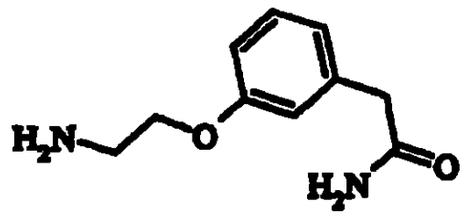
N-(4-Aminobutiril)metanosulfonamida



Cloruro 4-ftalimidobutirílico (*J. Am. Chem. Soc.*, 1981, **103**, 6750) (1.27 g) se calentó con metano sulfonamida (480 mg) a 100°C durante 15 minutos bajo argón. La mezcla se enfrió y se dejó reposar durante 17 horas. El residuo se trituró con etanol para proporcionar el intermedio requerido. El sólido (4 g) se trató con hidróxido de potasio (75 g) en agua (100 ml) a temperatura ambiente durante 2 horas. Se agregó ácido clorhídrico concentrado hasta que el pH de la solución llegó a 9. La solución se extrajo usando EtOAc. Las capas orgánicas combinadas se concentraron y el residuo se trituró usando una mezcla de éter dietílico /petróleo y se filtraron. El residuo (5.7 g) se tomó en agua (150 ml) y ácido clorhídrico diluido (1 M) hasta que el pH llegó a 1. La mezcla se calentó en un baño de vapor durante 1 hora antes de enfriarse y se extrajo usando EtOAc. La fase acuosa se concentró y el residuo se trituró usando una mezcla de EtOAc/etanol para proporcionar el compuesto del título (1.5 g).

Método #25

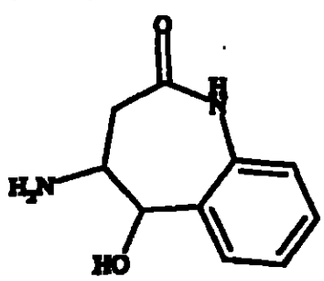
2-[3-(2-Aminoetoxi)fenil]acetamida



Ácido 3-hidroxifenilacético (30.4 ml) se disolvió en MeOH (160 ml). Se agregó ácido sulfúrico concentrado (1.6 ml) y la mezcla se calentó bajo reflujo durante 6 horas. La mezcla se concentró a bajo volumen antes de la adición de tolueno (120 ml). La mezcla se lavó con agua, bicarbonato de sodio acuoso saturado y salmuera. Las capas orgánicas combinadas se redujeron en volumen en una mitad antes de agitar con una solución de amoníaco (180 ml) durante 16 horas. La mezcla se concentró y se filtró. El sólido se lavó con agua y se secó. El residuo (24 g) se disolvió en MeOH (400 ml) con 1,2-dibromoetano (20 ml) e hidróxido de sodio (6 g). La solución se calentó bajo reflujo durante 36 horas antes de concentrarse. El residuo se porcionó entre agua y EtOAc. La fase orgánica se separó y se concentró. Este residuo se purificó por cromatografía de líquido a presión media, usando 5% MeOH en DCM como eluyente. El intermedio purificado (7.5 g) se disolvió en etanol (300 ml) con solución de amoníaco (500 ml). El recipiente de reacción se selló y la mezcla se agitó a temperatura ambiente durante 6 horas antes de dejarse reposar durante 2.5 días. La solución se concentró y el residuo se purificó empleando cromatografía de líquido a presión media, usando 25% MeOH en DCM como eluyente, para proporcionar el compuesto del título (4.1 g).

Método #26

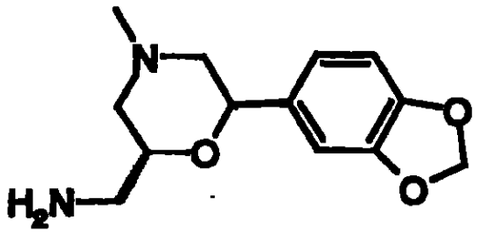
(*trans*)-4-Amino-5-hidroxi-1,3,4,5-tetrahidro-2*H*-1-benzazepin-2-ona



Tolueno anhidro (33 ml) y etanol (2.2 ml) se calentaron con potasio (0.3 g) hasta que todo el metal se disolvió. Se agregó 3,4-dihidro-1*H*-1-benzazepine-2,5-diona (*J. Org. Chem.*, 1972, 37, 208) (11.6 g) y la mezcla se calentó bajo reflujo durante 2 minutos antes de enfriarse a temperatura ambiente. Se agregó nitrito de butilo (1.7 ml) y la mezcla se agitó durante 4 horas antes de dejarse reposar durante 3 días. El solvente se decantó y el residuo se pasó por una columna Fluorisil®, usando 5% MeOH en cloroformo como eluyente. El producto (1.0 g) se disolvió en agua (40 ml) y MeOH (14 ml) que contenía paladio sobre carbón vegetal (5%, 500 mg). La mezcla se agitó bajo una atmósfera de hidrógeno durante 1 hora. La mezcla se filtró y el filtrado se concentró. El residuo se re-cristalizó usando etanol para proporcionar el compuesto del título.

Método #27

(2*R*,5*S*)-2-Aminometil-5-(1,3-benzodioxol-5-il)-4-metilmorfolina

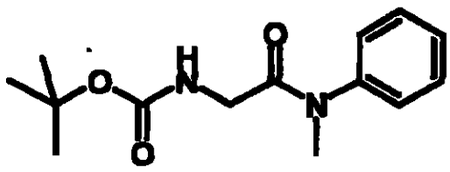


Una solución de 1-(1,3-benzodioxol-5-il)-2-(metilamino)etanol (*Synthesis*, 1979, 423) (28.65 g) y oxirano-2-carboxamida (*Bull. Chem. Soc. Jpn.*, 1989, **62**, 3202) (14.0 g) en etanol (500 ml) se calentó bajo reflujo durante 1.5 horas. La solución se concentró y el residuo se trituró usando éter dietílico. Se filtró un polvo blanco. Este producto (3.0 g) se agregó en porciones a ácido trifluoroacético (30 ml) a temperatura ambiente. La solución se agitó durante 45 minutos antes de concentrarse. El residuo se basificó usando bicarbonato de sodio acuoso saturado. La mezcla se filtró y el filtrado se concentró. El aceite residual se purificó por cromatografía de columna de destello, usando una gradiente de MeOH en EtOAc como eluyente, para proprocionar los dos isómeros *cis*- y *trans*- del intermedio requerido. El isómero *trans*- (1.6 g) se disolvió en éter dietílico seco (180

ml). La solución se calentó bajo reflujo usando equipo Soxhlet con hidruro aluminio litio (2.0 g) durante 16 horas. La solución se enfrió y se agregó agua (2 ml) con solución de hidróxido de sodio (3 M, 2 ml), seguida por más agua (6 ml). Se retiraron los residuos metálicos mediante filtración y el filtrado se extrajo usando DCM. Las capas orgánicas combinadas se secaron, se filtraron y se concentraron. El residuo se trituró usando etanol para proporcionar el compuesto del título como un sólido blanco.

Método #28

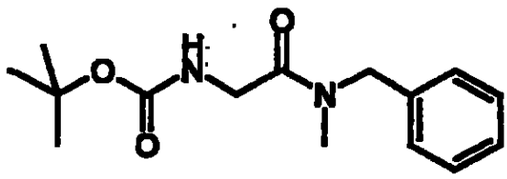
N-Metil-*N*-fenil-2-(*tert*-butoxicarbonilamino)acetamida



Por un procedimiento similar al Método #5 se preparó el *compuesto del título* usando *N*-metilanilina para producir un aceite de color anaranjado pálido (771mg, 58%); NMR: ($CDCl_3$): 7.4 (3H, m), 7. 1 (2H, m), 5.3 (1H, br), 3.6 (2H, br), 3,2 (3H, s), 1.4 (9H, s); m/z 265.42.

Método #29

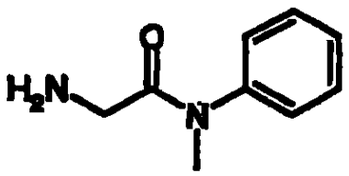
N-Bencil-*N*-metil-*N*-fenilacetamida



Por un procedimiento similar al Método #5 se preparó el *compuesto del título* usando *N*-benciletilamina para producir un aceite amarillo (670mg, 48%); NMR: ($CDCl_3$): 7.2 (5H, m), 5.5 (1H, br), 4.6 (1.33H, s), 4.4 (0.67H, s), 3.9 (2H, br), 2.9 (1H, s), 2.8 (2H, s), 1.4 (9H, s); m/z 279.50

Método #30

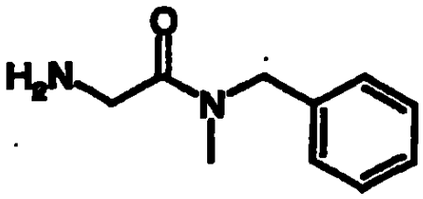
2-Amino-*N*-metil-*N*-fenilacetamida



Por un procedimiento similar al Método #6 se preparó el *compuesto del título* usando *N*-metil-*N*-fenil-2-*(tert* butoxicarbonilamino)acetamida (Método #28) para producir el *compuesto del título* como un aceite claro (231mg, 56%); NMR: ($CDCl_3$): 7.3 (3H, m), 7. 1 (2H, d), 3,2 (3H, s), (2H, br); m/z 165.17

Método #31

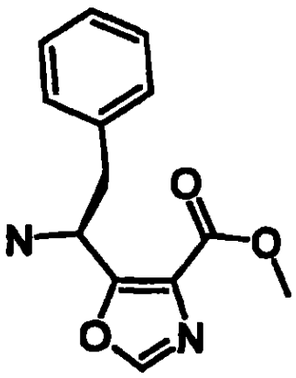
2-Amino-*N*-metil-*N*-bencilacetamida



Por un procedimiento similar al Método #6 usando *N*-bencil-*N*-fenil-2-*(tert*-butoxicarbonilamino)acetamida (Método #29) se preparó el *compuesto del título* para producir el *compuesto del título* como un aceite claro (256mg, 73%); NMR: ($CDCl_3$): 7.3 (5H, m), 4.6 (1.33H, s), 4.4 (0.67H, s), 3.4 (2H, br), 2.95 (1.33H, s), 2.8 (2,34H, s), (1.33H, s); m/z 179.23

Método #32

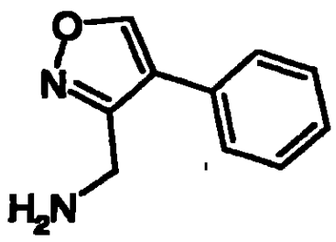
Trifluoroacetato de metil (*S*)-5-(□-aminofenetil)oxazol-4-carboxilato



Metil (*S*)-5-[□-(*tert*-butoxicarbonilamino)fenetil]-oxazol-4-carboxilato, (Tett. Lett., 1982,23,235; 417mg) se disolvió en ácido trifluoroacético (3ml) y se dejó reposar a temperatura ambiente durante 1 hora y se concentró para producir un aceite. La trituración con éter dietílico produjo el compuesto del título como un sólido blanco (281mg); NMR 3.1-3,25 (1H, m); 3.3-3.4 (1H, m); 3.7 (3H, s); 5.2-5.3 (1H, m); 7.05 (2H, d); 7.2-7.3 (3H, m); 8.7 (1H, s); 8.75-8.85 (3H, bs).

Método #33

3-Aminometil-4-fenilisoxazol



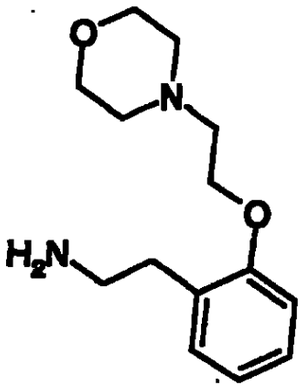
Éster etílico de ácido 4-fenilisoxazol-3-carboxílico (JOC 50 13 2372 1983; 404mg, 1.86mmol) disuelto en THF 10ml bajo nitrógeno se trató borohidruro de litio 2M en THF (1.86ml, 3.72mmol). La mezcla resultante se agitó a 0° C durante 5 horas, luego se dejó calentar a temperatura del recinto durante la noche. Se agregó gota a gota ácido acético 1M hasta que cesó la efervescencia, se añadieron otros 20 ml de agua y la solución resultante se extrajo con acetato de etilo (3x20 ml), se lavaron los extractos orgánicos con solución de bicarbonato de sodio saturado (10ml) y salmuera saturada (10ml), se secaron sobre sulfato de magnesio anhidro y se evaporaron a sequedad bajo presión reducida para producir 3-hidroximetil-4-fenilisoxazol (295mg); NMR ($CDCl_3$): 4.9 (2H, d), 7.3-7.5 (5H, m), 8.5 (1H, s) m/z 176 (M+H)

3-Hidroximetil-4-fenilisoxazol (295mg, 1.68mmol) se disolvió en THF 5ml bajo nitrógeno junto con ftalimida (292mg, 1.68mmol) y trifenilfosfina (440mg, 1.68mmol), la solución resultante agitada se enfrió a 0 °C y se trató con DIAD (330ul, 1.68mmol) gota a gota durante 30 minutos, luego se dejó calentar a temperatura del recinto durante la noche.

Luego de la evaporación a sequedad la mezcla se purificó por cromatografía en una columna de sílice Bond Elute 20g eluyendo con 1: 1 DCM : hexano para producir 4-fenil-3-ftalimidometilisoxazol (316mg): m/z 305 (M+H). Éste se disolvió en metanol 3 ml con hidrato de hidrazina (114ul, 2.4mmol) y se hizo refluir durante 30 minutos. La suspensión resultante se filtró, el sólido se lavó con etanol (2x5ml) y el filtrado se evaporó luego a sequedad, este residuo se tomó en 2N HCl y cualquier material insoluble se retiró nuevamente mediante filtración. El filtrado se basificó con bicarbonato de sodio saturado y se extrajo con acetato de etilo (3x10ml), los extractos orgánicos combinados se lavaron con agua (5ml) y salmuera saturada (5ml), luego se secaron sobre sulfato de magnesio y se evaporaron bajo presión reducida para producir 3-aminometil-4-fenilisoxazol (130mg); NMR ($CDCl_3$): 4.1 (2H, s), 7.3-7.5 (5H, m), 8.4 (1H, s); m/z 175 (M+H)

Método #34

2-[2-(2-Morfolinoetoxi)fenil]etilamina



2-(2-Hidroxifenil)etilamina (1.73g, 10mmol) disuelta en DCM 60ml se trató con una solución de bicarbonato de sodio (1.68g, 20mmol) en agua, la emulsión se agitó vigorosamente en un baño de hielo y se agregó gota a gota cloroformato de bencilo (1.785g, 10.5mmol) durante 10 minutos y la mezcla se agitó durante la noche a la temperatura del recinto.

Se retiró la fase DCM y se extrajo la fase acuosa con DCM (2x20ml). Seguidamente los orgánicos combinados se secaron sobre sulfato de magnesio y se evaporaron bajo presión reducida, el producto se purificó por

cromatografía en bond elute de sílice 20g, eluyendo con DCM para producir *N*-(benciloxicarbonil)-2-(2-hidroxifenil)etilamina (1.4g); NMR ($CDCl_3$) : 2.8 (2H, q), 3.4 (2H, q), 5.1 (3H, m), 6.4 (1H, s), 6.8 (2H, m), 7.1 (2H, m), 7.3-7.4 (5H, m)

N-(Benciloxicarbonil)-2-(2-hidroxifenil)etilamina (542mg, 2mmol) disuelta en DMF 5ml se trató con carbonato de potasio (325 ancho de malla, 350mg, 2.5mmol) y 2-cloroetil p-toluenosulfonato (484ul, 2.6mmol) y la mezcla se agitó a 60°C durante la noche. Luego de enfriar, se agregaron 10ml de agua y la mezcla se extrajo con éter dietílico (3x20ml), se secó sobre sulfato de magnesio y se evaporó bajo presión reducida, el producto se purificó por cromatografía en bond elute de sílice 20g, eluyendo con DCM para producir *N*-(benciloxicarbonil)-2-[2-(2-cloroetoxi)fenil]etilamina (450mg); NMR ($CDCl_3$): 2.9 (2H, q), 3.5 (2H, m), 3.8 (2H, m), 4.2 (2H, m), 4.9 (1H, b), 5.1 (2H, s), 6.8 (1H, d), 6.9 (1H, t), 7.1 (2H, m), 7.3-7.4 (5H, m). Columna C18 HPLC Hichrome acetonitrilo/agua/0.1 %TFA 5-95% durante 7.5 min Rt 4.98 min.

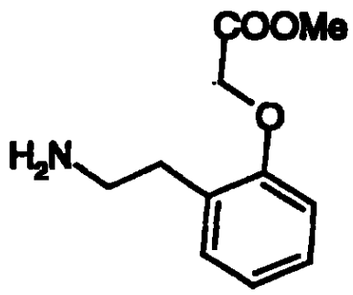
N-(Benciloxicarbonil)-2-[2-(2-cloroetoxi)fenil]etilamina (110mg, 0.33mmol) disuelta en NMP 3ml se calentó con morfolina (174ul, 2mmol) a 80°C durante la noche. Se agregó agua (5ml) y la mezcla se extrajo con acetato de etilo (30ml), la fase orgánica se lavó con agua (2x5ml), se secó sobre sulfato de magnesio y se evaporó bajo presión reducida para producir *N*-(benciloxicarbonil)-2-[2-(2-morfolinoetoxi)fenil]etilamina (143mg); NMR ($CDCl_3$): 2.5 (4H, q), 2.8 (4H, m), 3.4 (2H, q), 3.7 (4H, q), 4.1 (2H, t), 5.0 (2H, s), 5.3 (1H, b), 6.8 (2H, m), 7.1 (1H, d), 7.2 (1H, t), 7.3-7.4 (5H, m). Columna C18 HPLC Hichrome acetonitrilo/agua/0.1 %TFA 5-95% durante 7.5 min Rt 3.73 min m/z 385 (M+H) .

N-(Benciloxicarbonil)-2-[2-(2-morfolinoetoxi)fenil]etilamina (143mg) disuelta en metanol se trató con 10% paladio sobre carbono y se hidrogenó durante 2 horas. El sólido se retiró mediante filtración; se lavó con metanol (2x2ml), el fitrado de evaporó bajo presión reducida y se destiló azeotrópicamente dos veces con tolueno para producir el compuesto

del título (83mg) m/z 251 (M+H), el cual se usó directamente en el siguiente paso.

Método #35

Metil 2-[2-(2-aminoetil)fenoxi]acetato

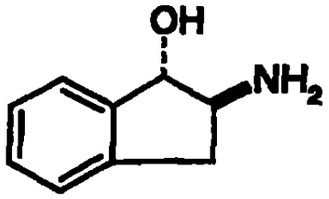


N-(Benciloxicarbonil)-2-(2-hidroxifenil)etilamina (véase Método #34: 718mg, 2.65mmol) disuelta en DMF 6ml se trató con carbonato de potasio (-325 ancho de malla, 397mg, 4.0mmol), bromoacetato de metilo (362ul, 3.7mmol) y la mezcla se agitó durante la noche a la temperatura del recinto. Luego de enfriar, se agregó agua 10ml y la mezcla se extrajo con éter dietílico (3x20ml), se secó sobre sulfato de magnesio y se evaporó bajo presión reducida para producir 2-{2-[2-(benciloxicarbonil(amino)etil)]fenoxi}acetato de metilo (847mg); NMR ($CDCl_3$): 2.8 (2H, q), 3.5 (2H, m), 3.8 (3H, s), 4.6 (2H, s), 5.1 (3H, m), 6.7 (1H, d), 6.9 (1H, t), 7.1-7.4 (7H, m).

2-{2-[2-(Benciloxicarbonilamino)etil]fenoxi}acetato de metilo (343mg, 1mmol) disuelto en metanol junto con ácido p-toluenosulfónico (190mg,1mmol) se trató con 10% paladio sobre carbono y se hidrogenó durante 2 horas. El sólido se retiró mediante filtración, se lavó con metanol (2x2ml), el filtrado se evaporó bajo presión reducida y se destiló azeotrópicamente dos veces con tolueno para producir 2-[2-(2-aminoetil)fenoxi]acetato de metilo (403mg), m/z 210 (M+H)el cual se empleó sin purificación adicional.

Método #36

2-Aminoindan-1-ol

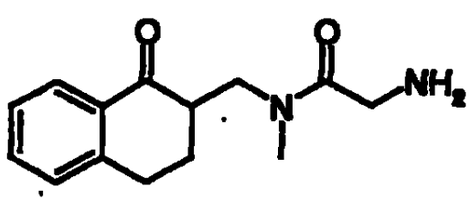


Nitrito isoamílico (15 ml, 108 mmol) se agregó a una solución de indan-1,2-diona (12 g, 90 mmol) en metanol (380 ml) a 45°C seguido por HCl concentrado (12 ml) gota a gota durante 5 minutos. La mezcla de reacción se agitó durante 3 horas a temperatura del recinto. Se agregó un exceso de nitrito isoamílico (1 ml) y HCl concentrado (1 ml) y la suspensión se agitó durante 15 minutos más. Al enfriar a la temperatura del recinto se formó un precipitado blanco. El precipitado se filtró y se lavó con metanol frío (40 ml) seguido por éter dietílico (40 ml) para proporcionar indan-1,2-dion-2-oxima como un sólido blanco (6.2 g, 43%). NMR: 3.8 (2H, s), 7.4 (1H, t), 7.6 (1H, d), 7. 7 (2H, t); m/z 162 (M+H)

Una solución de indan-1,2-dion-2-oxima (6.2 g, 39 mmol) en etanol (470 ml) y 4M HCl/dioxano (36 ml) se hidrogenó a la temperatura del recinto y 40 psi. La mezcla de reacción se filtró a través de celita, se lavó con etanol (30 ml) y se concentró bajo presión reducida para producir 10 g de un sólido blancuzco el cual se re-cristalizó de etanol para producir el compuesto del título como un sólido blanco (5 g, 86%). NMR: 2.8 (1H, dd), 3,2 (1H, dd), 3.7 (1H, q), 5.1 (1H, t), 6.0 (1H, d), 7.1-7.3 (4H, m), 8.6 (2H, s).

Método #37

2-Amino-*N*-metil-*N*-(1-oxo-1,2,3,4-tetrahidronaft-2il)metilacetamida

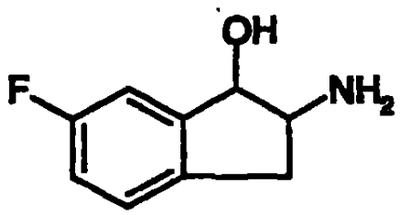


Tetralona (1 eq, 100 mmol, 15 g) y clorhidrato de metilamina (2.5 eq, 250 mmol, 15 g) y paraformaldehído (1 eq, 100 mmol, 3 g) en etanol (100 ml) se calentaron bajo reflujo durante 16 horas. La mezcla de reacción se enfrió y se filtró para proporcionar 2-(metilaminometil)-3,4,dihidro-1-(2H)-naftalenona como un sólido (14 g).

2-(Metilaminometil)-3,4,dihidro-1-(2H)-naftalenona (1 eq, 20 mmol, 4.5 g), HOBT (1 eq, 20 mmol, 2.7 g), *N*-benciloxicarbonilglicina (1 eq, 20 mmol, 4.18 g), trietilamina (1.25 eq, 25 mmol, 3 ml) y diciclohexilcarbodiimida (1 eq, 20 mmol, 4.12 g) se disolvieron en diclorometano (130 ml) y se agitaron a temperatura ambiente durante 18 horas antes de enfriarse a 0°C y se filtraron. El filtrado se concentró y el residuo se tomó en acetato de etilo antes de lavarlo con bicarbonato de sodio acuoso, se secó, se filtró y se concentró. El residuo se dejó reposar en una solución de bromuro de hidrógeno en ácido acético durante 30 minutos. La mezcla se trituró con éter dietílico y se decantó el solvente. El residuo se trató con solución de amoníaco y éste se extrajo con cloroformo. El cloroformo se concentró y el residuo se re-cristalizó de etanol para proporcionar el compuesto del título.

Método #38

2-Amino-6-fluoro-1-indanol



A una solución de carbonato de sodio (0.8 g, 7.2 mmol) en agua (13 ml) se agregó 4-fluorofenilalanina (1.3 g, 7.2 mmol) seguida por una solución de *N*-etoxicarbonilftalamida (1.6 g, 7.2 mmol) en acetato de etilo (10 ml). La mezcla de reacción de dos fases se agitó durante 24 horas a la temperatura del recinto. La fase orgánica se separó y se descartó y la fase acuosa se acidificó con HCl concentrado a pH 2. La fase acuosa se extrajo

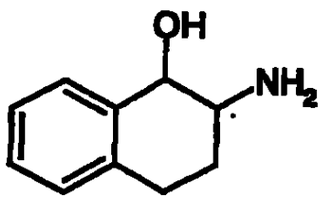
a continuación con acetato de etilo (3 x 20 ml) y los extractos combinados se secaron sobre sulfato de magnesio, luego se concentraron bajo presión reducida para producir ácido 3-(4-fluorofenil)-2-ftalimidopropanoico como un sólido blanco (2g, 89%); NMR 3.3 (1H, dd), 3.5 (1H, dd), 5.1 (1H, dd), 6.3 (1H, brs), 7.0 (2H, t), 7.1 (2H, dd), 7.8 (4H, s).

A una solución de ácido 3-(4-fluorofenil)-2-ftalimidopropanoico (2.0 g, 6.4 mmol) en DCM (20 ml) se agregó cloruro de tionilo (0.6 ml, 6.4 mmol) y 1 gota de DMF. La mezcla de reacción se agitó a temperatura del recinto durante 1 hora. Se agregó cloruro de aluminio (2.6 g, 19.2 mmol) y la mezcla de reacción se agitó durante 3 horas a la temperatura del recinto. La mezcla resultante se vertió en hielo y HCl concentrado (20 ml) y se agitó durante 10 minutos. Esta mezcla se extrajo con DCM (3 x 20 ml) y los extractos orgánicos combinados se lavaron con agua (2 x 20 ml), carbonato hidrogenado de sodio saturado (1 x 20 ml) y agua (1 x 20 ml). A continuación la fase orgánica se secó sobre sulfato de magnesio y se concentró bajo presión reducida para producir 6-fluoro-2-ftalamido-indan-1-ona como un sólido blanco (1g, 53%). NMR 3.3 (1H, dd), 3.5 (1H, dd), 5.1 (1H, dd), 6.8 (1H, t), 7.0 (1H, dd), 7.7- 8.0 (5H, m); *m/z* 296 (M+H)

Borohidruro de sodio (512 mg, 14 mmol) se agregó a una solución de 6-fluoro-2-ftalamido-indan-1-ona (800 mg, 2.7 mmol) en isopropanol/agua (6: 1, 10.5 ml) y la solución se agitó a la temperatura del recinto durante 24 horas. A continuación se agregó un exceso de ácido acético a la mezcla de reacción y la solución resultante se calentó a 60°C durante 6 horas. La mezcla de reacción se enfrió luego a la temperatura del recinto y se concentró bajo presión reducida para producir un sólido blanco que se purificó por cromatografía de intercambio de iones usando Dowex 50wx2 (agua : metanol 1:1 que contenía 3% amoníaco) para producir el compuesto del título como un sólido blanco (141 mg, 31%); NMR 3.3 (1H, dd), 3.5 (1H, dd), 4.8 (1H, m), 4.9 (1H, d), 6.8-7.4 (3H, m); m/Z 168 (M+H).

Método #39

2-Amino-1,2,3,4-tetrahidronaft-1-ol



A una solución de carbonato de sodio (0.8 g, 7.2 mmol) en agua (13 ml) se agregó homofenilalanina (1.3 g, 7.2 mmol) seguida por una solución de N-etoxicarbonilftalamida (1.6 g, 7.2 mmol) en acetato de etilo (10 ml). La mezcla de reacción de dos fases se agitó durante 24 horas a la temperatura del recinto. Se separó la fase orgánica y se descartó y la fase acuoasa se acidificó con HCl concentrado a pH 2. A continuación se extrajo la fase acuosa con acetato de etilo (3 x 20 ml) y los extractos combinados se secaron sobre sulfato de magnesio, luego se concentraron bajo presión reducida para producir ácido 4-fenil-2-ftalimidobutanoico como un sólido blanco (1.5 g, 67%); m/z 308 (M-H).

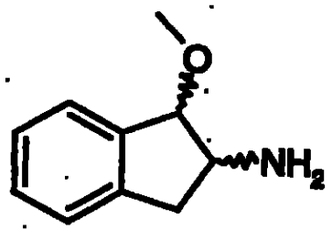
A una solución de ácido 4-fenil-2-ftalimidobutanoico (1.5 g, 4.9 mmol) en DCM (20 ml) se agregó cloruro de tionilo (0.4 ml, 4.9 mmol) y 1 gota de DMF. La mezcla de reacción se agitó a temperatura del recinto durante 1 hora. Se agregó cloruro de (2.0 g, 14.7 mmol) y la mezcla de reacción se agitó durante 3 horas a la temperatura del recinto. La mezcla resultante se vertió en hielo y HCl concentrado (20 ml) y se agitó durante 10 minutos. Esta mezcla se extrajo con DCM (3 x 20 ml) y los extractos orgánicos combinados se lavaron con agua (2 x 20 ml), carbonato hidrogenado de sodio saturado (1 x 20 ml) y agua (1 x 20 ml).
Seguidamente la fase orgánica se secó sobre sulfato de magnesio y se concentró bajo presión reducida para producir 2-ftalamido-3,4-dihidro-(2*H*)-naftalen-1-ona como un sólido blanco (880 mg, 62%). NMR 2,3 (1H, m), 2.7 (1H, m), 3.1 (1H, dt), 3.3 (1H, m), 5.2 (1H, dd), 7.3-8.0 (8H, m); m/z 292 (M+H).

A una solución de 2-ftalamido-3,4-dihidro-(2H)-naftalen-1-ona (880 mg, 3 mmol) en isopropanol/agua (6:1, 11.5 ml) se agregó borohidruro de sodio (567 mg, 15 mmol) y la solución se agitó a la temperatura del recinto durante 24 horas. Luego se agregó un exceso de ácido acético a la mezcla

de reacción y la solución resultante se calentó a 60°C durante 6 horas. La mezcla de reacción se enfrió entonces a la temperatura del recinto y se concentró bajo presión reducida para producir un sólido blanco que se purificó mediante cromatografía de intercambio de iones usando Dowex 50wx2 (agua:metanol 1:1 que contenía 3% amoníaco) para producir el compuesto del título como un sólido blanco (150 mg, 30 %). NMR 2.8 (1H, dd), 3.0 (1H, dd), 3.3 (1H, m), 3.5 (1H, m), 4.5 (1H, m), 4.8 (1H, d), 7.1-7.4 (4H, m); m/z 164 (M+H).

Método #40

(+/–) *Trans*-2-Amino-1-metoxiindano



Una solución de (+/–) *trans*-2-bromo-1-hidroxiindano (21.0g, 0.1mol) y ftalimida de potasio (42.0g, 0.22 mol) en DMF seco (120ml) se calentó a 100°C durante 5 horas. La mezcla de reacción se enfrió y se evaporó en un aceite que se trituró con acetato de etilo y se filtró. Los filtrados se evaporaron y se purificaron mediante cromatografía en sílice con 2:1 *iso*-hexano:acetato de etilo como eluyente para producir (+/–)-*trans*-1-hidroxi-2-ftalimidoindano como un polvo amorfo de color amarillo pálido (17.7g, 63%). NMR 2.8 (1H, dd), 3.15 (1H, dd), 4.8-5.0 (1H, m), 5.4 (1H, d), 5.45 (1H, d), 7.0-7.3 (4H, m), 7.75-8.95 (4H, m).

A una solución de (+/–)-*trans*-1-hidroxi-2-ftalimidoindano (1.4g, 5.0mmol) en tetrahidrofurano seco (20ml) se agregó 60% hidruro de sodio (300mg, 7.5mmol). La mezcla se agitó a temperatura del recinto durante 2 horas y luego se agregó yoduro de metilo (0.62ml, 10.0mmol).

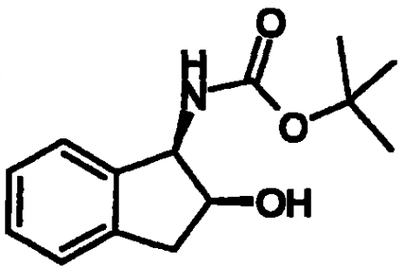
La mezcla se agitó durante 2 horas más y luego 5% agua en tetrahidrofurano (10ml) y acetato de etilo (75ml). La solución se lavó con agua, se secó sobre sulfato de magnesio y se evaporó para producir (+/–)-

trans-1-metoxi-2-ftalimidoindano como un sólido blanco (1.2g, 82%). NMR 2.85 (1H, dd), 3,25 (3H, s), 3.5 (1H, dd), 4.5-4.65 (1H, m), 5.55 (1H, d), 7.05-7.3 (4H, m), 7.85 (4H, s).

Una mezcla de (+/−)-*trans*-1-metoxi-2-ftalimidoindano (850mg, 2.9mmol) e hidrato de hidrazina (5ml) en etanol se agitó a temperatura del recinto durante 24 horas. La mezcla se evaporó y se purificó mediante cromatografía de intercambio de iones (Dowex 50W X2 forma H^+) y el compuesto del título se eluyó con 50% metanol acuoso que contenía 3% hidróxido de amonio para producir el compuesto del título como un sólido blanco (400mg, 85%). NMR 2.8 (1H, dd), 3.35 (3H, s), 3.38 (1H, dd), 4.05-4.15 (1H, m), 4.5-4.6 (1H, m), 7.2-7.35 (3H, m), 7.45-7.55 (1H, m); m/z 164 (M+H).

Método #41

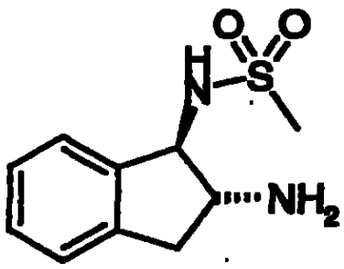
(1*R*,2*S*)-1-[(1,1-dimetiletoxi)carbonilamino]-2-hidroxiindano



(1*R*,2S)-1-Amino-2-hidroxiindano (10.0g, 67.1mmol) se disolvió en diclorometano (550ml) y trietilamina (18.7ml, 134.2mmol). Se agregó bicarbonato di-*tert*-butílico (18.3g, 83,9mmol) en diclorometano (50ml) y la mezcla se agitó a la temperatura del recinto durante 20 horas, luego se evaporó. Se agregó acetato de etilo (200ml), la solución se lavó con agua, se secó sobre sulfato de magnesio y se evaporó. El producto crudo se purificó por cromatografía en sílice con 4:1 *iso*-hexano:acetato de etilo como eluyente para producir el compuesto del título como un sólido blanco (16.1g, 96%); NMR 1.42 (9H, s), 2.78 (1H, dd), 3.0 (1H, dd), 4.3-4.42 (1H, m), 4.78-4.9 (1H, m), 4.9-5.0 (1H, m), 6.3 (1H, d), 7.0-7.25 (4H, m).

Método #42

(1*R*,2*R*)-2-Amino-1-metanosulfonamidoindano



(1*R*,2*S*)-1-Amino-2-hidroxiindano (3.0g, 20mmol) se disolvió en tetrahidrofurano seco (40ml) y trietilamina (8.4ml, 60.0mmol) a 10°C. Se agregó cloruro de metanosulfonilo (5.0g, 44.0mmol) disuelto en tetrahidrofurano (10ml) en una rata tal que la temperatura interna permaneció por debajo de 15°C. Tras la adición la mezcla se agitó a temperatura del recinto durante 20 horas y luego se evaporó. Se agregó acetato de etilo (100ml) al residuo y la mezcla se lavó con bicarbonato de sodio acuoso saturado y luego agua. La solución orgánica se secó sobre sulfato de magnesio y se evaporó para producir (1*R*,2*S*)-1-metanosulfonamido-2-metilsulfoniloxiindano como un sólido de color amarillo pálido (5.7g, 93%).

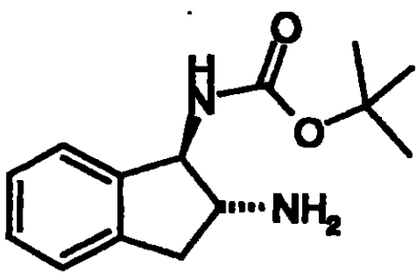
NMR: 3.0-3.35 (2H, m), 3.1 (3H, s), 3.25 (3H, s), 5.05-5.2 (1H, m), 5.3-5.4 (1H, m), 7.2-7.4 (4H, m), 7.85-8.0 (1H, m). m/z 304.2 (M-H).

(1*R*,2*S*)-1-Metanosulfonamido-2-metilsulfoniloxiindano (2.0g, 6.56mmol) se disolvió en acetamida seca de dimetilo (20ml). Se agregó azida de sodio (1.7g, 26.2mmol) y la mezcla se calentó a 90°C durante 1 hora. La reacción se enfrió, se diluyó con acetato de etilo (100ml), se lavó con agua (6 x 50ml), se secó sobre sulfato de magnesio y se filtró. Se agregó 10% paladio sobre carbón activado y la mezcla se agitó bajo una atmósfera de hidrógeno durante 3 horas. La filtración a través de celita seguida por evaporación produjo el compuesto del título como un sólido de color verde pálido (1.25g, 83%). NMR ($CDCl_3$): 1.68 (2H, s amplia), 2.67

(1H, dd), 3.2 (3H, s), 3.23 (1H, dd), 4.5-4.6 (1H, m), 4.6-4.8 (1H, m), 7.15-7.35 (4H, m); m/z 227.4 (M+H).

Método #43

(1*R*, 2*R*)-2-Amino-1-[(1,1-dimetiletoxi)carbonilamino]indano

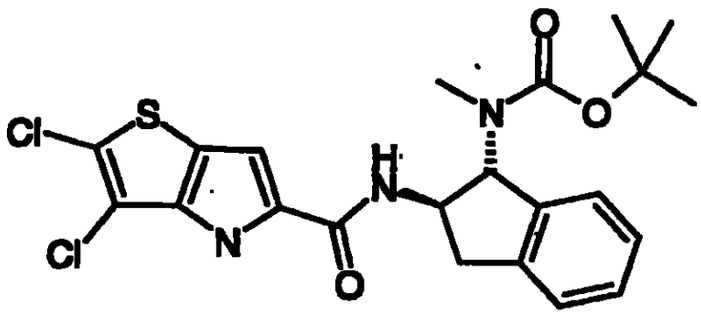


(1*R*,2*S*)-1-[(1,1-Dimetiletoxi)carbonilamino]-2-hidroxiindano (Método #41, 7.5g, 30.1mmol) se disolvió en tetrahidrofurano seco (90ml) y trietilamina (6.3ml, 45.0mmol). Se agregó cloruro de metanosulfonilo (3.78g, 33.0mmol) disuelto en tetrahidrofurano seco (10ml) y la mezcla se agitó a la temperatura del recinto durante 20 horas. La mezcla se evaporó y se agregó acetato de etilo (250ml). Luego de lavar con agua y secar sobre sulfato de magnesio la solución orgánica se evaporó a (1*H*,2*S*)-1-[(1,1-dimetiletoxi)carbonilamino]-2-metanosulfoniloxiindano como un sólido blanco (9.7g, 98%). NMR 1.45 (9H, s), 3.05-3.35 (2H, m), 3.18 (3H, s), 5.15-5.25 (1H, m), 5.28-5.38 (1H, m), 7.15- 7.22 (4H, m), 7.45(1H, d).

(1*R*,2*S*)-1-[(1,1-Dimetiletoxi)carbonilamino]-2-metanosulfoniloxiindano (3.5 g, 10.7mmol) se disolvió en acetamida seca de dimetilo (50ml). Se agregó azida de sodio (3.5g, 53.9mmol) y la mezcla se calentó a 90°C durante 3 horas. La reacción se enfrió, se diluyó con acetato de etilo (150ml), se lavó con agua (6 x 50ml) y se secó sobre sulfato de magnesio. Se agregó 10% paladio en carbón activado y la mezcla se agitó bajo una atmósfera de hidrógeno durante 4 horas. La filtración a través de celita seguida por evaporación produjo el compuesto del título como un sólido blanco (2.6g, 98%). NMR: 1.45 (9H, s), 2.5 (1H, dd), 3.0 (1H, dd), 3.2-3.45 (3H, m), 4.5-4.6 (1H, m), 7.0-7.25 (5H, m).

Método #44

2,3-Dicloro-5-[*N*-(1{*N*-[(1,1-dimetiletoxi)carbonil]-*N*-metilamino}indan-2-il)carbamoil]-4*H*-tieno[3,2-b}]pirrol



A una solución de (1*R*,2*S*)-1-[(1,1-dimetiletoxi)carbonilamino]-2-hidroxiindano (Método #41, 7.0g, 28.1mmol) en diclorometano (50ml) se agregó 3,4-dihidro-2*H*-pirano (4.7g, 56.2mmol) y tolueno-4-sulfonato de piridinio (100mg). La mezcla se agitó durante 4 horas, se diluyó con acetato de etilo (200ml), se lavó con agua (2 x 50ml), se secó sobre sulfato de magnesio y se evaporó para producir (1*R*,2*S*)-1-[(1,1-dimetiletoxi)carbonilamino]-2-[(tetrahidropiran-2-il)oxi]indano como un sólido blanco (8.9g, 96%). NMR 1.25-1.85 (6H, m), 1.45 (9H, d), 2.85-3.1 (2H. m), 3.35-3.5 (1H, m), 3.68-3.9 (1H, m), 4.35-5.1 (3H, m), 6.8 (1H, dd), 7.1-7.3 (4H, m).

(1*R*,2*S*)-1-[(1,1-Dimetiletoxi)carbonilamino]-2-[(tetrahidropiran-2-il)oxi]indano (4.0g, 12.0mmol) se disolvió en DMA seco (25ml) a 10°C y se agregó 60% hidruro de sodio (575mg. 14.4mmol). La mezcla se agitó a temperatura del recinto durante 30 minutos y luego se agregó yoduro de metilo (2.0g, 14.4mmol) tras lo cual la reacción se agitó durante 3 horas más a la temperatura del recinto. La mezcla se diluyó con acetato de etilo (50ml), se lavó con agua (6 x 50ml), se secó sobre sulfato de magnesio y se evaporó para producir (1*R*,2*S*)-1-{N-[(1,1-dimetiletoxi)]carbonil-*N*-metil-amino}-2-(tetrahidropiran-2-il)oxiindano como un aceite (4.1g, 98%). NMR 1.4-1.9 (6H, m), 1.5 (9H, d), 2.7 (3H, dd), 2.85-3.3 (2H, m), 3.47-3.6

(1H, m), 3.72-4.0 (1H, m), 4.7-5.0 (2H, m), 5.5-5.84 (1H, m), 7.15-7.35 (4H, m); m/z 348.6 (M+H).

A una solución de (1*R*,2*S*)-1-{*N*-[(1,1-dimetiletoxi)carbonil]-*N*-metilamino}-2-(tetrahidropiran-2-il)oxiindano (4.0g, 11.5mmol) en metanol (50ml) se agregó ácido tolueno-4-sulfónico (100mg) y la mezcla se agitó a la temperatura del recinto durante 2 horas. Se agregó bicarbonato de sodio acuoso saturado (50ml) y agua (10ml) y la mezcla se extrajo con acetato de etilo. El extracto orgánico se lavó con agua, se secó sobre sulfato de magnesio y se evaporó para producir (1*R*,2*S*)-1-{*N*-[(1,1-dimetiletoxi)carbonil]-*N*-metilamino}-2-hidroxiindano como un aceite (3.0g, 100%). NMR 1.45 (9H, s), 2.6 (3H, s), 2.75 (1H, dd), 3.05 (1H, dd), 4.4-4.57 (1H, m), 5.0-5,12(1H, m). 5,34 (1H, dd), 7.03-7.33 (4H, m).

A una solución de (1*R*,2*S*)-1-{N-[(1,1-dimetiletoxi)carbonil]-*N*-metilamino}-2-hidroxiindano (3.0g, 11.4mmol) en tetrahidrofurano seco (40mmol) se agregó trietilamina (2.4ml, 17.1mmol) y cloruro de metanosulfonilo (1.44g, 12.55mmol). La mezcla se agitó a temperatura del recinto durante 1 hora, se evaporó y se diluyó con acetato de etilo (100ml). La solución orgánica se lavó con bicarbonato de sodio acuoso saturado y luego agua, se secó sobre sulfato de magnesio y se evaporó para producir un jarabe de color amarillo pálido. El material crudo se purificó mediante cromatografía de sílice con 4:1 *iso*-hexano:acetato de etilo como eluyente en (1*R*,2*S*)-1-{*N*-[(1,1-dimetiletoxi)carbonil]-*N*-metil-amino}-2-metanosulfoniloxiindano como un jarabe incoloro claro (3.1g, 80%). NMR ($CDCl_3$): 1.54 (9H, s), 2.7 (3H, d), 3.0 (3H, s), 3.16- 3.42 (2H, m), 5.35-5.51 (1H, m), 5.78 (1H, dd), 7.2-7.35 (4H, m); m/z 342.5 (M+H).

(1*R*,2*S*)-1-{*N*-[(1,1-Dimetiletoxi)carbonil]-*N*-metil-amino}-2-metanosulfoniloxiindano (3.0g, 8.8mmol) se disolvió en DMA seco (30ml) y se agregó azida de sodio (2,3g, 35.2mmol). La mezcla se calentó 90°C durante 6 horas, se enfrió y se diluyó con acetato de etilo (100ml). La

solución se lavó con agua (6 x 50ml), se secó sobre sulfato de magnesio y se filtró. Se agregó 10% paladio sobre carbón activado y la mezcla se agitó bajo una atmósfera de hidrógeno durante 4 horas. La mezcla se filtró, se evaporó y se purificó mediante cromatografía de sílice con 10% metanol en diclorometano para producir (1*R*,2*S*)-2-amino-1-{*N*-[(1,1-dimetiletoxi)]carbonil-*N*-metil-amino}indano como un aceite (1.2g, 55%). NMR 1.36-1.56 (9H, m), 2.6 (3H, s), 2.7-2.87 (1H, m), 3,2-3.35 (1H, m), 4.37-4.54 (1H, m), 5.4-5.7 (1H, m), 6.93-7.1 (1H, m), 7.12-7.5 (4H, m); m/z 263.48 (M+H).

5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-b]pirrol (Método #9, 472mg, 2.0 mmol), (1*R*,2*S*)-2-amino-1-{*N*-[(1,1-dimetiletoxi)]carbonil-*N*-metil-amino}indano (524mg, 2.0mmol), DIPEA (0.348ml, 2.0mmol) y HOBT (270mg, 2.0mmol) se agitó en diclorometano (10ml) a la temperatura del recinto durante 2 minutos. Se agregó EDAC (480mg, 2.5mmol) y la mezcla se agitó a la temperatura del recinto durante 20 horas. La reacción se evaporó, se agregó acetato de etilo (50ml) y se lavó con agua. La fase orgánica se secó sobre sulfato de magnesio y se evaporó para producir el compuesto del título como una espuma de color café pálido (900mg, 94%). NMR 1.2-1.45 (9H, m), 2.77 (3H, s), 2.9-3,26 (2H, m), 4.7-4.94 (1H, m), 5.5-5.8 (1H, m), 6.9-7.34 (5H, m), 8.55-8.73 (1H, m), 12.25 (1H, s amplia); m/z 480.3/482.1 (M+H).

Ejemplo 155

Lo siguiente ilustra formas representativas de dosificación farmacéutica que contienen el compuesto de fórmula (I), o su sal de aceptación farmacéutica o éster hidrolizable *in vivo* (en lo sucesivo compuesto X), para el uso terapéutico o profiláctico en humanos:-

(a): Comprimido I	mg/comprimido
Compuesto X	100

Lactosa Ph.Eur	182.75
Croscarmellose sodium	12.0
Pasta de almidón de maíz (5% w/v pasta)	2.25
Estearato de magnesio	3.0

(b): Comprimido II	**mg/comprimido**
Compuesto X	50
Lactosa Ph.Eur	223.75
Sodio de croscarmelosa	6.0
Almidón de maíz	15.0
Polivinilpirrolidona (pasta 5% p/v)	2.25
Estearato de magnesio	3.0
(c): Comprimido III	**mg/comprimido**
Compuesto X	1.0
Lactosa Ph.Eur	93,25
Sodio de croscarmelosa	4.0
Pasta de almidón de maíz (5% p/v)	0.75
Estearato de magnesio	1.0

(d): Cápsula	**mg/cápsula**
Compuesto X	10
Lactosa Ph.Eur	488.5
Estearato de magnesio	1.5

(e): Inyección I	**(50 mg/ml)**
Compuesto X	5.0% p/v
Solución 1M de hidróxido de sodio	15.0% v/v
Ácido clorhídrico 0.1M	(para ahustar pH a 7.6)
Polietilen glicol 400	4.5% p/v
Agua para inyección	a 100%

(f): Inyección II	10 mg/ml
Compuesto X	1.0% p/v
Fosfato de sodio BP	3.6% p/v
Solución 0.1M de hidróxido de sodio	15.0% v/v
Agua para inyección	a 100%

(g): Inyección III	(1mg/ml, tamponada a pH 6)
Compuesto X	0.1% p/v
Fosfato de sodio BP	2.26% p/v
Ácido cítrico	0.38% p/v
Polietilen glicol 400	3.5% p/v
Agua para inyección	a 100%

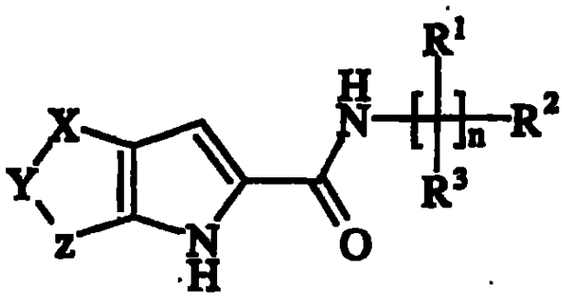
Nota

Las formulaciones anteriores pueden obtenerse mediante procedimientos convencionales bien conocidos en el arte farmacéutico. Los comprimidos (a)-(c) pueden recubrirse entéricamente por medios convencionales, por ejemplo para proporcionar un recubrimiento de ftalato de acetato de celulosa.

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Reivindicaciones

1. Un compuesto de fórmula (I):



en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^6-CR^4=CR^5- y -CR^4=CR^5-NR^6;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquilamino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

R^6 es hidrógeno o C_{1-6}alquilo;

R^1 se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquilsulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, C_{3-8}cicloalquilC_{1-6}alquilo, arilo, arilC_{1-6}alquilo, grupo heterocíclico y (grupo heterocíclico)C_{1-}

$_{6}$alquilo; en donde R^1 pueden sustituirse opcionalmente por uno o más grupos seleccionados de P y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R;

R^2 se selecciona de hidrógeno halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N* -(C_{1-4}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, sulfamoilamino, *N*-(C_{1-6}alquil)sulfamoilamino, *N,N*-(C_{1-6}alquil)$_2$sulfamoilamino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonilaminocarbonilo, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino y un grupo -E-F-G-H;

en donde E y G se seleccionan independientemente de un enlace directo, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- y -C(O)NR^aSO_2-; en donde R^a y R^b se seleccionan independientemente de hidrógeno o C_{1-6}alquilo que se selecciona opcionalmente por un grupo V ;

F es C_{1-6}alquileno sustituido opcionalmente por uno o más Q o un enlace directo;

H se selecciona de arilo, C_{3-8}cicloalquilo y grupo heterocíclico; en donde H puede sustituirse opcionalmente en carbono por uno o más grupos seleccionados de S y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de T;

R^3 es hidrógeno o C_{1-6}alquilo;

n se selecciona de 0-4; en donde los valores de R^1 pueden ser los mismos o diferentes; y en donde los valores de R^3 pueden ser los mismos o diferentes;

P, S y Q se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, arilo y grupo heterocíclico; en donde P, S y Q pueden sustituirse independiente y opcionalmente por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

V se selecciona de halo, litro, ciano, hidroxi,. trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N*,*N*-dimetilcarbamoilo, *N*,*N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N*,*N*-dimetilsulfamoilo, *N*,*N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

R, T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonilo, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo en donde R, T y U pueden

sustituirse opcional e independientemente en carbono por uno o más grupos seleccionados de V;

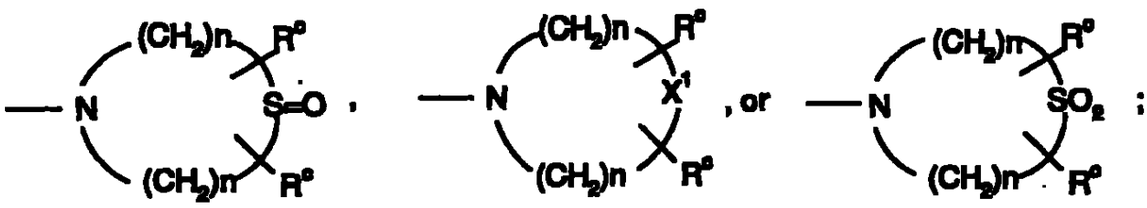
o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*; con las condiciones:

i) cuando -X- Y-Z- es -S-CH=CH-, R^2-(CR^1R^3)$_n$- no puede ser amino, 1-fenil-5-metil-1H-1,5-benzodiazepin-2,4(3H,5H)dion-3-ilo, 1-metil-5-fenil-2-oxo-2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo, 2-(4-fenil-1,2,5,6-tetrahidropirid-1-il)etilo, 3-(4-fenil-1,2,5,6-tetrahidropirid-1-il)propilo, 2-(4-fenilpiperazin-1-il)etilo, 2-(*N*-metilamino)etilo, 2-morfolinoetilo o 2-(*N*-metil-*N*-bencilamino)etilo;

ii) cuando -X-Y-Z- es -CH=CH-S-, R^2-(CR^1R^3)$_n$- no puede ser amino o 1-metil-5-fenil-2-oxo-2,3-dihidro-1H-benzo(E)(1,4)diazepin-3-ilo;

iii) cuando -X-Y-Z- es -CH=C(SO_2NH_2)-S-, R^2-(CR^1R^3)$_n$- no puede ser metilo isobutilo; y

iv) cuando -X-Y-Z- es como se definió inicialmente, n es 1, R^1 es arilmetilo, arilmetilo sustituido, (grupo heterocíclico)metilo y (grupo heterocíclico)metilo sustituido y R^3 es hidrógeno entonces R^2 no es un grupo -C(=O)-A o un grupo -CH(OH)-C(=O)-A en el cual A es NR^dR^d,-$NR^aCH_2CH_2OR^a$, o



cada R^a y R^b es independientemente hidrógeno o -C_1-C_8alquilo;

cada R^d es independientemente hidrógeno C_1-C_8alquilo, C_1-C_8alcoxi, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^c es independientemente hidrógeno -C(=O)OR^a, -OR^a, -SR^a, o -NR^aR^a; y cada n es independientemente 1-3, y

X^1 es NR^a, -CH_2-, O ó S.

2. Un compuesto de fórmula (I) de acuerdo con reivindicación 1 en donde:

-X-Y-Z- se selecciona de -S-CR^4=CR^5- ó -CR^4=CR^5-S-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino;

n es 0;

R^2 es un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo;

H es un C_{3-12}cicloalquilo que se fusiona opcionalmente a un anillo benz en donde H puede sustituirse opcionalmente en carbono por uno o más grupos S que se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, grupos arilo y heterocíclico; en donde S puede sustituirse opcionalmente por uno o más grupos seleccionados de V;

V se selecciona de halo, litro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-

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etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonil, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica.

3. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1 en donde:

-X- Y -Z- se selecciona de -S-CR^4=CR^5- ó -CR^4=CR^5-S-;

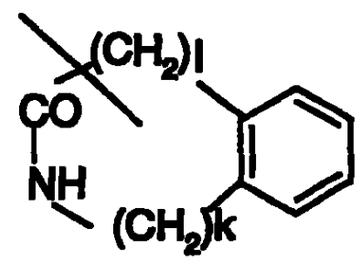
en donde R^4 y R^5 se seleccionan independientemente de hidrógeno halo, litro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*- (C_{1-6}alquil)amino;

n es 0;

R^2 es un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo; y

H es una amida cíclica de fórmula



En el cual k es 0,1,2 ó 3 y l es 0,1,2 ó 3 tal que la suma de k y l es 2 ó 3 y en donde uno de los átomos de carbono regidos por k ó l puede reemplazarse por azufre y en donde H se sustituye opcionalmente en

carbono por uno o más grupos seleccionados de S y pueden sustituirse opcionalmente en forma independiente en nitrógeno por un grupo seleccionado de T;

S se selecciona de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, grupos arilo y heterocíclico; en donde S pueden sustituirse independiente y opcionalmente por uno o más grupos seleccionados de V y en donde si dicho grupo heterocíclico contiene una mitad -NH- ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de U;

T y U se seleccionan independientemente de C_{1-4}alquilo, C_{1-4}alcanoilo, C_{1-4}alquilsulfonil, C_{1-4}alcoxicarbonilo, carbamoilo, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)carbamoilo, fenilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo en donde R, T y U pueden sustituirse independiente y opcionalmente por uno o más grupos seleccionados de V;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonil, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*.

4. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1 en donde:

-X- Y -Z- se selecciona de -S-CR^4=CR^5- ó -CR^4=CR^5-S-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno halo o C_{1-6}alquilo.

n es 1;

R^1 es hidrógeno o arilC_{1-6}alquilo;

R^2 se selecciona de un grupo -E-F-G-H;

en donde E, F y G son cada uno un enlace directo;

H es un grupo heterocíclico insaturado de 5 miembros que contiene por lo menos un átomo de nitrógeno y uno o dos átomos de anillo seleccionados de oxígeno y azufre y en donde H puede sustituirse opcionalmente en carbono por uno o más grupos S que se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N* -(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo y grupos arilo;

R^3 es hidrógeno o C_{1-6}alquilo;

o su sal de aceptación farmacéutica.

5. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1 en donde: -X-Y-Z- se selecciona de -S-CR^4=CR^5- ó -CR^4=CR^5-S-;

en donde R^4 y R^5 se seleccionan independientemente de hidrógeno, halo o C_{1-6}alquilo.

n es 0;

R^2 es un grupo -E-F-G-H;

en donde E es un enlace directo;

F es metileno;

en donde G es -C(O)NR^a-, en donde R^a se selecciona de hidrógeno o C_{1-6}alquilo que se selecciona opcionalmente por un grupo V;

H es arilo que puede sustituirse opcionalmente por uno o más grupos seleccionados de S;

S se selecciona de halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C1-6alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)-*N*-(C_{1-6}alcoxi)carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, C_{3-8}cicloalquilo, grupo arilo y heterocíclico; en donde S puede sustituirse independiente y opcionalmente por uno o más grupos seleccionados de V;

V se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonil, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, morfolino, morfolinocarbonilo, *N*-bencilcarbamoilo, y 4-hidroxipiperidinocarbonilo;

o su sal de aceptación farmacéutica.

6. Un compuesto seleccionado de

2,3-dicloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]
pirrol;

2,3-dicloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[(2-piridil)amino]etil}carbamoil)-4H-tieno[3,2-*b*
]pirrol;

2,3-dicloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-
il)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4H-tieno[3,2-*b*]pirrol;

5-[*N*-(benzoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3,2-*b*]
pirrol;

3-cloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-il)
etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(benzoilmetil)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]
pirrol;

3-cloro-5-{*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

3-cloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]
pirrol;

3-cloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]
pirrol;

3-cloro-5-[*N*-(2-fenoxietil)carbamoil]-4*H*-tieno[3 ,2-*b*]pirrol;

3-cloro-5-{*N*-[2-(1-fenilmetanosulfonamido)etil]carbamoil}-4*H*-tieno[3,2-
b]pirrol;

3-cloro-5-[*N*-(4-oxo-2,3,4,5-tetrahidrobenz[1,5]tialzepin-3-il)carbamoil]-
4*H*-tieno[3 ,2-*b*]pirrol;

2-cloro- 5- [*N*-(benzoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(2-fenil-1-ciclopropil)carbamoil]-4*H*-tieno[3,2-*b*]
pirrol;
2-cloro-5- [*N*-(*N*-fenilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-(*N*-{2-[(2-piridil)amino]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[2-(2-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-[*N* -(2- fenoxietil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[2-(2-tienil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[2-(4-fluorofenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[2-(*N*-metilmetanosulfonamido)-1-(tiazol-2-
il)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[2-(tiomorfolino)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-[*N*-(2,3-dimetil-5-oxo-1-fenil-2,5-dihidro-1*H*-pirazol-4-
il)carbamoil]-4*H*-tieno[3 ,2-*b*]pirrol;
2,3-dicloro-5-[*N*-(4-sulfamoilfenilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-[*N*-(2-hidroxi-1-fenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-{*N*-(2-[3-trifluorometilpirid-2-il)amino]etil)carbamoil]-4*H*-
tieno[3,2-*b*]pirrol;
2,3-dicloro-5-{*N*-[3-(5-tetrazolil)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-[*N*-(5-oxo-3-fenil-4,5-dihidroisoxazol-4-il)carbamoil]-4*H*-
tieno[3,2-*b*]pirrol;
2,3-cloro-5-[*N*-(5-hidroxi-2-oxo-2,3,4,5-tetrahidro-1*H*-benz[*b*]azepin-4-
il)carbamoil]-4H-tieno[3,2-*b*]pirrol;
2-cloro-5-{*N*-[3-(benciloxicarbonilamino)propil]carbamoil]-4*H*-tieno[3,2-*b*
]pirrol;
2,3-dicloro-5-{*N*-[(4-dimetilaminofenil)metil]carbamoil}-4*H*-tieno[3,2-*b*
]pirrol;
5-[*N*-(1-bencil-2-hidroxietil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-{*N*-[2-(fenilamino)etil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-{*N*-(β-(*R*)hidroxifenetil-α-metilfenetil) carbamoil)
-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-[*N*-(β-hidroxifenetil)carbamoil)-4*H*-tieno[3,2-*b*]pirrol;
2,3-dicloro-5-{*N*-[2-(4-hidroxifenil)etil]carbamoil}4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(benzimidazol-2-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-clorofenil)-2-hidroxi-1-(metoxicarbonil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(imidazo[1,2-*a*]pirid-2-il)carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-{*N*-[(benztiazol-2-il)metil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(6-trifluorometilpirid-3-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[(2-piridazinil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxi-3-fenoxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-metilisotiazol-5-l)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(piridazin-3-iloxi)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-(*N*-{2-[(3-trifluorometilpirid-2-il)amino]etil}carbamoil)-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(4-sulfamoilfenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(2-piridil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[1-hidroximetil-2-(4-imidazol)etil]carbamoil}-4*H*-tieno[3 ,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-[(3-quinolil)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

5-{*N*-[3-(4-acetamidofenoxi)-2-hidroxipropil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[3(*N*-metilsulfonilcarbamoil)propil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-{[2-(guanidino)tiazol-4-il]metiltio}etil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-[2-(2,4-dioxoimidazolidin-1-il)etil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

5-{*N*-[2-benciltio-1-(hidroximetil)etil]carbamoil}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-[2-(dimetilaminosulfonilamino)etil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(6-metoxipirid-3-il)metil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

(S)-2,3-dicloro-5-[*N*-(2-oxo-3-fenil-2,3,4,5-tetrahidrooxazol-5-il)metil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[3-(carbamoilmetil)fenoxi]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{[6-(benzo[1,3]dioxol-5-il)-4-metilmorfolin-2-il]metil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-bencilcarbamoil)- 2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-fenetilcarbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(3-fenilpropil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{N-[2-(2-hidroxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(α,α-dimetilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-fenilciclobutil)metil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(β-metilfenetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(*N*-bencilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(*N*-bencil-*N*-metilcarbamoilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-metil-*N*-fenilcarbamoilmetil)carbamoil-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-cianoetil)-*N*-fenilcarbamoilmetil) carbamoil-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-metoxifenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-fluorofenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-nitrofenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,6-dimetilfenil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-metil-*N*-(4-metilfenil)carbamoilmetil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-metil-*N*-(3-metilfenil)carbamoilmetil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-clorofenil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-fenilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(1,1-dimetil-2-hidroxietil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-hidroxietil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-hidroxipropil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroxibutil)carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-[bis(hidroximetil)metil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,3-dihidroxipropil)carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroximetilfenil)carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(5-isoquinolil)carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(3-hidroximetil)fenil]carbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-[4-(2-hidroxietil)fenil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2,4-difluorofenil)-*N*-metil-carbamoilmetil] carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(1,2,3,4-tetrahidro-1-quinolil)carbamoilmetil} carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(2-cianoetil)-*N*-metilcarbamoilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[*N*-(4-hidroxipiperidino)carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-ciclopentilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-isopropilcarbamoilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(*N*-isopropil-*N*-metilcarbamoilmetil)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(tiomorfolinocarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(morfolinocarbonilmetil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(1,1-dioxotiomorfolino)carbonilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(1-oxotiomorfolino)carbonilmetil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(2-indanil)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

5-[*N*-(benz[1,2]oxazol-3-ilmetil)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(hidroximetil)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[(4-fenilisoxasol-3-ilmetil)carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(2-morfolinoetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

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2,3-dicloro-5-(*N*-{2-[2-(metoxicarbonilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-{2-[2-(carboximetoxi)fenil]etil}carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[2-(3-metoxifenil)etil]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-(2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(2-metoxietoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{2-[2-(carbamoilmetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(*N*-metilcarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(*N,N*-dimetilcarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(morfolinocarbonilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

5-(*N*-{2-[2-(*N*-bencilcarbamoilmetoxi)fenil]etil}carbamoil)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{2-[2-(4-hidroxipiperidinocarbamoilmetoxi)fenil]etil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

(*S*)-2-cloro-5-{*N*-[α-(5-etoxicarbonil-1,3,4-oxadiazol-2-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

(*S*)-2-cloro-5-{*N*-[α-(4-metoxicarboniloxazol-5-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-{*N*-[α-(3-piridil)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-{*N*-[*α*-(3-piridil)fenetil)]carbamoil}-4H-tieno[3,2-*b*]pirrol;

(*S*)-2-cloro-5-{*N*-[α-(3-fenil-1,2,4-oxadiazol-5-il)fenetil]carbamoil}-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-((1*S*,2*S*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-((1*R*,2*R*)-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-hidroxi-1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(6-fluoro-1-hidroxiindan-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(7-metoxi-1-oxo-1,2,3,4-tetrahidronaft-2-il)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(2-indanil)carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(3-metilisoxazol-5-il)metil]carbamoil]-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-[*N*-(4-hidroxi-1,1-dioxotetrahidrotiofen-3-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-(*N*-{*N*-metil-*N*-[(1-oxo-1,2,3,4-tetrahidronaft-2-il) metil]carbamoilmetil}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

2-cloro-5-[*N*-(2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-[*N*-(1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-[*N*-(1-metil-2-oxo-1,2,3,4-tetrahidroquinol-3-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2-cloro-5-[*N*-(3-oxo-2,3,4,5-tetrahidro-1*H*-benz[2]azepin-4-il)carbamoil]-6*H*-tieno[2,3-*b*]pirrol;

2,3-dicloro-5-[*N*-(1-metoxiindan-2-il)carbamoil]-4*H*-tieno [3,2-*b*]pirrol;

2,3-dicloro-5-(N-{1-[*N*-(1,1-dimetiletoxi)carbonilamino]indan-2-il }carbamoil)-4*H*- tieno[3,2-*b*]pirrol;

5-[*N*-(1-aminoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol;

5-[*N*-(1-acetamidoindan-2-il)carbamoil]-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol;

2,3-dicloro-5-{*N*-[1-(metanosulfonamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol;

2,3-dicloro-5-{*N*-[1-(*N*-metilacetamido)indan-2-il]carbamoil}-4*H*-tieno[3,2-*b*]pirrol; o su sal de aceptación farmacéutica.

7. Una composición farmacéutica que comprende un compuesto de la formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-6, o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto en asociación con un diluyente o portador de aceptación farmacéutica.

8. El uso de un compuesto de la fórmula como se reivindica en una cualquiera de las reivindicaciones 1 a 6 o su sal de aceptación farmacéutica o éster hidrolizable *in vivo* como un medicamento.

9. El uso de un compuesto de la fórmula como se reivindica en una cualquiera de las reivindicaciones 1 a 6 o su sal de aceptación farmacéutica o éster hidrolizable *in vivo*, como se define más arriba en el texto en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de glucógeno fosforilasa en un animal de sangre caliente tal como un hombre.

INFORME DE BÚSQUEDA INTERNACIONAL

PTC/SE 01/01880

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

IPC7: C07D 495/04, C07D 491/04, C07D 513/04, C07D 487/04, A61K 31/407, A61P 3/10, A61P 9/10

De acuerdo con la Clasificación Internacional de Patentes (IPC) o con ambas, la Clasificación Nacional e IPC

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido y símbolos de clasificación)

IPC7: C07D, A61P

Documentación buscada distinta de la documentación mínima siempre que dichos documentos se incluyan en los campos buscados

SE, DK, FI, sin clases como arriba

Base electrónica de datos consultada durante la búsqueda internacional (nombre de la base de datos y, eventualmente, términos de búsqueda empleados)

EPO-INTERNAL, CHEM. ABS. DATA

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
X	WO 9639384 A1 (PFIZER, INC), 12 de diciembre de 1996 (12.12.96)	1-9
X	EP 0846464 A2 (PFIZER, INC.), 10 de junio de1998 (10.06.98)	1-9
X	US 5998463 A (BERNARD HULIN ET AL), 7 de diciembre de 1999 (07.12.99)	1-9
E, A	EP 1088824 A2 (PFIZER, INC.), 4 de abril de 2001 (04.04.01)	1-9

☒ Otros documentos se enumeran en la continuación de cuadro C.

☒ Véase anexo de la familia de patente.

* Categorías especiales de los documentos citados:

"A" documento que define el estado general del arte pero que no se considera que sea de relevancia particular

"E" documento anterior pero publicado en la fecha de presentación internacional o después

"L" documento que puede arrojar dudas con respecto a la reivindicación (reivindicaciones) de prioridad o que se cita para establecer la fecha de publicación de otra designación u otra razón especial (como se especifica)

"O" documento referente a una divulgación verbal, uso, exhibición u otros medios

"P" documento publicado con anterioridad a la fecha de presentación internacional, pero con posterioridad a la fecha de prioridad reclamada

"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la aplicación pero citado para entender el principio o teoría subyacente a la invención.

"X" documento de particular relevancia; la invención reivindicada no puede considerarse nueva o no puede considerarse que implica un paso innovador si el documento se toma solo.

"Y" documento de particular relevancia; la invención reivindicada no puede considerarse que implica un paso innovador si el documento se combina con uno o más de dichos documentos, siendo obvia dicha combinación a una persona con habilidades en el arte.

"&" documento miembro de la misma familia de patente

Fecha de la conclusión actual de la búsqueda internacional	Fecha de envío por correo del informe de búsqueda internacional
19 de diciembre de 2001	03/01/2002
Nombre y dirección postal de la Oficina de Búsqueda Internacional (ISA) Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsímile No. + 46 8 666 02 86	**Funcionario autorizado** Eva Johansson/Eö Teléfono No. + 46 8 782 25 00

Formulario PCT/ISA/210 (segunda hoja) (julio 1998)

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/SE 01/01880

C. (continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría [*]	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
A	WO 9946268 A1 (NOVO NORDISK A/S), 16 de septiembre de 1999 (16.09.99)	1-9
A	ES 2081747 A1 (LABORATORIOS DEL DR. ESTEVE, S.A.), 1 de marzo de 1996 (01.03.96)	1-9

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de familia de patente

06/11/01

Solicitud Internacional No.
PCT-SE 01/01880

Documento de patente citado en el informe de búsqueda			Fecha de Publicación	Miembro (s) de familia de patente			Fecha de publica//ión
WO	969384	A1	12/12/96	AP	623	A	19/12/97
				AP	9600803	D	00/00/00
				AU	701465	B	28/01/99
				AU	5462696	A	19/12/96
				BG	100547	A	31/12/96
				BR	9602542	A	27/10/98
				CA	2224062	A	12/12/96
				CN	1140709	A	22/01/97
				CN	1142492	A	12/02/97
				CZ	9601573	A	12/03/97
				EP	0832065	A, B	01/04/98
				SE	0832065	T3	
				FI	974436	A	27/01/98
				HR	960244	A	31/12/97
				HU	9601475	A	28/09/98
				IL	118029	D	00/00/00
				JP	10511687	T	10/11/98
				LV	11613	A, B	20/12/96
				NO	306398	B	01/11/99
				NO	911664	A	09/12/96
				NZ	286460	A	24/09/98
				PL	314561	A	09/12/96
				SG	44947	A	19/12/97
				SI	9600177	A	28/02/97
				SK	69996	A	06/08/97
				AT	206702	T	15/10/01
				KR	191992	B	15/06/99
				NO	990405	A	28/01/99
				RU	2143424	C	27/12/99
				TR	961048	A	00/00/00
				US	6107329	A	22/08/00
EP	0846464	A2	10/06/98	AU	717547	B	30/03/00
				AU	4686997	A	11/06/98
				CA	2223317	A	05/06/98
				HU	9702356	A	28/08/98
				IL	122313	D	00/00/00
				JP	10194990	A	28/07/98
				US	5952322	A	14/09/99
				ZA	9710907	A	04/06/99
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				JP	2001131181	A	15/05/01
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				BR	9908723	A	21/11/00
				CN	1300279	T	20/06/01
				EP	1062218	A	27/12/00
				EP	1080068	A	07/03/01
				NO	20004526	A	08/11/00
				PL	342851	A	16/07/01
				WO	9946237	A	16/09/99

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de familia de patente

06/11/01

Solicitud Internacional No. PCT/SE 01/01880

Documento de patente citado en el informe de búsqueda	Fecha de Publicación	Miembro (s) de familia de patente	Fecha de publicación
ES 2081747 A1	01/03/96	ES 1025262 U, Y	01/12/93

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional No.
PTC/SE 01/01880

Cuadro I Observaciones donde se comprobó la imposibilidad de búsqueda de ciertas reivindicaciones (Continuación del ítem 1 de la primera hoja)

El presente informe de búsqueda internacional no se ha establecido con respecto a ciertas reivindicaciones bajo artículo 17(2)(a) por las siguientes razones:

1. ☒ Reivindicaciones Nos.: **8**
porque se refieren a un asunto que no se requiere buscar por esta administración, a saber:
véase hoja siguiente

2. ☐ Reivindicaciones Nos.:
porque se refieren a partes de la solicitud internacional que no cumplen los requerimientos prescritos en tal medida que no puede llevarse a cabo una búsqueda internacional significativa, específicamente:

3. ☐ Reivindicaciones Nos.:
porque son reivindicaciones dependientes y no están redactadas de acuerdo con las frases segunda y tercera de la regla 6.4(a).

Cuadro II Observaciones donde falta la unidad de invención (Continuación del ítem 2 de la primera hoja)

Esta Administración de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. ☐ Como todos los honorarios requeridos de búsqueda adicional fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre todas las reivindicaciones susceptibles de búsqueda.

2. ☐ Como todas las reivindicaciones susceptibles de búsqueda pudieron buscarse sin un esfuerzo que justificara unos honorarios adicionales, esta administración no solicitó el pago de honorarios adicionales de ningún tipo.

3. ☐ Como sólo algunos de los honorarios requeridos de búsqueda adicional fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre únicamente aquellas reivindicaciones para las cuales se pagaron honorarios, específicamente las reivindicaciones Nos.:

4. ☐ No se pagaron oportunamente los honorarios requeridos de búsqueda adicional por el solicitante. En consecuencia, este informe de búsqueda internacional se restringe a la invención mencionada primeramente en las reivindicaciones; ella está cubierta por las reivindicaciones Nos.:

Anotación de protesta ☐ Los honorarios de búsqueda adicional fueron acompañados por la protesta del solicitante.

☐ Los honorarios de búsqueda adicional no estuvieron acompañados de protesta.

INFORME DE BÚSQUEDA INTERNACIONAL	Solicitud Internacional No. PTC/SE 01/01880

Reivindicación 8 se refiere a un método de tratamiento del organismo humano o animal mediante cirugía o mediante terapia/un método diagnóstico practicado en el organismo humano o animal/regla 39.1 (iv). No obstante, se ha realizado una búsqueda para esta reivindicación. La búsqueda se basó en los supuestos efectos del compuesto/composición.

90.116 169

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

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WO 02/20530 A1

(54) Title: BICYCLIC PYRROLYL AMIDES AS GLUCOGEN PHOSPHORYLASE INHIBITORS

(57) Abstract: Heterocyclic amide derivatives, of formula (I): wherein -X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^6-CR^4=CR^5- and -CR^4=CR^5-NR^6-; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof; (with provisos); possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of said heterocyclic amide derivatives and pharmaceutical compositions containing them are described.

Bicyclic pyrrolyl amides as glucogen phos phorylase inhibitors

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof. These heterocyclic amides possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods for the treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., et al, (1992) Diabetes Care 15; 318 - 355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) Lancet 348, 1657-1658; Coutinho, M. et al (1999) Diabetes Care 22; 233-240; Shaw, J.E. et al (2000) Diabetes Care 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); the reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 diabetes.

It has been estimated that, after an overnight fast, 74% of HGO is derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al (1997) Am J Physiol, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues such as muscle and neuronal tissue.

Liver glycogen phosphorylase activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetalogia 43, 589-597).

Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP91149 and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81, WO 96/39384 and WO 96/39385). Additionally, plasma glucose concentration is reduced, in a dose related manner, in db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of such agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose levels following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physiol, 273: E868).

ES 2,081,747 discloses that certain amide derivatives of 4*H*-thieno[3,2-b]pyrroles and 4*H*-thieno[2,3-b]pyrroles are CCK antagonists and are useful in the treatment of gastric secretion disorders and in the regulation of appetite. The compounds disclosed in this document are disclaimed from the compound claims of the present invention.

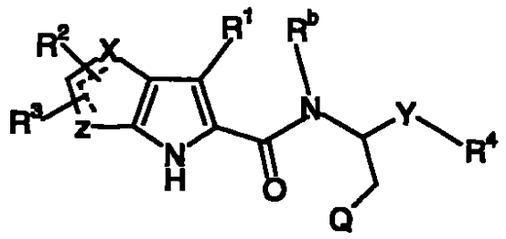
US 3,706,810 discloses that certain N-(aminoalkyl) derivatives of thieno[3,2-b]pyrrole-5-carboxamide are useful as analgesic and anti-depressant agents. The compounds disclosed in this document are disclaimed from the compound claims of the present invention.

US 4,751,231 discloses that certain thieno[2,3-b]pyrrole-5-sulfonamides are useful in the treatment of elevated intraocular pressure and glaucoma. Certain amides are disclosed as intermediates. The compounds disclosed in this document are disclaimed from the compound claims of the present invention.

US 4,794,120 discloses 4*H*-thieno[3,2-b]pyrrole-5-carboxylic acid hydrazide and *6H*-thieno[2,3-b]pyrrole-5-carboxylic acid hydrazide as intermediates in the preparation of corresponding (5-nitro-2-furanyl)methylenehydrazides which are antibacterials, fungicides and protozoacides. The compounds disclosed in this document are disclaimed from the compound claims of the present invention.

Co-pending application EP 1088824 discloses that a compound of Formula A:

a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically



A

acceptable salt of the prodrug,

wherein

Q is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each z and X are independently (C, CH or CH_2), N, O or S;

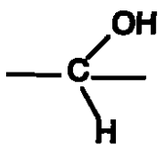
X^1 is NR^a, $-CH_2-$, O or S;

each — is independently a bond or is absent, provided that both — are not simultaneously bonds;

R^1 is hydrogen, halogen, $-OC_1-C_8$alkyl, $-SC_1-C_8$alkyl, $-C_1-C_8$alkyl, $-CF_3$, $-NH_2$, $-NHC_1-C_8$alkyl, $-N(C_1-C_8alkyl)_2$, $-NO_2$, -CN, $-CO_2H$, $-CO_2C_1-C_8$alkyl, $-C_2-C_8$alkenyl, or $-C_2-C_8$alkynyl;

each R^a and R^b is independently hydrogen or $-C_1-C_8$alkyl;

Y is



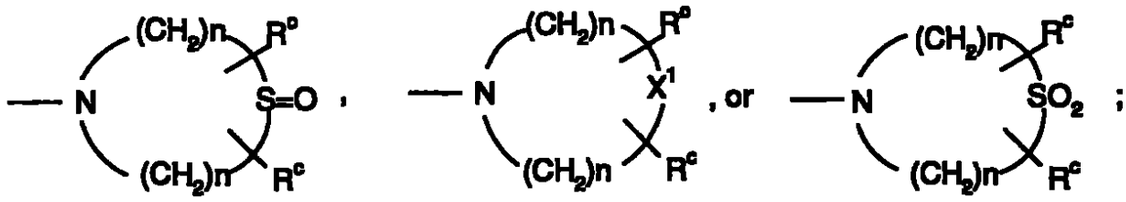
or absent;

R^2 and R^3 are independently hydrogen, halogen, $-C_1-C_8$alkyl, -CN, $-C\equiv C-Si(CH_3)_3$, $-OC_1-C_8$alkyl, $-SC_1-C_8$alkyl, $-CF_3$, $-NH_2$, $-NHC_1-C_8$alkyl, $-N(C_1-C_8alkyl)_2$, $-NO_2$, $-CO_2H$, $-CO_2C_1-C_8$alkyl, $-C_2-C_8$alkenyl, or

$-C_2$-C_8alkynyl, or R^2 and R^3 together with the atoms on the ring to which they are attached form a five or six membered ring containing from 0 to 3 heteroatoms and from 0 to 2 double bonds;

R^4 is $-C(=O)$-A;

A is $-NR^dR^d$, $-NR^aCH_2CH_2OR^a$,



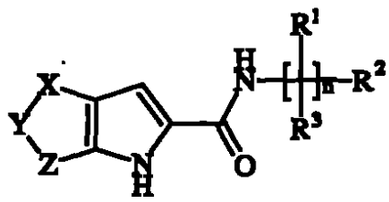
each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3,

are useful in treating diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia. These compounds are disclaimed from the present application.

The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

The present invention provides a compound of formula (I):



(I)

wherein:

-X-Y-Z- is selected from $-S-CR^4=CR^5-$, $-CR^4=CR^5-S-$, $-O-CR^4=CR^5-$, $-CR^4=CR^5-O-$, $-N=CR^4-S-$, $-S-CR^4=N-$, $-NR^6-CR^4=CR^5-$ and $-CR^4=CR^5-NR^6-$;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

R^6 is hydrogen or C_{1-6}alkyl;

R^1 is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- and

-C(O)NR^{a}SO$_2$-; wherein R^a and R^b are independently selected from hydrogen or C$_{1-6}$alkyl which is optionally substituted by a group V ;

F is C$_{1-6}$alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C$_{3-8}$cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

R^3 is hydrogen or C$_{1-6}$alkyl;

n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{1-6}$alkoxy, C$_{1-6}$alkanoyl, C$_{1-6}$alkanoyloxy, *N*-(C$_{1-6}$alkyl)amino, *N,N*-(C$_{1-6}$alkyl)$_2$amino, C$_{1-6}$alkanoylamino, *N*-(C$_{1-6}$alkyl)carbamoyl, *N,N*-(C$_{1-6}$alkyl)$_2$carbamoyl, *N*-(C$_{1-6}$alkyl)-*N*-(C$_{1-6}$alkoxy)carbamoyl, C$_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, C$_{1-6}$alkoxycarbonyl, C$_{1-6}$alkoxycarbonylamino, *N*-(C$_{1-6}$alkyl)sulphamoyl, *N,N*-(C$_{1-6}$alkyl)$_2$sulphamoyl, C$_{1-6}$alkylsulphonylamino, C$_{1-6}$alkylsulphonyl-*N*-(C$_{1-6}$alkyl)amino, C$_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from C$_{1-4}$alkyl, C$_{1-4}$alkanoyl, C$_{1-4}$alkylsulphonyl, C$_{1-4}$alkoxycarbonyl, carbamoyl, *N*-(C$_{1-4}$alkyl)carbamoyl,

N,N-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

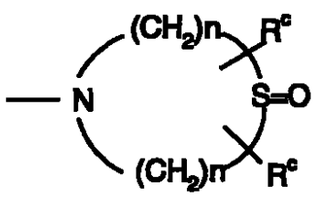
with the provisos:

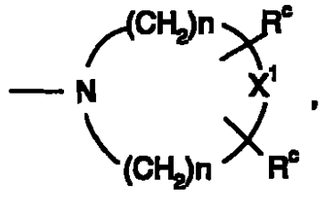
i) when -X-Y-Z- is -S-CH=CH-, R^2-(CR^1R^3)$_n$- cannot be amino, 1-phenyl-5-methyl-1H-1,5-benzodiazepine-2,4(3H,5H)dion-3-yl, 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl, 2-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)ethyl, 3-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)propyl, 2-(4-phenylpiperazin-1-yl)ethyl, 2-(*N*-methylamino)ethyl, 2-morpholinoethyl or 2-(*N*-methyl-*N*-benzylamino)ethyl;

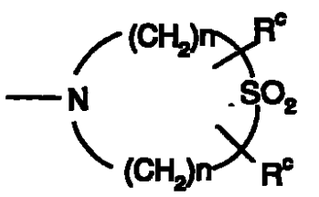
ii) when -X-Y-Z- is -CH=CH-S-, R^2-(CR^1R^3)$_n$- cannot be amino or 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl;

iii) when -X-Y-Z- is -CH=C(SO_2NH_2)-S-, R^2-(CR^1R^3)$_n$- cannot be methyl or isobutyl; and

iv) when -X-Y-Z- is as initially defined, n is 1, R^1 is arylmethyl, substituted arylmethyl, (heterocyclic group)methyl and substituted (heterocyclic group)methyl and R^3 is hydrogen then R^2 is not a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, -$NR^aCH_2CH_2OR^a$, or



,


, or


;

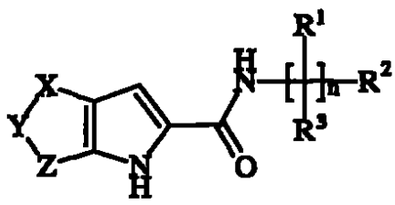
each R^a and R^b is independently hydrogen or –C_1-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, -C(=O)OR^a, -OR^a, -SR^a, or -NR^aR^a; and each n is independently 1-3, and

X^1 is NR^a, -CH_2-, O or S.

In another aspect the present invention provides a compound of formula (I):



(I)

wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^6-CR^4=CR^5- and -CR^4=CR^5-NR^6-;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy; C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

R^6 is hydrogen or C_{1-6}alkyl;

R^1 is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (*heterocyclic group*)C_{1-6}alkyl; *wherein R^1 may be optionally substituted on carbon by one or* more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl,

C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO$_2$-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^{a}C(O)-, -C(O)NR^a-, -SO$_2$NR^a-, -NR^{a}SO$_2$-, -NR^{a}C(O)NR^b-, -OC(O)NR^a-, -NR^{a}C(O)O-, -NR^{a}SO$_2$NR^b-, -SO$_2$NR^{a}C(O)- and -C(O)NR^{a}SO$_2$-; wherein R^a and R^b are independently selected from hydrogen or C_{1-6}alkyl;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

R^3 is hydrogen or C_{1-6}alkyl;

n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl; C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

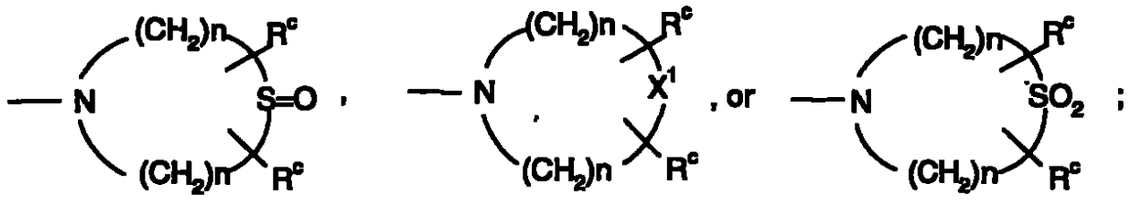
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl,

acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

R, T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

with the provisos:i)when -X-Y-Z- is -S-CH=CH-, R^2-$(CR^1R^3)_n$- cannot be amino, 1-phenyl-5-methyl-1H-1,5-benzodiazepine-2,4(3H,5H)dion-3-yl, 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl, 2-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)ethyl, 3-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)propyl, 2-(4-phenylpiperazin-1-yl)ethyl, 2-(*N*-methylamino)ethyl, 2-morpholinoethyl or 2-(*N*-methyl-*N*-benzylamino)ethyl;

ii)when -X-Y-Z- is -CH=CH-S-, R^2-$(CR^1R^3)_n$- cannot be amino or 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl; iii)when -X-Y-Z- is -CH=C(SO_2NH_2)-S-, R^2-$(CR^1R^3)_n$- cannot be methyl or isobutyl; and iv) when -X-Y-Z- is as initially defined, n is 1, R^1 is arylmethyl, substituted arylmethyl, (heterocyclic group)methyl and substituted (heterocyclic group)methyl and R^3 is hydrogen then R^2 is not a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, $-NR^aCH_2CH_2OR^a$, or



each R^a and R^b is independently hydrogen or –C_1-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3, and

X^1 is NR^a, $-CH_2-$, O or S.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "arylC_{1-6}alkyl" includes arylC_{1-4}alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxide(s). Examples and suitable values of the term "heterocyclic group" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, 1,3-dioxolanyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, 2-oxazolidinonyl, 5-isoxazolonyl, benz-3-azepinyl, 1,4-benzodioxanyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-pyrazolin-5-onyl, tetrahydropyranyl, benzimidazolyl, benzthiazolyl, imidazo[1,2-a]pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone 2,3-dihydro-1,5-benzothiazepin-4(5H)-one. Preferably a "heterocyclic group" is pyridyl, imidazolyl, thiazolyl, quinolyl, thienyl, 1,3-benzodioxolyl, 1,3-dioxolanyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, 2-oxazolidinonyl, 5-isoxazolonyl, benz-3-azepinyl, hydantoinyl, 1,4-benzodioxanyl, thiomorpholino, 3-pyrazolin-5-onyl, benzimidazolyl, benzthiazolyl, imidazo[1,2-a]pyridyl, pyrimidyl, pyrazinyl, and 2,3-dihydro-1,5-benzothiazepin-4(5H)-one

"Aryl" is a partially saturated or unsaturated, mono or bicyclic ring containing 4-12 carbon atoms, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Preferably aryl is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl (tetralinyl) or indanyl. More preferably aryl is phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl. Most preferably aryl is phenyl, or naphthyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include C_{1-4}alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" include methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2" include C_{1-4}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkylsulphonylamino" include methylsulphonylamino, ethylsulphonylamino and propylsulphonylamino. Examples of "C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino" include methylsulphonyl-*N*-methylamino, ethylsulphonyl-*N*-methylamino and propylsulphonyl-*N*-ethylamino. Examples of "C_{1-6}alkanoyl" include C_{1-4}alkanoyl, propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-(C_{1-4}alkyl)carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{3-8}cycloalkyl ring" are cyclopropyl and cyclohexyl. Examples of "(heterocyclic group)C_{1-6}alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of "C_{3-8}cycloalkylC_{1-6}cycloalkyl" include cyclopropylmethyl and 2-cyclohexylpropyl. "*N*-(C_{1-6}alkyl)sulphamoylamino" are *N*-(methyl)sulphamoylamino and *N*-(ethyl)sulphamoylamino. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoylamino" are *N,N*-(dimethyl)sulphamoylamino and *N*-(methyl)-*N*-(ethyl)sulphamoylamino. Examples of "C_{1-6}alkylsulphonylaminocarbonyl" include methylsulphonylaminocarbonyl, ethylsulphonylaminocarbonyl and propylsulphonylaminocarbonyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is

sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess glycogen phosphorylase inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess glycogen phosphorylase inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be

understood that the invention encompasses all such solvated forms which possess glycogen phosphorylase inhibitory activity.

Preferred values of R^1, R^2, R^3, -X-Y-Z-and n are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably -X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5- and -N=CR^4-S-.

More preferably -X-Y-Z- is selected from -S-CR^4=CR^5- and -CR^4=CR^5-S-.

In one aspect of the invention preferably -X-Y-Z- is selected from -S-CR^4=CR^5-.

In another aspect of the invention preferably -X-Y-Z- is selected from -CR^4=CR^5-S-.

Preferably R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

More preferably R^4 and R^5 are independently selected from hydrogen, chloro, bromo or methyl.

Particularly R^4 and R^5 are independently selected from hydrogen or chloro.

More particularly R^4 and R^5 are both chloro.

Preferably -X-Y-Z- is selected from -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH- , -N=C(Me)-S- and -S-CH=CCl-.More preferably -X-Y-Z- is selected from -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH- and -N=C(Me)-S-.

Most preferably -X-Y-Z- is selected from -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH- and -S-CH=C(Cl)-.

Particularly -X-Y-Z- is selected from -S-C(Cl)=C(Cl)-.

In one aspect of the invention, preferably R^6 is hydrogen.

In another aspect of the invention, preferably R^6 is C_{1-6}alkyl.

Preferably R^1 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, arylC_{1-6}alkyl and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P; and

P is selected from hydroxy and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino.

More preferably R^1 is selected from hydrogen, hydroxy, methyl, methoxycarbonyl, benzyl and imidazol-4-ylmethyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P; and

P is selected from hydroxy and mesyl-*N*-(methyl)amino.

Particularly R^1 is selected from hydrogen, hydroxy, methyl, methoxycarbonyl, mesyl-*N*-(methyl)aminomethyl, benzyl, hydroxymethyl and imidazol-4-ylmethyl.

More particularly R^1 is selected from hydrogen, mesyl-*N*-(methyl)aminomethyl or benzyl.

Preferably R^2 is selected from *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylaminocarbonyl and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- and -$NR^aC(O)O$-; wherein R^a is hydrogen;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

S is selected from halo, hydroxy, trifluoromethyl, sulphamoyl, ureido, C_{1-6}alkyl, C_{1-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino and aryl; wherein S may be optionally substituted on carbon by one or more groups selected from V;

Q is hydroxy;

V is carbamoyl; and

T is independently selected from C_{1-4}alkyl or phenyl.

More preferably R^2 is selected from *N,N*-dimethylcarbamoyl, *N,N*-dimethylsulphamoylamino, mesylaminocarbonyl and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- and -$NR^aC(O)O$-; wherein R^a is hydrogen;

F is methylene optionally substituted by one or more Q or a direct bond;

H is selected from phenyl, naphthyl, cyclopropyl, thiomorpholino, pyridyl, thiazolyl, isothiazolyl, morpholinyl, 2,3-dihydro-1,5-benzothiazepin-4(5H)-onyl, 5-oxo-3-pyrazolinyl, 2-oxazolidinonyl, 5-hydroxy-1,3,4,5-tetrahydro-benzo[b]azepin-2-onyl, 5-oxo-2-isoxazolinyl, imidazo[1,2-a]pyridinyl, benzothiazolyl, 2,5-dioxoimidazolidinyl, pyrazinyl, pyridazinyl, imidazolyl, benzimidazolyl, tetrazolyl, quinolyl, 1,3-dioxolanyl and thienyl; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if a heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

S is selected from fluoro, chloro, hydroxy, trifluoromethyl, sulphamoyl, ureido, methyl, ethyl, methoxy, *N,N*-dimethylamino, acetamido and phenyl; wherein S may be optionally substituted on carbon by one or more groups selected from V;

Q is hydroxy;

V is carbamoyl; and

T is independently selected from methyl or phenyl.

Particularly R^2 is selected from *N,N*-dimethylcarbamoyl, *N,N*-dimethylsulphamoyl-amino, mesylaminocarbonyl, 2-methoxyphenyl, phenoxy, 2-phenylcyclopropyl, thien-2-yl, 4-fluorophenyl, benzoyl, thiomorpholino, anilinocarbonyl, pyrid-2-ylamino, thiazol-2-yl, benzylsulphonylamino, 2,3-dihydro-1,5-benzothiazepin-4(5H)-one-3-yl, 1-phenyl-2,3-dimethyl-5-oxo-3-pyrazolin-4-yl, 3-phenyl-2-oxazolidinon-5-yl, 5-hydroxy-1,3,4,5-tetrahydro-benzo[b]azepin-2-onyl, 3-phenyl-5-oxo-2-isoxazolin-4-yl, imidazo[1,2-a]pyridin-2-yl, benzothiazol-2-yl, 2,5-dioxoimidazolidin-3-yl, naphth-2-ylaminocarbonyl, phenyl, 4-sulphamoylphenethyl, 4-(*N,N*-dimethylamino)phenyl, 4-sulphamoylphenyl, anilino, 4-hydroxyphenyl, quinolin-3-yl, 4-chlorophenyl, 2-methoxypyrid-5-yl, 3-methylisothiazol-5-yl, 3-trifluoromethylpyrid-2-yl, tetrazol-5-yl, benzyloxycarbonylamino, benzimidazol-2-yl, 2-trifluoromethylpyrid-5-yl, pyridazin-2-yl, pyridazin-3-yloxy, pyrid-2-yl, imidazol-5-yl, 4-acetamidophenoxy, 2-ureidothiazol-4-yl, benzylthio, 2-phenyl-1,3-dioxolan-2-yl, 4-carbamoylmethylphenoxy, (*N*-benzylcarbamoylmethyl), phenethyl, 3-phenylpropyl, [2-(2-hydroxyphenyl)ethyl], -(α,α-dimethylphenethyl), (1-phenylcyclobutyl)methyl), (β-methylphenethyl), (1,2,3,4-tetrahydronaphth-2-yl), benzyl, (*N*-benzyl-*N*-methylcarbamoylmethyl), (*N*-methyl-*N*-phenylcarbamoylmethyl), [*N*-(2-cyanoethyl)-*N*-phenylcarbamoylmethyl], [N-(4-methoxyphenyl)carbamoylmethyl], [*N*-(4-fluorophenyl)carbamoylmethyl], [*N*-(4-nitrophenyl)carbamoylmethyl], [*N*-(2,6-dimethylphenyl)carbamoylmethyl], [*N*-methyl-*N*-(4-methylphenyl)carbamoylmethyl], [*N*-methyl-*N*-(3-methylphenyl)carbamoylmethyl], [*N*-(3-chlorophenyl) *N*-methylcarbamoyl-methyl], [*N*-(2-hydroxyethyl)-*N*-phenylcarbamoylmethyl], [*N*-(1,1-dimethyl-2-hydroxyethyl)carbamoylmethyl], [*N*-(2-hydroxyethyl)-*N*-methylcarbamoyl-methyl], [*N*-(2-hydroxyethyl)carbamoylmethyl] , [*N*-(3-hydroxypropyl)carbamoylmethyl], [*N*-(4-hydroxybutyl)carbamoylmethyl], {*N*-[bis(hydroxymethyl)methyl]carbamoylmethyl}, [*N*-(2,3-dihydroxypropyl)carbamoylmethyl], [N-(4-hydroxymethylphenyl)-carbamoylmethyl], [*N*-(5-isoquinolyl)carbamoylmethyl], [*N*-(3-hydroxymethy)lphenyl]-carbamoylmethyl], {*N*-[4-

(2-hydroxyethyl)phenyl]carbamoyl-methyl}, [*N*-(2,4-difluorophenyl)-*N*-methyl-carbamoylmethyl], [(1,2,3,4-tetrahydro-1-quinolyl)carbonyl-methyl], [*N*-(2-cyanoethyl)-*N*-methylcarbamoylmethyl], [*N*-(4-hydroxypiperidino)-carbamoylmethyl], (*N*-cyclopentylcarbamoylmethyl), (*N*-isopropyl-carbamoylmethyl), (*N*-isopropyl-*N*-methylcarbamoylmethyl), (thiomorpholin-carbonylmethyl), (morpholino-carbonylmethyl), [(1,1-dioxothiomorpholino)carbonyl-methyl], [(1-oxothiomorpholino)-carbonylmethyl], (2-indanyl), (benz[1,2]oxazol-3-ylmethyl), {2-[2-(hydroxymethyl)phenyl]-ethyl}, (4-phenylisoxazol-3-ylmethyl), {2-[2-(2-morpholino-ethoxy)phenyl]ethyl}, {2-[2-(methoxycarbonyl-methoxy)phenyl]ethyl}, {2-[2-(carboxy-methoxy)phenyl]ethyl}, [2-(3-methoxyphenyl)ethyl], (2-oxo-1,2,3,4-tetrahydroquinol-3-yl), {2-[2-(2-methoxyethoxy)phenyl]ethyl}, {2-[2-(carbamoylmethoxy)phenyl]ethyl}, {2-[2-(N-methylcarbamoylmethoxy)phenyl]ethyl}, {2-[2-(N,N-dimethylcarbamoyl-methoxy)phenyl]ethyl}, 2-[2-(morpholinocarbonylmethoxy)-phenyl]ethyl, 2-[2-(N-benzylcarbamoylmethoxy)phenyl]ethyl, 2-[2-(4-hydroxypiperidinocarbonylmethoxy)-phenyl]ethyl,[1-(5-ethoxycarbonyl-1,3,4-oxadiazo-2-yl)-2-phenylethyl], [1-(4-methoxycarbonyl-oxazo-5-yl)-2-phenylethyl], [2-phenylethyl-1-(pyrid-3-yl)], [2-phenylethyl - 1-(3-phenyl-1,2,4-oxadiazo-5-yl)], (1-hydroxyindan-2-yl), [(1S,2S)-2-indan-1-ol], [(1R,2R)-2-indan-1-ol], (3-indanyl), (1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl) , (6-fluoro-1-hydroxyindan-2-yl), (7-methoxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl), -(3-methylisoxazol-5-yl)methyl], (4-hydroxy-1,1-dioxotetrahydrothiophen-3-yl), -{*N*-methyl-*N*-[(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methyl]carbamoylmethyl}, (3-methylisoxazol-5-yl)methyl], (4-hydroxy-1,1-dioxotetrahydrothiophen-3-yl), {*N*-methyl-*N*-[(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methyl]carbamoylmethyl}, (2-oxo-1,2,3,4-tetrahydroquinol-3-yl), (1,2,3,4-tetrahydroquinol-3-yl), (1-methyl-2-oxo-1,2,3,4-tetrahydroquinol-3-yl), (3-oxo-2,3,4,5-tetrahydro-1*H*-benz[2]azepin-4-yl), (1-methoxyindan-2-yl), {1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}, (1-aminoindan-2-yl)], (1-acetamidoindan-2-yl), [1-(methanesulphonamido)indan-2-yl], [1-(methylamino)indan-2-yl], or [1-(*N*-methylacetamido)indan-2-yl] .

More particularly R^2 is selected from *N,N*-dimethylcarbamoyl, *N,N*-dimethylsulphamoylamino, mesylaminocarbonyl, 2-methoxyphenyl, phenoxy, 2-phenylcyclopropyl, thien-2-yl, 4-fluorophenyl, benzoyl, thiomorpholino, anilinocarbonyl, pyrid-2-ylamino, thiazol-2-yl, benzylsulphonylamino, 2,3-dihydro-1,5-benzothiazepin-4(5H)-

one-3-yl, 1-phenyl-2,3-dimethyl-5-oxo-3-pyrazolin-4-yl, 3-phenyl-2-oxazolidinon-5-yl, 5-hydroxy-1,3,4,5-tetrahydro-benzo[b]azepin-2-onyl, 3-phenyl-5-oxo-2-isoxazolin-4-yl, imidazo[1,2-a]pyridin-2-yl, benzothiazol-2-yl, 2,5-dioxoimidazolidin-3-yl, naphth-2-ylaminocarbonyl, phenyl, 4-sulphamoylphenethyl, 4-(*N,N*-dimethylamino)phenyl, 4-sulphamoylphenyl, anilino, 4-hydroxyphenyl, quinolin-3-yl, 4-chlorophenyl, 2-methoxypyrid-5-yl, 3-methylisothiazol-5-yl, 3-trifluoromethylpyrid-2-yl, tetrazol-5-yl, benzyloxycarbonylamino, benzimidazol-2-yl, 2-trifluoromethylpyrid-5-yl, pyridazin-2-yl, pyridazin-3-yloxy, pyrid-2-yl, imidazol-5-yl, 4-acetamidophenoxy, 2-ureidothiazol-4-yl, benzylthio, 2-phenyl-1,3-dioxolan-2-yl and 4-carbamoylmethylphenoxy.

Most particularly R^2 is selected from *N,N*-dimethylcarbamoyl, phenoxy, 2-phenylcyclopropyl, thien-2-yl, 4-fluorophenyl, benzoyl, thiomorpholino, anilinocarbonyl, pyrid-2-ylamino or thiazol-2-yl.

Preferably R^3 is hydrogen.

Preferably n is selected from 0-3; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different.

More preferably n is selected from 0-2; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different.

In one aspect of the invention preferably n is 2; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different.

In one aspect of the invention preferably n is 1..

In one aspect of the invention preferably n is 0.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5- and -N=CR^4-S-;

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

R^1 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, arylC_{1-6}alkyl and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P; and

P is selected from hydroxy and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

R^2 is selected from *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylaminocarbonyl and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -C(O)-, -NR^a-, -C(O)NR^a-, -NR^aSO_2- and -$NR^aC(O)O$-; wherein R^a is hydrogen;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

S is selected from halo, hydroxy, trifluoromethyl, sulphamoyl, ureido, C_{1-6}alkyl, C_{1-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino and aryl; wherein S may be optionally substituted on carbon by one or more groups selected from V;

Q is hydroxy;

V is carbamoyl; and

T is independently selected from C_{1-4}alkyl or phenyl;

R^3 is hydrogen;

n is selected from 0-3; wherein the values of R^1 may be the same or different;

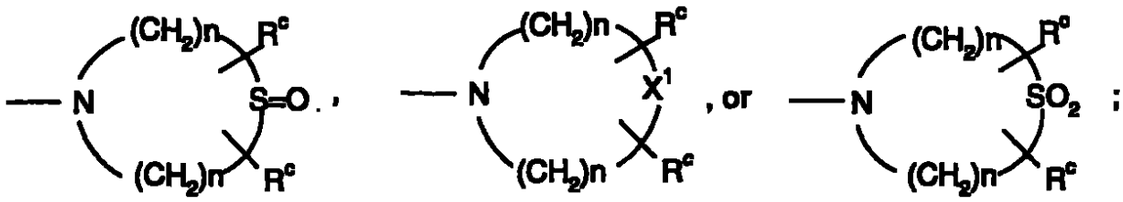
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

with the provisos:

i) when -X-Y-Z- is -S-CH=CH-, R^2-(CR^1R^3)$_n$- cannot be 1-phenyl-5-methyl-1H-1,5-benzodiazepine-2,4(3H,5H)dion-3-yl, 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl, 2-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)ethyl, 3-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)propyl, 2-(4-phenylpiperazin-1-yl)ethyl or 2-morpholinoethyl;

ii) when -X-Y-Z- is -CH=CH-S-, R^2-(CR^1R^3)$_n$- cannot be 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl;and

iii) when -X-Y-Z- is as initially defined, n is 1, R^1 is arylmethyl, substituted arylmethyl, (heterocyclic group)methyl and substituted (heterocyclic group)methyl and R^3 is hydrogen then R^2 is not a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, -$NR^aCH_2CH_2OR^a$, or



each R^a and R^b is independently hydrogen or $-C_1$-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3, and

X^1 is NR^a, $-CH_2-$, O or S.

In yet another aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from -S-C(Cl)=C(Cl)-, -S-C(Cl)=CH-, -S-CH=C(Cl)-, -S-C(Br)=CH-, -S-CH=CH-, -CH=CH-S-, -O-CH=CH- and -N=C(Me)-S-;

R^1 is selected from hydrogen, hydroxy, methyl, methoxycarbonyl, mesyl-*N*-(methyl)aminomethyl and hydroxymethyl ;

R^2 is selected from *N,N*-dimethylcarbamoyl, *N,N*-dimethylsulphamoylamino, mesylaminocarbonyl, 2-methoxyphenyl, phenoxy, 2-phenylcyclopropyl, thien-2-yl, 4-fluorophenyl, benzoyl, thiomorpholino, anilinocarbonyl, pyrid-2-ylamino, thiazol-2-yl, benzylsulphonylamino, 2,3-dihydro-1,5-benzothiazepin-4(5H)-one-3-yl, 1-phenyl-2,3-dimethyl-5-oxo-3-pyrazolin-4-yl, 3-phenyl-2-oxazolidinon-5-yl, 5-hydroxy-1,3,4,5-tetrahydro-benzo[B]azepin-2-onyl, 3-phenyl-5-oxo-2-isoxazolin-4-yl, imidazo[1,2-a]pyridin-2-yl, benzothiazol-2-yl, 2,5-dioxoimidazolidin-3-yl, naphth-2-ylaminocarbonyl, phenyl, 4-sulphamoylphenethyl, 4-(*N,N*-dimethylamino)phenyl, 4-sulphamoylphenyl, anilino, 4-hydroxyphenyl, quinolin-3-yl, 4-chlorophenyl, 2-methoxypyrid-5-yl, 3-methylisothiazol-5-yl, 3-trifluoromethylpyrid-2-yl, tetrazol-5-yl, benzyloxycarbonylamino, benzimidazol-2-yl, 2-trifluoromethylpyrid-5-yl, pyridazin-2-yl, pyridazin-3-yloxy, pyrid-2-yl, imidazol-5-yl, 4-acetamidophenoxy, 2-ureidothiazol-4-yl, benzylthio, 2-phenyl-1,3-dioxolan-2-yl and 4-carbamoylmethylphenoxy;

R^3 is hydrogen; and

n is selected from 0-3; wherein the values of R^1 may be the same or different;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In a first preferred aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

n is 0;

R^2 is a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is a C_{3-12}cycloalkyl which is optionally fused to a benz ring wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic groups; wherein S may be optionally substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl,

N-methyl-*N*-ethylsulphamoyl, morpholino , morpholinocarbonyl , *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt thereof.

Preferred values of R^2, R^4, and R^5 are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In this first preferred aspect preferably R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

In this first preferred aspect preferably H is indanyl, 1,2,3,4-tetrahydronaphthyl or cyclopropyl. More preferably H is indanyl or 1,2,3,4-tetrahydronaphthyl. Most preferably H is indanyl.

In this first preferred aspect preferably S is independently selected from from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, C_{3-8}cycloalkyl and aryl. More preferably S is selected from hydroxy, amino, C_{1-6}alkoxy and C_{1-6}alkoxycarbonylamino.

In a second preferred aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

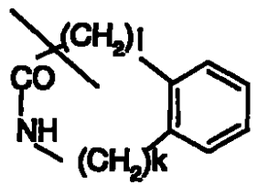
wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

n is 0;

R^2 is a group -E-F-G-H;

wherein E, F and G are each a direct bond; and

H is a cyclic amide of formula



in which k is 0, 1, 2 or 3 and l is 0, 1, 2 or 3 such that the sum of k and l is 2 or 3 and wherein one of the carbon atoms governed by k or l may be replaced by sulphur and wherein H is optionally substituted on carbon by one or more groups selected from S and may be independently optionally substituted on nitrogen by a group selected from T;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl,

N-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred values of R^4, R^5 and H are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In this second preferred aspect preferably R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

In this second preferred aspect preferably H is 1,2,3,4-tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, 4-oxo-2,3,4,5-tetrahydrobenz[1,5]thiazepin-3-yl, 2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepinyl, 2,3,4,5-tetrahydro-1H-benz[*b*]azepinyl or 3-oxo-2,3,4,5-tetrahydro-1H-benz[*c*]azepinyl each optionally substituted on carbon by one or more groups selected from S wherein S is selected from hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, and each independently optionally substituted on nitrogen by a group selected from T wherein T is selected from C_{1-4}alkyl or C_{1-4}alkanoyl.

More preferably H is 2-oxo-1,2,3,4-tetrahydroquinol-3-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydroquinol-3-yl, 4-oxo-2,3,4,5-tetrahydrobenz[1,5]thiazepin-3-yl, 5-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepin-4-yl, 2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepin-3-yl or 3-oxo-2,3,4,5-tetrahydro-1H-benz[*c*]azepin-4-yl.

In a third preferred aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from $-S-CR^4=CR^5-$ or $-CR^4=CR^5-S-$;

wherein R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

n is 1;

R^1 is hydrogen or arylC_{1-6}alkyl;

R^2 is selected from a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is an unsaturated five membered heterocyclic group containing at least one nitrogen atom and one or two ring atoms selected from oxygen and sulphur and wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N*,*N*-(C_{1-6}alkyl)$_2$amino,

C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkyl*S*(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl and aryl groups;

R^3 is hydrogen or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

Preferred values of R^1, R^3 and H are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In this third preferred aspect preferably R^1 is selected from hydrogen or benzyl and more preferably benzyl.

In this third preferred aspect preferably R^3 is hydrogen.

In this third preferred aspect preferably H is 1,3,4-oxadiazolyl, isoxazolyl, oxazolyl or 1,2,4-oxadiazolyl. More preferably H is 5-ethoxycarbonyl-1,3,4-oxadiazol-2-yl, 4-phenylisoxazol-3-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 4-methoxycarbonyloxazol-5-yl or 3-methylisoxazol-5-yl.

In this third preferred aspect preferably H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, carboxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonyl, C_{3-8}cycloalkyl and aryl groups. Preferably S is C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl or phenyl.

In a fourth preferred aspect the present invention provides a compound of formula (I) (as depicted above) wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

wherein R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

n is 0;

R^2 is a group -E-F-G-H;

wherein E is a direct bond;

F is methylene;

wherein G is -C(O)NR^a-, wherein R^a is selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V ;

H is aryl which may be optionally substituted on carbon by one or more groups selected from S;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V ;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl , and 4-hydroxypiperidinocarbonyl;

or a pharmaceutically acceptable salt thereof.

Preferred values of R^1, R^2, R^3, -X-Y-Z-and n are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In this fourth preferred aspect preferably H is aryl.

In this fourth preferred aspect preferably V is cyano or hydroxy.

Specific compounds of the present invention are:

2,3-dichloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(benzoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(1-phenylmethanesulphonamido)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(4-oxo-2,3,4,5-tetrahydrobenz[1,5]thiazepin-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-sulphamoylphenylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-hydroxy-1-phenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[3-(5-tetrazolyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(5-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepin-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[3-(benzyloxycarbonylamino)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(4-dimethylaminophenyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-benzyl-2-hydroxyethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(phenylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-*(R)*-hydroxy-α-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-hydroxyphenethyl)carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-hydroxyphenyl)ethyl]carbamoyl}4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(benzimidazol-2-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-chlorophenyl)-2-hydroxy-1-(methoxycarbonyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(imidazo[1,2-*a*]pyrid-2-yl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[(benzthiazol-2-yl)methyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(6-trifluoromethylpyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(2-pyridazinyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxy-3-phenoxypropyl)carbamoylmethyl] carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-methylisothiazol-5-yl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(pyridazin-3-yloxy)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-(*N*-{2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-sulphamoylphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-pyridyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[1-hydroxymethyl-2-(4-imidazolyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(3-quinolyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[3-(4-acetamidophenoxy)-2-hydroxypropyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[3-(*N*-methylsulphonylcarbamoyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-{[2-(guanidino)thiazol-4-yl]methylthio}ethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2,4-dioxoimidazolidin-1-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[2-benzylthio-1-(hydroxymethyl)ethyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(dimethyaminosulphonylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(6-methoxypyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(S)-2,3-dichloro-5-{*N*-[(2-oxo-3-phenyl-2,3,4,5-tetrahydrooxazol-5-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[3-(carbamoylmethyl)phenoxy]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{[6-(benzo[1,3]dioxol-5-yl)-4-methylmorpholin-2-yl]methyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-benzylcarbamoyl)- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-phenethylcarbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(3-phenylpropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-hydroxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(α,α-dimethylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-phenylcyclobutyl)methyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(*N*-benzylcarbamoylmethyl)carbamoyl]- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(*N*-benzyl-*N*-methylcarbamoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-phenylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-methoxyphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-fluorophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-nitrophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,6-dimethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(4-methylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(3-methylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-chlorophenyl) *N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-phenylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(1,1-dimethyl-2-hydroxyethyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-hydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxybutyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-[bis(hydroxymethyl)methyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,3-dihydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxymethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(5-isoquinolyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-hydroxymethy)lphenyl]carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-[4-(2-hydroxyethyl)phenyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,4-difluorophenyl)-*N*-methyl-carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(1,2,3,4-tetrahydro-1-quinolyl)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxypiperidino)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*- cyclopentylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-isopropylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-isopropyl-*N*-methylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(thiomorpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(morpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(1,1-dioxothiomorpholino)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2*b*]-pyrrole;

2,3-dichloro-5-{*N*-[(1-oxothiomorpholino)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-indanyl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

5-[*N*-(benz[1,2]oxazol-3-ylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(hydroxymethyl)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-phenylisoxazol-3-ylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(2-morpholinoethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(methoxycarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(carboxymethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(3-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(2-methoxyethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(carbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(*N*-methylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(*N*,*N*-dimethylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(morpholinocarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(*N*-benzylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(4-hydroxypiperidinocarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(5-ethoxycarbonyl-1,3,4-oxadiazol-2-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(4-methoxycarbonyloxazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-{*N*-[α-(3-pyridyl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-{*N*-[α-(3-pyridyl)phenethyl)]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(3-phenyl-1,2,4-oxadiazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-((*1S,2S*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-((*1R,2R*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(7-methoxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-indanyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(3-methylisoxazol-5-yl)methyl]carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-hydroxy-1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-methyl-*N*-[(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(3-oxo-2,3,4,5-tetrahydro-1*H*-benz[2]azepin-4-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

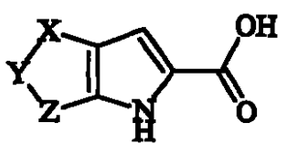
2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole; and

2,3-dichloro-5-{*N*-[1-(*N*-methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

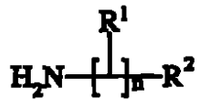
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein R^1, R^2, R^3, -X-Y-Z-and n are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reacting an acid of the formula (II):



(II)

or an activated derivative thereof; with an amine of formula (III):



(III)

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

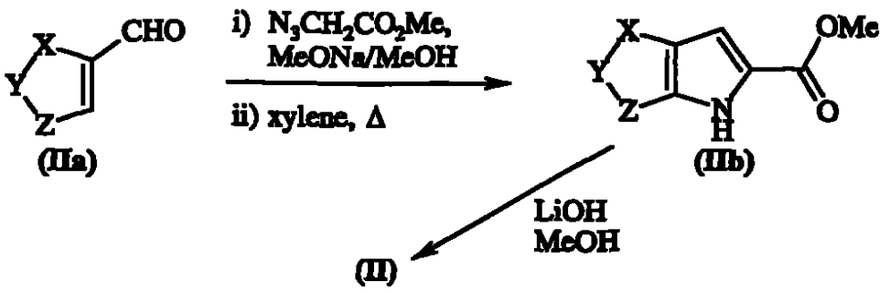
iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (II) and amines of formula (III) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

The acids of formula (II) may be prepared according to *Scheme 1*:



Scheme 1

Compounds of formula (IIa) and amines of formula (III) are commercially available or they are known compounds or they are prepared by processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali

metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds in the direction of glycogen synthesis, the conversion of glucose-1-phosphate into glycogen with the release of inorganic phosphate, as described in EP 0 846 464 A2. The reactions were in 96well microplate format in a volume of 100µl. The change in optical

density due to inorganic phosphate formation was measured at 620nM in a Labsystems iEMS Reader MF by the general method of (Nordlie R.C and Arion W.J, Methods of Enzymology, 1966, 619-625). The reaction is in 50mM HEPES, 2.5mM $MgCl_2$, 2.25mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 2mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution, with 0.1mg type III glycogen, 0.15ug glycogen phosphorylase *a* (GP*a*) from rabbit muscle and 0.5mM glucose-1-phosphate. GP*a* is pre-incubated in the assay buffer solution with the type III glycogen at 2.5 mg ml^{-1} for 30 minutes. 40µl of the enzyme solution is added to 25µl assay buffer solution and the reaction started with the addition of 25µl 2mM glucose-1-phosphate. Compounds to be tested are prepared in 10µl 10% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10µl 10% DMSO in assay buffer solution and maximum inhibition measured in the presence of 30µM CP320626 (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). The reaction is stopped after 30min with the addition of 50µl acidic ammonium molybdate solution, 12ug ml^{-1} in 3.48% H_2SO_4 with 1% sodium lauryl sulphate and 10ug ml^{-1} ascorbic acid. After 30 minutes at room temperature the absorbency at 620nm is measured.

The assay is performed at a test concentration of inhibitor of 10µM or 100µM. Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC_{50}, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

% inhibition = (1 - (compound OD620 - fully inhibited OD620)/ (non-inhibited rate OD620 - fully inhibited OD620)) * 100.

OD620 = optical density at 620nM.

Typical IC_{50} values for compounds of the invention when tested in the above assay are in the range 100µM to 1nM.

The activity of the compounds is alternatively determined by measuring the inhibitory effect of the compounds on glycogen degradation, the production of glucose-1-phosphate from glycogen is monitored by the multienzyme coupled assay, as described in EP 0 846 464 A2, general method of Pesce et al (Pesce, M A, Bodourian, S H, Harris, R C, and Nicholson, J F (1977) Clinical Chemistry 23, 1171 - 1717). The reactions were in 384well microplate format in a volume of 50µl. The change in fluorescence due to the conversion of the co-factor NAD

to NADH is measured at 340nM excitation, 465nm emission in a Tecan Ultra Multifunctional Microplate Reader. The reaction is in 50mM HEPES, 3.5mM KH_2PO_4, 2.5mM $MgCl_2$, 2.5mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 8mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution. Human recombinant liver glycogen phosphorylase *a* (hrl GP*a*) 20nM is pre-incubated in assay buffer solution with 6.25mM NAD, 1.25mg type III glycogen at 1.25 mg ml^{-1} the reagent buffer, for 30 minutes. The coupling enzymes, phosphoglucomutase and glucose-6-phosphate dehydrogenase (Sigma) are prepared in reagent buffer, final concentration 0.25Units per well. 20µl of the hrl GPa solution is added to 10µl compound solution and the reaction started with the addition of 20ul coupling enzyme solution. Compounds to be tested are prepared in 10µl 5% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10µl 5% DMSO in assay buffer solution and maximum inhibition measured in the presence of 5mgs ml^{-1} N-ethylmaleimide. After 6 hours at 30°C Relative Fluoresence Units (RFUs) are measured at 340nM excitation, 465nm emission .

The assay is performed at a test concentration of inhibitor of 10µM or 100µM. Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC_{50}, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

% inhibition = (1 - (compound RFUs - fully inhibited RFUs)/ (non-inhibited rate RFUs - fully inhibited RFUs)) * 100.

Typical IC_{50} values for compounds of the invention when tested in the above assay are in the range 100µM to 1nM.

The inhibitory activity of compounds was further tested in rat primary hepatocytes. Rat hepatocytes were isolated by the collagenase perfusion technique, general method of Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Cells were cultured on Nunclon six well culture plates in DMEM with high level of glucose containing 10% foetal calf serum, NEAA, Glutamine, penicillin /streptomycin ((100units/100ug)/ml) for 4 to 6 hours. The hepatocytes were then cultured in the DMEM solution without foetal calf serum and with 10nM insulin and 10nM dexamethasone. Experiments were initiated after 18-20 hours culture by washing the cells and adding Krebs-Henseleit bicarbonate buffer containing 2.5mM $CaCl_2$

and 1% gelatin. The test compound was added and 5 minutes later the cells were challenged with 25nM glucagon. The Krebs-Henseleit solution was removed after 60 min incubation at 37°C , 95%O_2/5%CO_2 and the glucose concentration of the Krebs-Henseleit solution measured.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

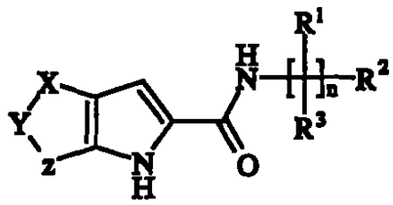
In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

According to an additional aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an another aspect of the invention there is provided the use of a compound of the formula (I'):



(I')

wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^6-CR^4=CR^5- and -CR^4=CR^5-NR^6-;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

R^6 is hydrogen or C_{1-6}alkyl;

R^1 is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl,

C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO$_2$-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^{a}C(O)-, -C(O)NR^a-, -SO$_2$NR^a-, -NR^{a}SO$_2$-, -NR^{a}C(O)NR^b-, -OC(O)NR^a-, -NR^{a}C(O)O-, -NR^{a}SO$_2$NR^b-, -SO$_2$NR^{a}C(O)- and -C(O)NR^{a}SO$_2$-; wherein R^a and R^b are independently selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V ;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

R^3 is hydrogen or C_{1-6}alkyl;

n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

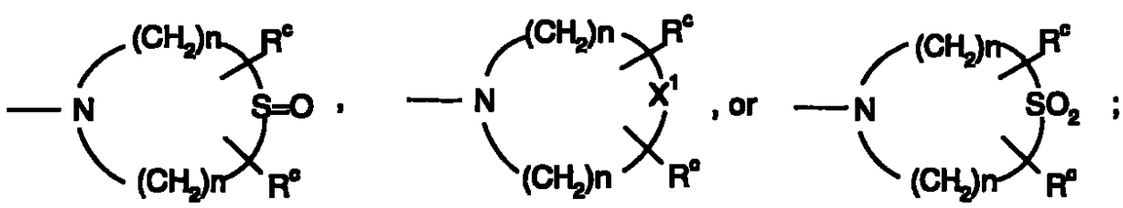
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino,

acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

with the proviso that

when -X-Y-Z- is as initially defined, n is 1, R^1 is arylmethyl, substituted arylmethyl, (heterocyclic group)methyl and substituted (heterocyclic group)methyl and R^3 is hydrogen then R^2 is not a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, -$NR^aCH_2CH_2OR^a$, or



each R^a and R^b is independently hydrogen or –C_1-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, -C(=O)OR^a, -OR^a, -SR^a, or -NR^aR^a; and each n is independently 1-3, and

X^1 is NR^a, -CH_2-, O or S;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a glycogen phosphorylase inhibitory effect in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (I'), or a pharmaceutically acceptable salt or *in vivo* hydrolysable

ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (I'), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I').

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I').

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I').

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a Bond Elut column is referred to, this means a column containing 10 g or 20 g or 50 g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; "Mega Bond Elut" is a trademark; where a Biotage cartridge is referred to this means a cartridge containing KP-SIL™ silica, 60 angstroms, particle size 32-63mM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent unless otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform $CDCl_3$;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z

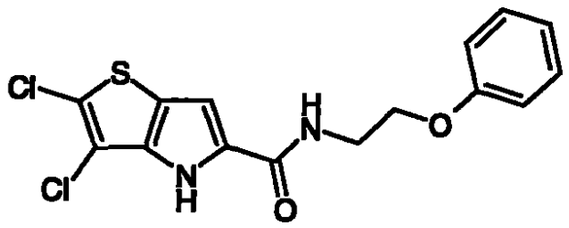
are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

(xi) The following abbreviations are used:

SM	starting material;
EtOAc	ethyl acetate;
MeOH	methanol;
DCM	dichloromethane
HOBT	1-hydroxybenzotriazole
DIAD	diisopropyl azodicarboxylate
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*, tetramethyluronium hexafluorophosphate
TFA	trifluoroacetic acid
DIPEA	di-isopropylethylamine; and
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride

Example #1

2,3-Dichloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 47 mg, 0.2 mmol) was dissolved in DCM (10 ml) containing 2-phenoxyethylamine (27 mg, 0.2 mmol), HOBT (27 mg, 0.2 mmol) and DIPEA (70 ml, 0.4 mmol). The mixture was stirred for 1 minute before the addition of EDAC (50 mg, 0.26 mmol). The mixture was stirred at ambient temperature for approximately 18 hours before being washed with water. The organic fraction was concentrated and was purified on a Bond Elut column (eluent 1:1 EtOAc/isohexane) to afford the title compound as an off white solid (32 mg). NMR: 12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, d), 7.1 (1H, s), 6.9 (2H, m), 3.5 (2H, m), 3.0 (2H, t); m/z 353.2.

Examples #2 - #9

The following compounds were made by the process of Example #1 using 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9) and the appropriate amine:

Example #2: 2,3-Dichloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #3: 2,3-Dichloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #4: 2,3-Dichloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

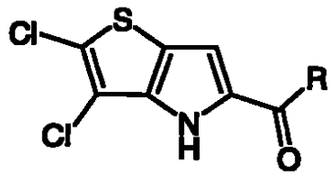
Example #5: 2,3-Dichloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

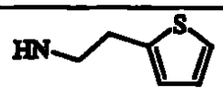
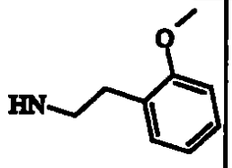
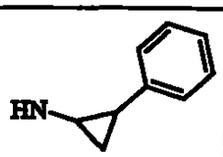
Example #6: 2,3-dichloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

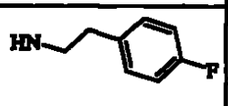
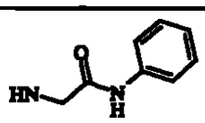
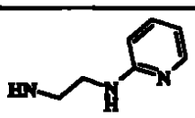
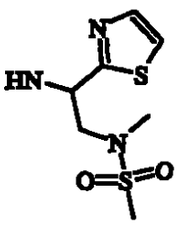
Example #7: 2,3-Dichloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #8: 2,3-Dichloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #9: 2,3-Dichloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



Ex	R	NMR	M/z
#2		12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, d), 7.1 (1H, s), 6.9 (2H, m), 3.5 (2H, m), 3.0 (2H, t)	343.1
#3		12.3 (1H, s), 8.3 (1H, t), 6.8-7.2 (5H, m), 3.8 (3H, s), 3.4 (2H, m), 2.8 (2H, t)	367.3
#4		12.4 (1H, s), 8.5 (1H, d), 7.2 (5H, m), 7.1 (1H, s), 3.0 (1H, m), 2.1 (1H, m), 1.3 (2H, m)	349.3

#5		12.3 (1H, s), 8.4 (1H, t), 7.3 (2H, m), 7.1 (3H, m), 3.4 (2H, m), 2.8 (2H, t)	355.3
#6 [1]		12.4 (1H, s), 10.0 (1H, s), 8.7 (1H, br), 7.1-7.6 (5H, m), 7.2 (1H, s), 4.1 (2H, d)	366.2
#7 [1, 2]		12.4 (1H, s), 8.4 (1H, s), 6.5-8.0 (5H, m), 6.6 (1H, s), 3.3 (4H, m)	353.3
#8 [3]		($CDCl_3$) 9.6 (1H, br), 7.8 (1H, m), 7.7 (1H, m), 7.3 (1H, m), 7.0 (1H, s), 5.6 (1H, m), 3.9 (1H, m), 3.7 (1H, m), 2.9 (3H, s), 2.8 (3H, s)	451.2
#9		($CDCl_3$) 9.8 (1H, br), 6.9 (1H, br), 6.7 (1H, s), 4.1 (2H, m), 3.6 (2H, m), 2.8 (8H, m)	362.2

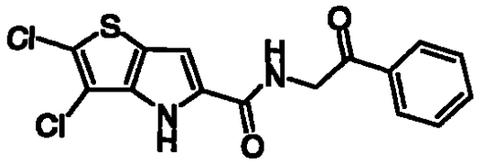
[1] Water was added and the title compound precipitated as a yellow solid which was filtered off, washed with water, dried under reduced pressure and was not purified further.

[2] Amine: Eur J Med Chem, 1987, 22, 91.

[3] Amine: Method #15

Example #10

5-[*N*-(Benzoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

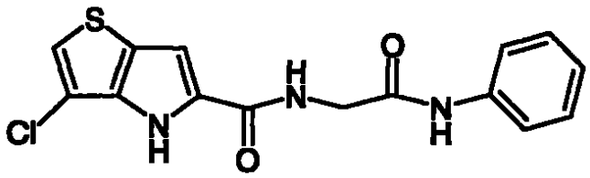


2,3-Dichloro-5-{*N*-[(2-phenyl-1,3-dioxolan-2-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole (Method #17; 80 mg, 0.2 mmol) was dissolved in acetone (15 ml) containing aqueous hydrochloric acid (2.0 M, 1 ml). The mixture was heated under reflux for 90 minutes. The white precipitate formed was filtered off and washed with acetone. The filtrate was concentrated and the residue was triturated with water. The solid formed was filtered off and

dried under reduced pressure to afford the title compound as a white solid (20 mg). NMR: 12.4 (1H, s), 8.6 (1H, t), 7.6-8.0 (5H, m), 7.2 (1H, s), 4.8 (2H, d); m/z 351.1.

Example #11

3-Chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-3-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #7; 100 mg, 0.5 mmol) was dissolved in DCM (6 ml) containing HOBT (68 mg, 0.5 mmol), DIPEA (176 ml, 1.0 mmol) and *N*-glycylaniline (75 mg, 0.5 mmol). The mixture was allowed to stand for one minute before the addition of EDAC (150 mg, 0.7 mmol). The solution was allowed to stand for approximately 18 hours before being washed with water. The organic phase was dried, filtered and concentrated under reduced pressure to afford the title compound (112 mg, 67%). NMR ($CDCl_3$) 9.7 (1H, br), 8.6 (1H, br), 7.0-8.0 (8H, m), 4.3 (2H, d); m/z 332.1.

Examples #12 - #21

The following compounds were made by the process of Example #11 using 5-carboxy-3-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #7) and the appropriate amine:

Example #12: 3-Chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #13: 3-Chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #14: 3-Chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #15: 3-Chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #16: 3-Chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

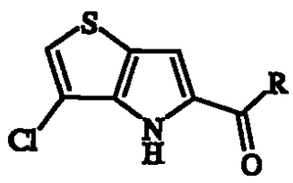
Example #17: 3-Chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

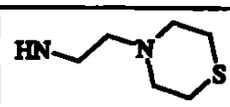
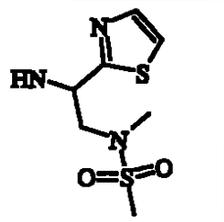
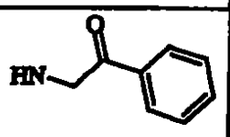
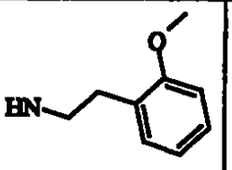
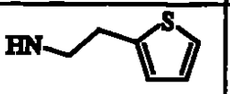
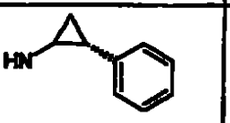
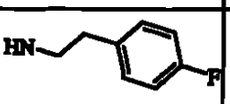
Example #18: 3-Chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

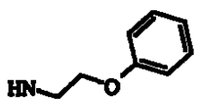
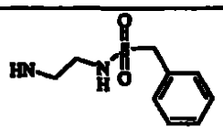
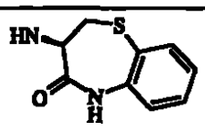
Example #19: 3-Chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #20: 3-Chloro-5-{*N*-[2-(1-phenylmethanesulphonamido)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #21: 3-Chloro-5-[*N*-(4-oxo-2,3,4,5-tetrahydrobenz[1,5]thiazepin-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



Ex	R	NMR	M/z
#12		($CDCl_3$) 9.6 (1H, br), 7.0 (1H, s), 6.7 (1H, s), 6.6 (1H, br), 4.1 (2H, m), 3.5 (2H, m), 2.7 (8H, m)	328.3
#13 [1]		($CDCl_3$) 9.5 (1H, br), 7.8 (1H, m), 7.6 (1H, m), 7.3 (1H, m), 7.0 (2H, 2 x s), 5.6 (1H, m), 3.9 (1H, m), 3.7 (1H, m), 2.9 (6H, 2 x s)	419.0 $(M+H)^+$
#14		($CDCl_3$) 9.6 (1H, s), 7.0-8.0 (8H, m), 5.0 (2H, m)	317.1
#15		($CDCl_3$) 9.6 (1H, br), 7.2 (2H, m), 7.0 (1H, s), 6.9 (2H, m), 6.6 (1H, s), 6.3 (1H, br), 3.9 (3H, s), 3.7 (2H, m), 2.9 (2H, t)	333.1
#16		($CDCl_3$) 9.8 (1H, br), 6.9-7.2 (4H, m), 6.7 (1H, s), 6.2 (1H, br), 3.8 (2H, m), 3.2 (2H, t)	309.1
#17		($CDCl_3$) 9.6 (1H, br), 7.0-7.3 (6H, m), 6.8 (1H, s), 6.3 (1H, br), 3.1 (1H, m), 2.2 (1H, m), 1.3 (2H, m)	315.1
#18		($CDCl_3$) 9.5 (1H, br), 7.0-7.2 (5H, m), 6.6 (1H, s), 5.9 (1H, br), 3.7 (2H, m), 2.9 (2H, t)	321.1

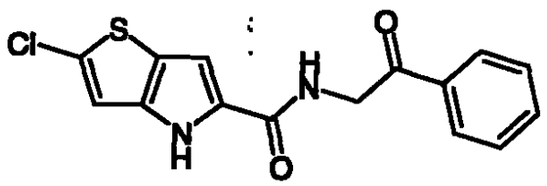
#19		($CDCl_3$) 9.6 (1H, br), 6.9-7.3 (6H, m), 6.8 (1H, s), 6.5 (1H, m), 4.2 (2H, t), 3.8 (2H, m)	319.1
#20		($CDCl_3$) 9.6 (1H, s), 6.8-7.4 (9H, m), 4.3 (2H, s), 3.4 (2H, m), 3.1 (2H, m)	396.1
#21 [2]		($CDCl_3$) 9.7 (1H, s), 8.0 (1H, s), 7.7 (1H, d), 7.1-7.4 (4H, m), 7.0 (1H, s), 6.9 (1H, s), 4.9 (1H, m), 4.0 (1H, m), 3.0 (1H, m)	378.1 $(M+H)^+$

[1] Amine: Method #15

[2] Amine: J Med Chem, 1985, 28, 1517

Example #22

2-Chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #8; 50 mg, 0.25 mmol) was dissolved in DCM (7 ml) containing HOBT (34 mg, 0.25 mmol), DIPEA (49 ml, 0.28 mmol) and 2-amino-1-phenylethanone (43 mg, 0.25 mmol). The mixture was stirred for one minute and EDAC (63 mg, 0.33 mmol) was added. The mixture was stirred at room temperature for approximately 18 hours. Water was added to the solution and a solid precipitated out. This solid was filtered off and was washed with water and DCM before being dried under reduced pressure to afford the title compound as a white solid (45 mg, 61%). NMR: 11.9 (1H, s), 8.6 (1H, t), 7.1-8.1 (7H, m), 4.8 (2H, d); m/z 317.3.

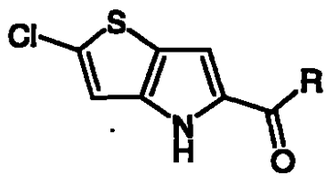
Examples #23 - #25

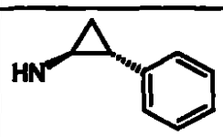
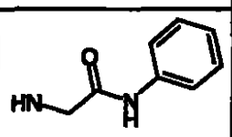
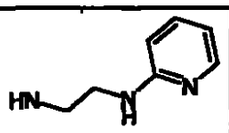
The following compounds were made by the process of Example #22 using 5-carboxy-2-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #8) and the appropriate amine:

Example #23: 2-Chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #24: 2-Chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #25: 2-Chloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

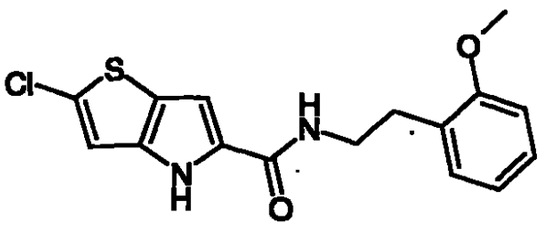


Ex	R	NMR	M/z
#23		11.8 (1H, s), 8.5 (1H, d), 7.0-7.3 (7H, m), 3.0 (1H, m), 2.1 (1H, m), 1.3 (2H, m)	315.3
#24		11.8 (1H, s), 10.0 (1H, br), 8.6 (1H, br), 7.0-7.6 (7H, m), 4.0 (2H, d)	332.3
#25 [1]		11.8 (1H, s), 8.4 (1H, s), 6.4-8.0 (6H, m), 6.6 (1H, br), 3.4 (4H, m)	319.3

[1] Amine: Eur J Med Chem, 1987, 22, 91.

Example #26

2-Chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

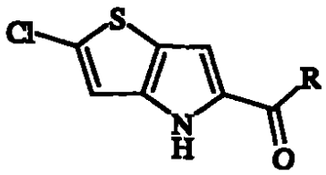


5-Carboxy-2-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #8; 50 mg, 0.25 mmol) was dissolved in DCM (7 ml) containing HOBT (34 mg, 0.25 mmol), DIPEA (49 ml, 0.28 mmol) and 2-(2-methoxyphenyl)ethylamine (43 mg, 0.25 mmol). The mixture was stirred for one minute and EDAC (63 mg, 0.33 mmol) was added. The mixture was stirred at room

temperature for approximately 18 hours. The reaction mixture was washed with water, the organic phase was dried, filtered and concentrated to afford the title compound as an off-white solid (84 mg, 100%). NMR ($CDCl_3$): 9.7 (1H, br), 6.9-7.2 (5H, m), 6.5 (1H, s), 6.3 (1H, br), 3.9 (3H, s), 3.7 (2H, m), 3.0 (2H, t); m/z 333.4.

Examples #27 - #31

The following compounds were made by the process of Example #26 using 5-carboxy-2-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #8) and the appropriate amine.



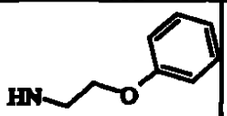
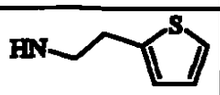
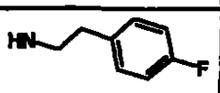
Example #27: 2-Chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

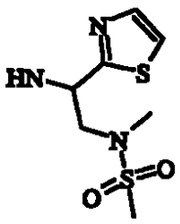
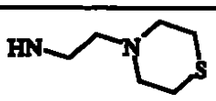
Example #28: 2-Chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #29: 2-Chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #30: 2-Chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #31: 2-Chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Ex	R	NMR	M/z
#27		($CDCl_3$) 9.5 (1H, s), 6.9-7.3 (6H, m), 6.7 (1H, s), 6.4 (1H, br), 4.2 (2H, m), 3.9 (2H, m)	319.3
#28		($CDCl_3$) 9.4 (1H, br), 6.6-7.2 (5H, m), 6.0 (1H, br), 3.7 (2H, m), 3.1 (2H, m)	309.3
#29		($CDCl_3$) 9.4 (1H, s), 7.0-7.2 (4H, m), 6.9 (1H, s), 6.6 (1H, s), 5.9 (1H, br), 3.7 (2H, m), 2.9 (2H, t)	321.3

#30 [1]		11.9 (1H, br), 9.0 (1H, d), 7.8 (1H, m), 7.7 (1H), 7.2 (1H, s), 7.0 (1H, s), 5.6 (1H, m), 3.9 (1H, m), 3.6 (1H, m), 2.9 (3H, s), 2.8 (3H, s)	417.2
#31		11.8 (1H, s), 8.1 (1H, t), 6.8-7.4 (2H, m), 2.5-4.0 (12H, m)	328.3

[1] Amine: Method #15

Examples #32 - #69

The following compounds were made by the process of Example #1 using 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9) or Example #22 using 5-carboxy-2-chloro-4*H*-thieno[3,2-*b*]pyrrole (Method #8) and the appropriate amine:

Example #32: 2,3-Dichloro-5-[*N*-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #33: 2,3-Dichloro-5-[*N*-(4-sulphamoylphenylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #34: 2,3-Dichloro-5-[*N*-(2-hydroxy-1-phenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #35: 2,3-Dichloro-5-{*N*-(2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #36: 2,3-Dichloro-5-{*N*-[3-(5-tetrazolyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #37: 2,3-Dichloro-5-[*N*-(5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #38: 2,3-Dichloro-5-[*N*-(5-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepin-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #39: 2-Chloro-5-{*N*-[3-(benzyloxycarbonylamino)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #40: 2,3-Dichloro-5-{*N*-[(4-dimethylaminophenyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #41: 5-[*N*-(1-Benzyl-2-hydroxyethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Example #42: 2,3-Dichloro-5-{*N*-[2-(phenylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #43: 2,3-Dichloro-5-[*N*-(β-*(R)*-hydroxy-α-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #44: 2,3-Dichloro-5-[*N*-(β-hydroxyphenethyl)carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #45: 2,3-Dichloro-5-{*N*-[2-(4-hydroxyphenyl)ethyl]carbamoyl}4*H*-thieno[3,2-*b*]pyrrole

Example #46: 2,3-Dichloro-5-{*N*-[(benzimidazol-2-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #47: 2,3-Dichloro-5-{*N*-[2-(4-chlorophenyl)-2-hydroxy-1-(methoxycarbonyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #48: 2,3-Dichloro-5-{*N*-(imidazo[1,2-*a*]pyrid-2-yl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #49: 5-{*N*-[(Benzthiazol-2-yl)methyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Example #50: 2,3-Dichloro-5-{*N*-[(6-trifluoromethylpyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #51: 2,3-Dichloro-5-{*N*-(2-[(2-pyridazinyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #52: 2,3-Dichloro-5-{*N*-[*N*-(2-hydroxy-3-phenoxypropyl)carbamoylmethyl] carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #53: 2,3-Dichloro-5-{*N*-[*N*-(3-methylisothiazol-5-yl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #54: 2,3-Dichloro-5-{*N*-[2-(pyridazin-3-yloxy)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #55: 2-Chloro-5-(*N*-{2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #56: 2,3-Dichloro-5-{*N*-[2-(4-sulphamoylphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #57: 2,3-Dichloro-5-{*N*-[2-(2-pyridyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #58: 2,3-Dichloro-5-{*N*-(2-[1-hydroxymethyl-2-(4-imidazolyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #59: 2,3-Dichloro-5-{*N*-(2-[(3-quinolyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #60: 5-{*N*-[3-(4-Acetamidophenoxy)-2-hydroxypropyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Example #61: 2,3-Dichloro-5-{*N*-[3-(*N*-methylsulphonylcarbamoyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #62: 2,3-Dichloro-5-[*N*-(2-{[2-(guanidino)thiazol-4-yl]methylthio}ethyl)-carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #63: 2,3-Dichloro-5-{*N*-[2-(2,4-dioxoimidazolidin-1-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #64: 5-{*N*-[2-Benzylthio-1-(hydroxymethyl)ethyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

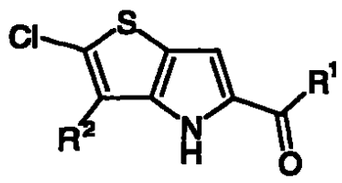
Example #65: 2,3-Dichloro-5-{*N*-[2-(dimethyaminosulphonylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #66: 2,3-Dichloro-5-{*N*-[(6-methoxypyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

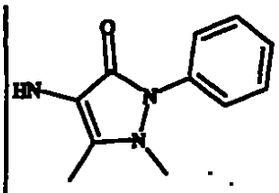
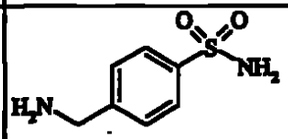
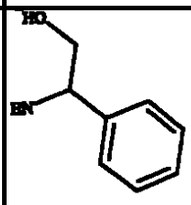
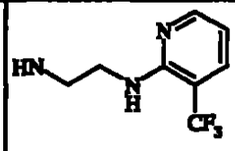
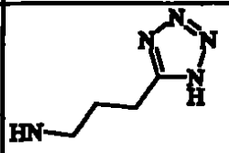
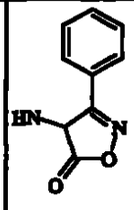
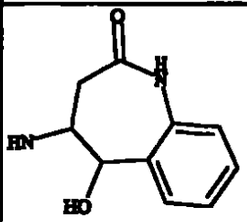
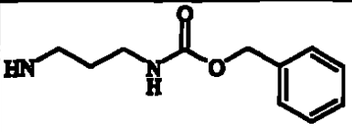
Example #67: *(S)*-2,3-Dichloro-5-{*N*-[(2-oxo-3-phenyl-2,3,4,5-tetrahydrooxazol-5-yl)-methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

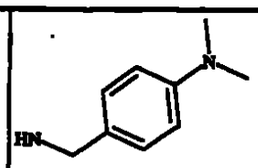
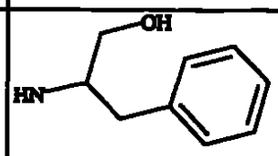
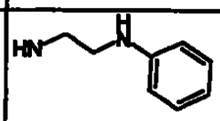
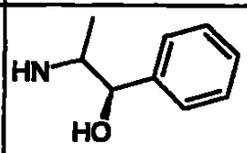
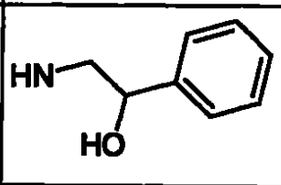
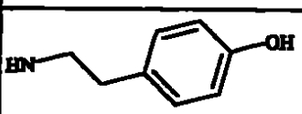
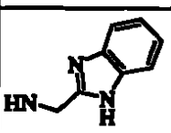
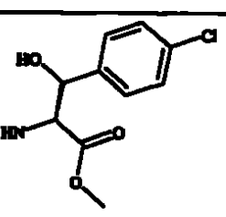
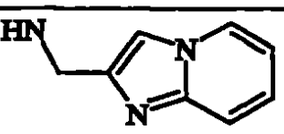
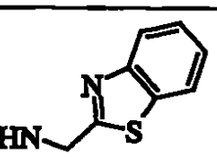
Example #68: 2,3-Dichloro-5-(*N*-{2-[3-(carbamoylmethyl)phenoxy]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

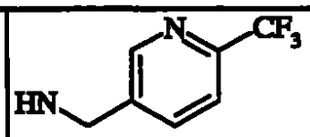
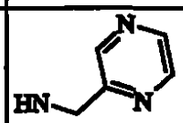
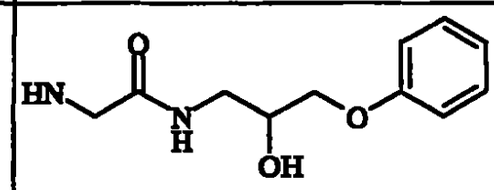
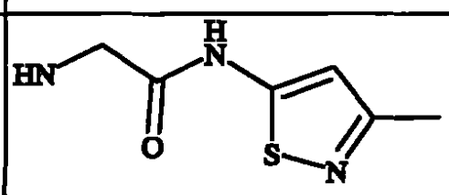
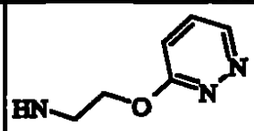
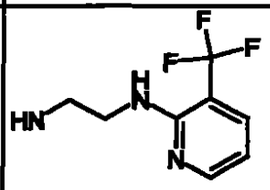
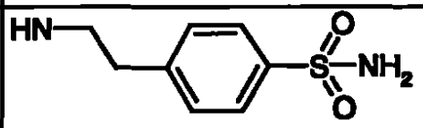
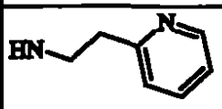
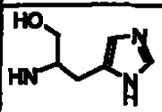
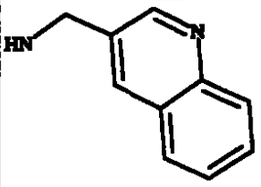
Example #69: 5-(*N*-{[6-(Benzo[1,3]dioxol-5-yl)-4-methylmorpholin-2-yl]methyl}-carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

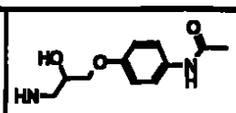
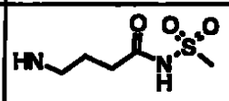
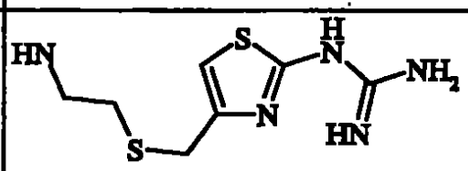
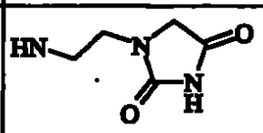
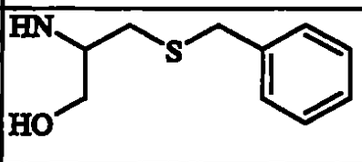
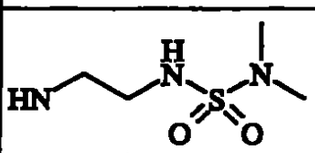
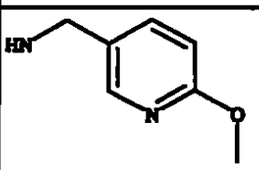
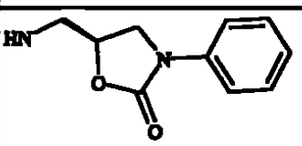
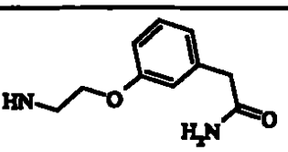
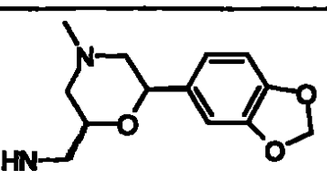


Ex	R^1	R^2	M/z $(M+H)^+$	Amine

32		Cl	421	commercially available
33		Cl	404	commercially available
34		Cl	355	commercially available
35		Cl	423	commercially available
36		Cl	345	Meth #19
37		Cl	394	Gazz. Chim. Ital., 1981, 111, 167
38	 amine and hydroxy group are trans to one another	Cl	410	Method #26
39		H	393	commercially available

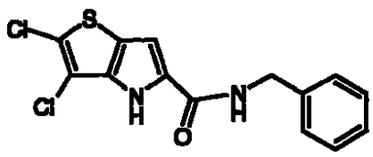
40		Cl	368	commercially available
41		Cl	369	commercially available
42		Cl	354	commercially available
43		Cl	369	commercially available
44		Cl	355	commercially available
45		Cl	355	commercially available
46		Cl	365	commercially available
47		Cl	448	commercially available
48		Cl	365	commercially available
49		Cl	382	commercially available

50		Cl	394	commercially available
51		Cl	327	commercially available
52		Cl	442	Method #20
53		Cl	389	Method #21
54		Cl	357	Method #22
55		H	388	commercially available
56		Cl	418	commercially available
57		Cl	340	commercially available
58		Cl	359	commercially available
59		Cl	376	commercially available

60		Cl	442	commercially available
61		Cl	398	Method #24
62		Cl	449	Eur. J. Med. Chem., 1993, 28, 601
63		Cl	361	Method #23
64		Cl	415	commercially available
65		Cl	385	commercially available
66		Cl	356	WO 9518097
67		Cl	410	J. Med. Chem., 1989, 32, 1673
68		Cl	412	Method #25
69		Cl	468	Method #27

Example #70

5-(*N*-Benzylcarbamoyl)- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method # 9, 118mg, 0.5mmol) was dissolved in dichloromethane (10ml) containing benzylamine (55 mg, 0.5 mmol), 1-HOBT (68mg, 0.5mmol) and DIPEA (258µl, 2mmol). The mixture was stirred for one minute before the addition of EDAC (125mg, 0.65mmol). The mixture was stirred at ambient temperature for approximately 16hours before being washed with water. The organic fraction was concentrated and was purified using Bond-Elut silica column chromatography (eluent: dichloromethane-dichloromethane/methanol 5% gradient) to afford the *title compound* as a white solid (121mg, 75%).

NMR: 12.4 (1H, br), 8.8 (1H, t), 7.3 (5H, m), 7.1 (1H, s), 4.5 (2H, d); m/z 323.27

The following compounds were made by the process of Example #70 using 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9) and the appropriate amine:

Example #71: 2,3-Dichloro-5-(*N*-phenethylcarbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #72: 2,3-Dichloro-5-[*N*-(3-phenylpropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #73: 2,3-Dichloro-5-{*N*-[2-(2-hydroxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #74: 2,3-Dichloro-5-[*N*-(α,α-dimethylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #75: 2,3-Dichloro-5-[*N*-(1-phenylcyclobutyl)methyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #76: 2,3-Dichloro-5-[*N*-(β-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

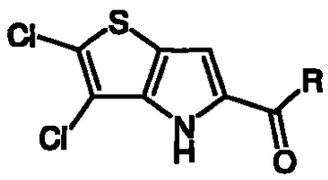
Example #77: 2,3-Dichloro-5-[*N*-(1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

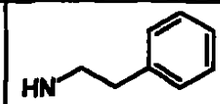
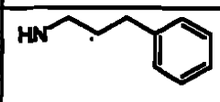
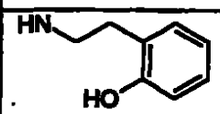
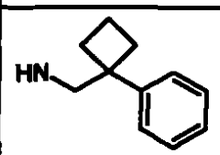
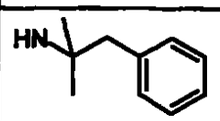
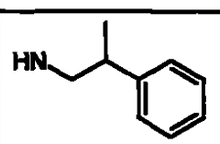
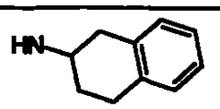
Example #78: 5-[*N*-(*N*-Benzylcarbamoylmethyl)carbamoyl]- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

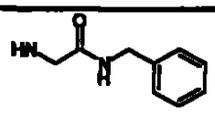
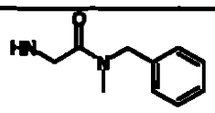
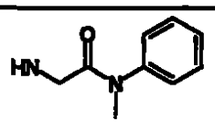
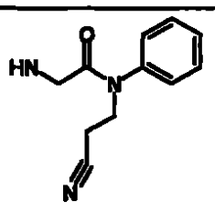
Example #79: 5-[*N*-(*N*-Benzyl-*N*-methylcarbamoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Example #80: 2,3-dichloro-5-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #81: 2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-phenylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



Ex	R	NMR	M/z
#71		12.33(1H, br), 8.4(1H, t), 7.3(5H, m), 7.1(1H, s), 3.5(2H, dd), 2.8(2H, t).	337.38
#72		12.35 (1H, br), 8.3 (1H, t), 7.2 (5H, m), 7.1 (1H, s), 3.3 (2H, q), 2.6 (2H, t), 1.8 (2H, m).	351.40
#73		12.3 (1H, br), 8.3 (1H, t), 7.0 (3H, m), 6.8 (1H, d), 6.7 (1H, t), 3.4 (2H, q), 2.8 (2H, t)	353.39
#74[1]		12.3 (1H, br), 8.1 (1H, t), 7.3 (2H, t), 7.15 (3H, m), 7.05 (1H, s), 3.6 (2H, d), 2.4 (2H, m), 2.2 (2H, m), 2.0 (1H, m), 1.8 (1H, m).	377.44
#75[2]		12.25 (1H, br), 7.4 (1H, s), 7.1 (6H, m), 3.1 (2H, s), 1.3 (6H, s)	365.41
#76[3]		12.3 (1H, br), 8.3 (1h, t), 7.2 (5H, m), 7.0 (1H, s), 3.4 (2H, m), 3.0 (1H, q), 1.2 (3H, d).	no mass ion
#77		12.35 (1H, br), 8.2 (1H, d), 7.1 (1H, s), 7.05 (4H, s), 4.2 (1H, br), 3.1 (1H, dd), 2.8 (3H, m), 2.0 (1H, m), 1.8 (1H, m).	363.35

#78[4]		12.4 (1H, br), 8.6 (1H, t), 8.4 (1H, t), 7.3 (5H, m), 4.3 (2H, d), 3.9 (2H, d).	380.41
#79[5]		12.45 (1h, br), 8.4(1H, m), 7.3 (5H, m), 7.2(1H, m), 4.6 (0.6, s), 4.5(1.4H, s), 4.2(2H, m), 3.0(2H, s), 2.8(1H, s)	394.44
#80[6]		12.4 (1H, br), 8.4(1H, t), 7.4(5H, m), 7.1(1H, s), 3.8(2H, br), 3.2(3H, s).	380.41
#81[7]		12.4 (1H, br), 8.4 (1H, t), 7.5 (5H, m), 7.1(1H, s), 3.9(2H, t), 3.7(2H, br), 2.7(2H, t).	419.41

[1] Amine: J. Org. Chem.; 1976, 41(14), 2502-2503

[2] Amine: J. Med. Chem .; 1993, 36(22), 3300-3307

[3] Amine: J. Am. Chem. Soc.; 1960, 82, 2577

[4] Amine: Method #6

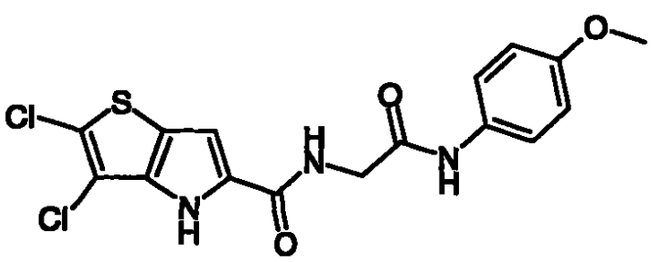
[5] Amine: Method #31

[6] Amine: Method #30

[7] Amine: Method #14

Example #82

2,3-dichloro-5-{*N*-[*N*-(4-methoxyphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



A solution of 5-(*N*-carboxymethylcarbamoyl)- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #12, 150mg, 0.51mmol) and 4-methoxyaniline (69mg, 0.56mmol) in tetrahydrofuran (THF) (6ml) was stirred at ambient temperature for 30 minutes. 4-(4,6-

dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (142mg, 0.51mmol) was added and the reaction mixture stirred at ambient temperature overnight, poured into water (15ml) and extracted with ethyl acetate (3x15ml). The organic extracts were combined and washed with 1N citric acid solution (15ml), sodium bicarbonate solution (15ml), dried over magnesium sulphate, filtered and concentrated to give the *title product* as a white solid NMR: 12.4 (1H, s), 9.9 (1H, s), 8.6 (1H, t), 7.5 (2H, d), 7.2 (1H, s), 6.85 (2H, d), 4.0 (2H, d), 3.7 (3H, s); m/z 396.38

The following compounds were made by the process of Example #82 using 2,3-dichloro-5-[*N*-carboxymethylcarbamoyl]-4*H*-thieno[3,2-*b*]pyrrole (Method #12) and the appropriate commercially available amine:

Example #83: 2,3-dichloro-5-{*N*-[*N*-(4-fluorophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #84: 2,3-dichloro-5-{*N*-[*N*-(4-nitrophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #85: 2,3-dichloro-5-{*N*-[*N*-(2,6-dimethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #86: 2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(4-methylphenyl)carbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #87: 2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(3-methylphenyl)carbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #88: 2,3-dichloro-5-{*N*-[*N*-(3-chlorophenyl) *N*-methylcarbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #89: 2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-phenylcarbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #90: 2,3-dichloro-5-{*N*-[*N*-(1,1-dimethyl-2-hydroxyethyl)carbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #91: 2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-methylcarbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

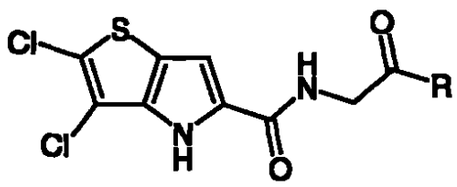
Example #92: 2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

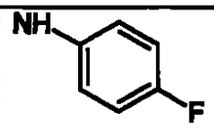
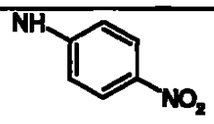
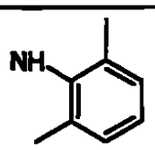
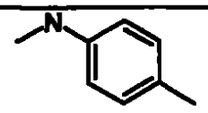
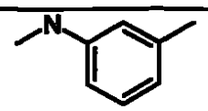
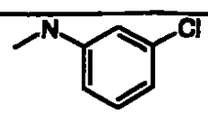
Example #93: 2,3-dichloro-5-{*N*-[*N*-(3-hydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

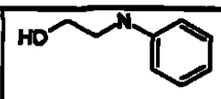
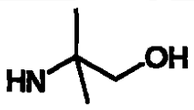
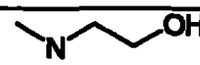
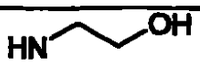
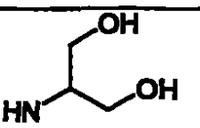
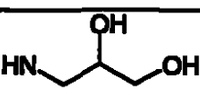
Example #94: 2,3-dichloro-5-{*N*-[*N*-(4-hydroxybutyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #95: 2,3-dichloro-5-(*N*-{*N*-[bis(hydroxymethyl)methyl]carbamoylmethyl}-carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #96: 2,3-dichloro-5-{*N*-[*N*-(2,3-dihydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

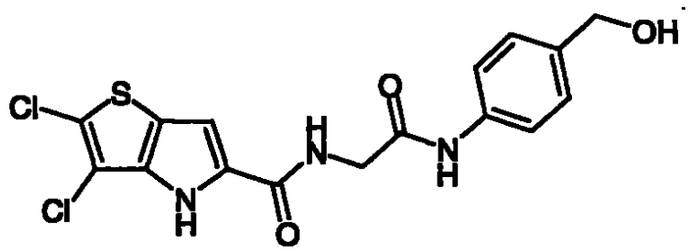


Ex	R	NMR	m/z
#83		12.42 (1H, br), 10.08 (1H, br), 8.6 (1H, t), 7.6 (2H, m), 7.1 (3H, m), 4.0 (2H, d)	384.20
#84		12.5 (1H, br), 10.74 (1H, br), 8.8 (1H, t), 8.3 (2H, d), 7.9 (2H, d), 7.2 (1H, s), 4.2 (2H, d).	411.36
#85		12.45 (1H, br), 9.3 (1H, br), 8.7 (1H, t), 7.2 (1H, s), 7.1 (3H, s), 4.1 (2H, d), 2.1 (6H, s).	394.39
#86		12.4 (1H, br), 8.4 (1H, t), 7.3 (4H, s), 7.1 (1H, s), 3.7 (2H, br), 3.2 (3H, s), 2.3 (3H, s)	394.17
#87		12.4 (1H, br), 8.4 (1H, t), 7.4 (1H, t), 7.2 (3H, m), 7.1 (1H, s), 3.8 (2H, br), 3.3 (3H, s), 2.3 (3H, s)	394.28
#88		12.4 (1H, br), 8.4 (1H, t), 7.5 (4H, m), 7.1 (1H, s), (3.9, br), 3.2 (3H, s).	no mass ion

#89		12.4 (1H, br), 8.4 (1H, t), 7.4 (5H, m), 7.1 (1H, s), 4.7 (1H, br), 3.7 (4H, m), 3.5 (2H, d).	410.54
#90		12.4 (1H, br), 8.4 (1H, t), 7.3 (1H, br), 7.1 (1H, s), 4.8 (1H, t), 3.8 (2H, d), 3.4 (1.3H, d), 3.1 (0.7H, d), 1.2 (6H, s)	362.33
#91		12.44 (1H, br), 8.3 (1H, br), 7.1 (1H, s), 4.9 (0.5H, t), 4.6 (0.5H, t), 4.1 (2H, dd), 3.4 (4H, m), 3.0 (1.5H, s), 2.8 (0.5H, s).	348.30
#92		12.42 (1H, br), 8.5 (1H, t), 7.8 (1H, t), 7.1 (1H, s), 4.6 (1H, br), 3.8 (2H, d), 3.4 (2H, br), 3.1 (2H, q).	334.34
#93		12.41 (1H, br), 8.5 (1H, t), 7.8 (1H, t), 7.1 (1H, s), 4.4 (1H, t, br), 3.8 (2H, d), 3.4 (2H, q, br), 3.1 (2H, q), 1.5 (2H, m).	348.38
#94		12.4 (1H, br), 8.5 (1H, t), 7.9 (1H, t), 7.1 (1H, s), 4.3 (1H, t), 3.8 (2H, d), 3.4 (2H, d), 3.1 (2H, q, br), 1.4 (4H, m).	362.36
#95		12.42 (1H, br), 8.5 (1H, t), 7.6 (1H, d), 7.1 (1H, s), 4.6 (2H, br), 3.9 (2H, d), 3.7 (1H, m), 3.4 (4H, br).	364.36
#96		12. 4 (1H, br), 8.5 (1H, br), 7.8 (1H, t), 7.1 (1H, s), 4.7 (1H, br) 4.5 (1H, br), 3.8 (2H, d), 3.5 (1H, m), 3.2 (3H, m), 3.0 (1H, m).	364.35

Example #97

2,3-dichloro-5-{*N*-[*N*-(4-hydroxymethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



A solution of 5-(*N*-carboxymethylcarbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #12) (150mg, 0.51mmol), and 4-aminobenzyl alcohol (70.5mg, 0.56mmol) in THF (6ml) was stirred at ambient temperature for 30 minutes. 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (142mg, 0.51mmol) was added and the reaction mixture stirred at ambient temperature overnight, then poured into water (15ml). The resultant precipitate was isolated by filtration, washed with water, ether and dried *in vacuo* to give the *title product* as a white solid (149mg, 73%)

NMR: 12.42 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.5 (2H, d), 7.2 (2H, d), 7.1 (1H, s), 5.0 (1H, br), 4.4 (2H, s), 4.0 (2H, d); m/z 396.21

The following compounds were made by the process of Example #97 using 5-(*N*-carboxymethylcarbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #12) and the appropriate commercially available amine:

Example #98: 2,3-dichloro-5-{*N*-[*N*-(5-isoquinolyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #99: 2,3-dichloro-5-{*N*-[*N*-(3-hydroxymethy)lphenyl]carbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #100: 2,3-dichloro-5-(*N*-{*N*-[4-(2-hydroxyethyl)phenyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #101: 2,3-dichloro-5-{*N*-[*N*-(2,4-difluorophenyl)-*N*-methyl-carbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #102: 2,3-dichloro-5-{*N*-[(1,2,3,4-tetrahydro-1-quinolyl)carbonylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #103: 2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-methylcarbamoylmethyl]-carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

Example #104: 2,3-dichloro-5-{*N*-[*N*-(4-hydroxypiperidino)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

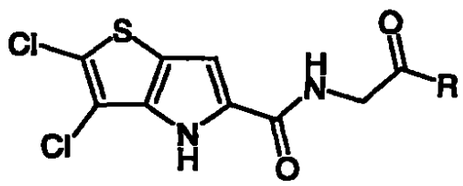
Example #105: 2,3-dichloro-5-[*N*-(*N*- cyclopentylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

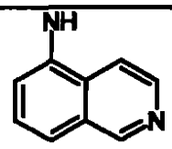
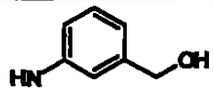
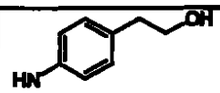
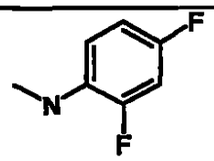
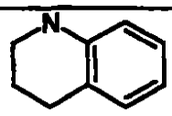
Example #106: 2,3-dichloro-5-[*N*-(*N*-isopropylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

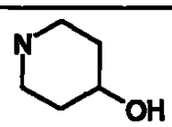
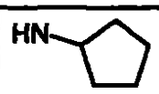
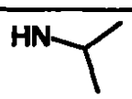
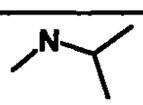
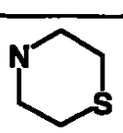
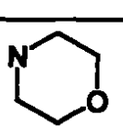
Example #107: 2,3-dichloro-5-[*N*-(*N*-isopropyl-*N*-methylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #108: 2,3-dichloro-5-[*N*-(thiomorpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #109: 2,3-dichloro-5-[*N*-(morpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



Ex	R	NMR	m/z
#98		12.5 (1H, s), 8.7 (1H, t), 8.5 (1H, d), 8.0 (3H, m), 7.7 (1H, t), 7.1 (1H, s), 4.2 (2H, d).	
#99		12.42 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.55 (1H, s), 7.45 (1H, d), 7.2 (1H, t), 7.1 (1H, s), 7.0 (1H, d), 5.1 (1H, br), 4.4 (2H, s), 4.0 (2H, d)	396.19
#100		12.41 (1H, br), 9.9 (1H, s), 8.6 (1H, t), 7.5 (1H, m), 7.1 (3H, m), 4.6 (1H, br), 4.0 (2H, d), 3.6 (2H, br), 2.6 (2H, t)	410.16
#101		12.4 (1H, br), 8.5 (1H, t), 7.7 (1H, q), 7.5 (1H, dt), 7.2 (1H, t, br), 7.1 (1H, s), 3.8 (1H, m), 3.6 (1H, m), 3.1 (3H, s).	No mass ion
#102		12.41 (1H, br), 8.5 (1H, t), 7.6 (1H, d), 7.1 (5H, m), 4.2 (2H, d), 3.7 (2H, t), 2.7 (2H, t), 1.9 (2H, m).	406.18

#103		12.42 (1H, br), 8.4 (1H, m), 7.1 (1H, s), 4.1(2H, m), 3.7 (0.5H, t), 3.6 (1.5H, t), 3.1 (2H, s), 2.9 (1.5H, m), 2.7 (1.5H, t).	357.27
#104		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.7 (1H, br), 4.1 (2H, d), 3.9 (1H, m), 3.7 (2H, m), 3.2 (1H, m), 3.0 (1H, m), 1.7 (2H, m), 1.3 (2H, m).	376.26
#105		12.4 (1H, br), 8.45 (1H, t), 7.8 (1H, d), 7.1 (1H, s), 4.0 (1H, m), 3.8 (2H, d), 1.8 (2H, m), 1.6 (2H, m), 1.5 (2H, m), 1.4 (2H, m).	358.35
#106		12.4 (1H, br), 8.5 (1H, t), 7.7 (1H, d), 7.1 (1H, s), 3.9 (1H, m), 3.8 (2H, d), 1.1 (6H, d).	332.34
#107		12.42 (1H, br), 8.3 (1H, m), 7.1 (1H, s), 4.6 (0.66H, m), 4.1 (2.33H, m), 2.8 (2H, s), 2.7 (1H, s), 1.15 (2.4H, d), 1.05 (3.6H, d).	346.34
#108		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (1H, d), 3.7 (4H, m), 2.7 (2H, br), 2.5 (2H, br).	no mass ion
#109		12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (2H, d), 3.6 (4H, br), 3.5 (4H, br).	360.30

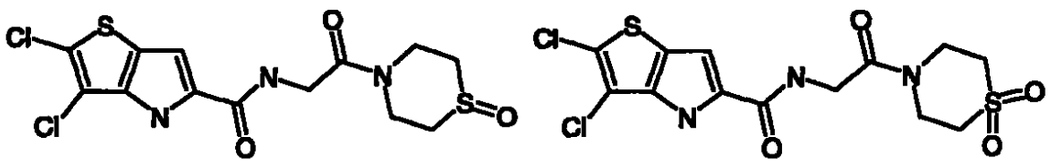
Example #110

2,3-dichloro-5-[*N*-[(1,1-dioxothiomorpholino)carbonylmethyl]carbamoyl]-4*H*-thieno[3,2*b*]-pyrrole

and

Example #111

2,3-dichloro-5-[*N*-[(1-oxothiomorpholino)carbonylmethyl]carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



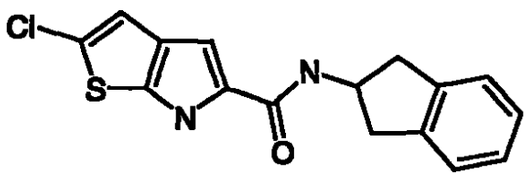
A solution of *m*-chloroperbenzoic acid (mCPBA) (14mg, 0.85mmol) in dichloromethane (5ml) was added dropwise to a suspension of 2,3-dichloro-5-[*N*-(thiomorpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole (example # 108) in dichloromethane and the reaction mixture stirred at ambient temperature for one hour. 5% sodium metabisulfite solution (5ml) was added and the mixture stirred for several minutes. The aqueous layer was extracted with ethyl acetate (2x15ml) and the combined organic extracts washed with sodium bicarbonate solution (2x15ml) and concentrated. The two component mixture was separated using bond-elute silica column chromatography (eluent: dichloromethane-dichloromethane/methanol 5% gradient) to afford the less polar product (sulfone) as a white powder (57mg 33%) and the more polar product (sulfoxide) as a white solid (62mg, 37%).

NMR: (sulfone) 12.43 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (2H, d), 3.9 (4H, br), 3.3 (2H, br), 3.1 (2H, br); m/z 408.33

NMR: (sulfoxide) 12.42 (1H, br), 8.4 (1H, t), 7.1 (1H, s), 4.2 (3H, m), 3.9 (2H, d), 3.6 (1H, m), 2.9 (4H, m).

Example #112

2-Chloro-5-[*N*-(2-indanyl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole



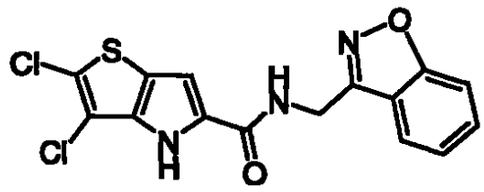
5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 101mg, 0.5mmol) was dissolved in dichloromethane (6ml) containing 2-aminoindane (68mg, 0.5mmol), 1-Hydroxybenotriazole (HOBT) (68mg, 0.5mmol) and DIPEA (355µl, 2.0mmol). The mixture was stirred for one minute before the addition of EDAC (125mg, 0.65mmol). The mixture was stirred at ambient temperature for approximately 16 hours before being washed with water. The organic fraction was concentrated and was purified using bon-elute silica column

chromatography (eluent: dichloromethane-dichloromethane/methanol 2.5% gradient) to afford the *title compound* as a beige solid (96mg, 61%).

NMR: 11.80 (1H, br), 8.3 (1H, t), 7.2 (5H, m), 7.0 (1H, s), 4.6 (1H, m), 4.7 (1H, d), 3.2 (2H, m), 2.9 (2H, m); m/z 315.46

Example #113

5-[*N*-(Benz[1,2]oxazol-3-ylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 118 mg, 0.5 mmol) was dissolved in DMF (5 ml) containing HOBT (83 mg, 0.55 mmol), DIPEA (52 ul, 0.30 mmol) and 1,2-Benzisoxazole-3-methylamine (Eur.J.Med.Chem-Chimica Therapeutica, Jan.-Feb.-10, No.1 p32) (89 mg, 0.6 mmol). The mixture was stirred for one minute and EDAC (106 mg, 0.55 mmol) was added. The mixture was stirred at room temperature for approximately 18 hours. Water was added to the solution and a solid precipitated out. This solid was filtered off and was washed with water before being dried under reduced pressure to afford the title compound as a white solid (174mg) 1H NMR : 4.9(2H,s), 7.1(1H,s), 7.4(1H,t), 7.6(1H,t), (7.8(1H,d), 8.0(1H,d), 9.2(1H,s), 12.5(1H,s); m/z 366 (M+H);
HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 4.9min m/z 366 (M+H)

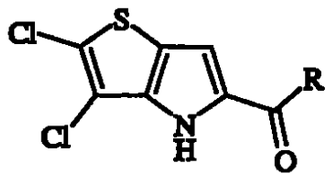
The following compounds were made by the process of Example #113 using 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9) and the appropriate amine:

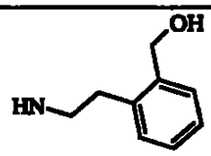
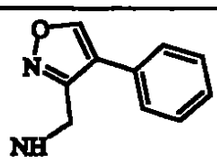
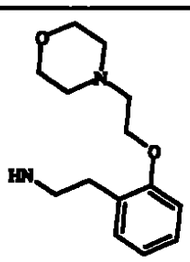
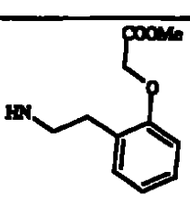
Example #114: 2,3-Dichloro-5-{*N*-{2-[2-(hydroxymethyl)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #115: 2,3-Dichloro-5-[*N*-(4-phenylisoxazol-3-ylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #116: 2,3-Dichloro-5-(*N*-{2-[2-(2-morpholinoethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #117: 2,3-Dichloro-5-(*N*-{2-[2-(methoxycarbonylmethoxy)phenyl]ethyl}-carbamoyl)-4*H*-thieno[3.2-*b*]pyrrole



Ex	R	NMR	Rt	M/z
#114[1]		1H NMR : 2.9(2H,q), 3.4(2H,q), 4.6(2H,d), 5.1(1H,t), 7.1(1H,s), 7.2(3H,m), 7.4(1H,m), 8.4(1H,m)	4.55	369
#115[2]		1H NMR : 4.7(2H,s), 7.1(1H,s), 7.4(3H,m), 7.6(2H,m), 8.8(1H,t), 9.2(1H,s)	5.01	392
#116[3]		1H NMR (CDCl3) : 2.6(4H,m), 2.8(2H,t), 3.0(2H,t), 3.7(6H,m), 4.1(2H,t), 6.3(1H,m), 6.6(1H,s), 6.9(2H,m), 7.2(2H,m), 9.8(1H,b)	4.26	468
#117[4]		(CDCl3) : 3.0(2H,q), 3.8(2H,q), 3.9(3H,s), 4.7(2H,s), 6.6(1H,s), 6.7(1H,s), 6.8(1H,d), 7.0(1H,t), 7.2(2H,m)	4.47	413

[1] Amine: EP86-300884

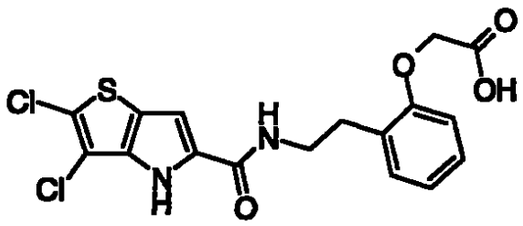
[2] Amine: Method #33

[3] Amine: Method #34

[4] Amine: Method #35

Example #118

5-(*N*-{2-[2-(Carboxymethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



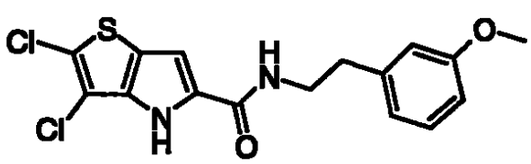
2,3-Dichloro-5-(*N*-{2-[2-(methoxycarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole (Example #117, 100mg,0.25mmol) dissolved in 2:1 THF : methanol (2ml), was treated with 1N Lithium hydroxide solution (0.25ml, 0.25mmol), followed by the addition of water till the solution was just opalescent and then stirred for 2 hours at room temperature. The organic solvents were removed by evaporation under reduced pressure, the solution filtered then acidified with 2N HCl to give a thick white precipitate which was isolated by filtration, washed with water and dried under reduced pressure over phosphorous pentoxide to give the title compound (83mg)

1H NMR : 2.9(2H,q), 3.5(2H,q), 4.7(2H,s), 6.8(2H,m), 7.1(1H,s), 7.2(2H,m), 8.4(1H,m), 12.4(1H,s)

HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 4.47min m/z 413 (M+H)

Example #119

2,3-Dichloro-5-{*N*-[2-(3-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

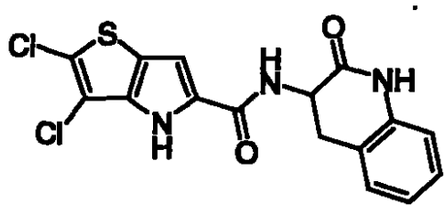


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 100mg, 0.42mmol) was suspended in DCM 10ml; 2M oxalyl chloride solution in DCM (750ul, 1.5mmol) was added dropwise followed by one drop of DMF and the resultant mixture stirred overnight at room temperature. The suspension was filtered, the residue washed with DCM and the filtrate

evaporated to dryness under reduced pressure and then azeotroped with toluene to give a yellow solid which was dissolved in DCM (6.9ml) under nitrogen. Calcium carbonate (60mg, 0.6mmol) was added followed by a solution of 3-methoxyphenethylamine; 90mg, 0.4mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered, the residue washed with DCM followed by 0.1 M HCl then water to give the title compound as a white solid (98mg) 1H NMR (CDCl3) : 2.9(2H,t), 3.7(2H,t), 3.9(3H,s), 6.0(1H,m), 6.6(1H,s), 6.8(3H,m), 7.2(2H,m), 9.9(1H,s)
m/z 369 (M+H)

Example #120

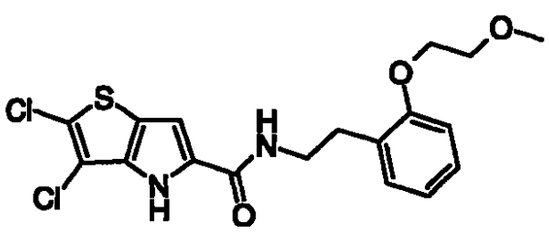
2,3-Dichloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



This was prepared following the procedure described in Example #97 using 3-aminohydrocarbostyril (Arch.Biochem&Biophys. 1963 109 48) was used in place of 4-aminobenzyl alcohol and 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9) was used in place of 5-(*N*-carboxymethylcarbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole to give the title compound: 1H NMR : 3.0(2H,d), 4.7(1H,q), 6.9(3H,m), 7.2(2H,m), 8.5(1H,d), 10.35(1H,s)
HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 4.44min
m/z 380 (M+H)

Example #121

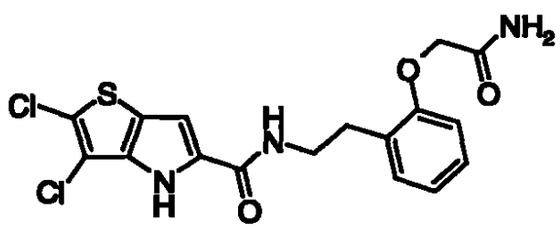
2,3-Dichloro-5-(*N*-{2-[2-(2-methoxyethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole



2,3-Dichloro-5-{*N*-[2-(2-hydroxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole (Example 73, 177.5mg, 0.5mmol) was dissolved in THF 3ml under nitrogen together with methoxyethanol (38µl, 0.5mmol) and triphenylphosphine (131mg, 0.5mmol), the resultant stirred solution was cooled to 0C and treated with DIAD (98µl,0.5mmol) dropwise over 30 mins, then allowed to warm to room temperature overnight. After evaporation to dryness the mixture was purified by chromatography on a 20g Bond Elute silica column eluting with DCM. The product was taken up in diethyl ether 20ml, washed with 2N NaOH (3x5ml), water (5ml) and saturated brine (5ml) then dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (45mg) 1H NMR (CDCl3) : 3.0(2H,t), 3.5(3H,s), 3.7(2H,m), 3.9(2H,m), 4.2(2H,m), 6.6(1H,m), 6.8(1H,s), 6.9(2H,m), 7.2(2H,m), 9.9(1H,s) HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 5.02min m/z 411 (M-H)

Example #122

5-(*N*-{2-[2-(Carbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



5-(*N*-{2-[2-(Carboxymethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Example #118,124mg, 0.3 mmol) was dissolved in DMF (3 ml) containing HOBT (50 mg, 0.33 mmol), DIPEA (140 µl, 0.69 mmol) and ammonium chloride (18mg, 0.36 mmol). The mixture was stirred for one minute and EDAC (64mg, 0.33 mmol) was added. The mixture was stirred at room temperature for approximately 18 hours. Water was added to the solution and a solid precipitated out. This solid was filtered off and was washed with water before being dried under reduced pressure to afford the title compound as a white solid (111mg)1H NMR : 2.9(2H,q), 3.5(2H,q), 4.5(2H,s), 6.8(2H,m), 7.0(1H,s), 7.2(2H,m), 7.5(1H,s), 7.6(1H,s), 8.4(1H,m), 12.4(1H,s)
HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 4.37min

m/z 412 (M+H)

The following compounds were made by the process of Example #122 using 5-(*N*-{2-[2-(Carboxymethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Example #118) and the appropriate amine:

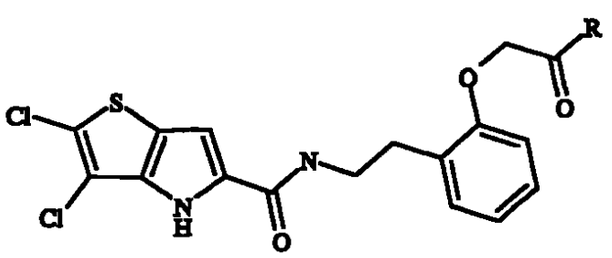
Example #123: 2,3-Dichloro-5-(*N*-{2-[2-(*N*-methylcarbamoylmethoxy)phenyl]ethyl}-carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #124: 2,3-Dichloro-5-(*N*-{2-[2-(*N,N*-dimethylcarbamoylmethoxy)phenyl]-ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

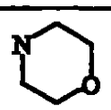
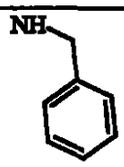
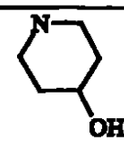
Example #125: 2,3-Dichloro-5-(*N*-{2-[2-(morpholinocarbonylmethoxy)phenyl]ethyl}-carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

Example #126: 5-(*N*-{2-[2-(*N*-Benzylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Example #127: 2,3-Dichloro-5-(*N*-{2-[2-(4-hydroxypiperidinocarbonylmethoxy)phenyl]-ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

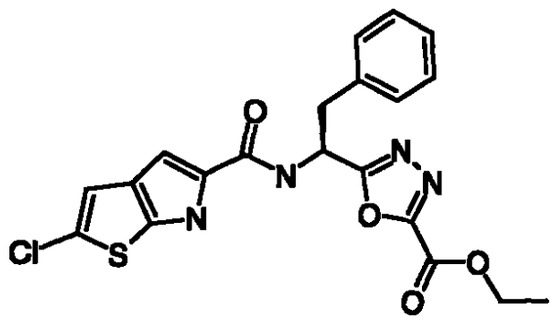


Ex	R	NMR	Rt	M/z
#123		1H NMR : 2.8(3H,d), 2.9(2H,q), 3.5(2H,q), 4.5(2H,s), 6.8(2H,m), 7.1(1H,s), 7.2(2H,m), 8.0(1H,m), 8.5(1H,m), 12.2(1H,s)	4.65	426
#124		1H NMR : 2.9(5H,m), 3.0(3H,s), 3.5(2H,q), 4.8(2H,s), 6.8(2H,m), 7.0(1H,s), 7.1(2H,m), 8.4(1H,m), 12.4(1H,s)	4.57	440

#125		1H NMR : 2.9(2H,q), 3.4-3.7(10H,m), 4.8(2H,s), 6.8(2H,m), 7.0(1H,s), 7.1(2H,m), 8.3(1H,m), 12.4(1H,s)	4.5	484
#126		1H NMR : 2.9(2H,q), 3.5(2H,q), 4.4(2H,d), 4.6(2H,s), 6.9(2H,m), 7.0(1H,s), 7.2-7.4(7H,m), 8.4(1H,m), 8.6(1H,m), 12.4(1H,s)	5.26	502
#127		1H NMR : 1.2-1.5(2H,m), 1.6-1.8(2H,m), 2.9(2H,q), 3.1(1H,q), 3.2(1H,q), 3.5(2H,q), 3.7(2H,q), 3.9(1H,m), 4.7(1H,d), 4.8(2H,s), 6.9(2H,m), 7.1(1H,s), 7.2(2H,m), 8.0(1H,s), 8.4(1H,m), 12.4(1H,s)	4.2	496

Example #128

(S)-2-Chloro-5-{*N*-[α-(5-ethoxycarbonyl-1,3,4-oxadiazol-2-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole

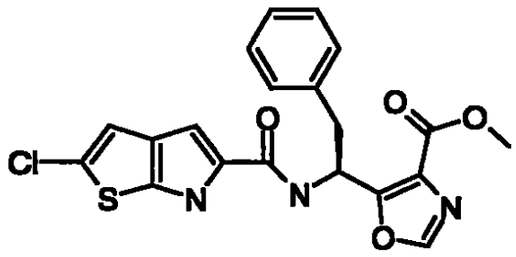


5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10 172mg, 0.86mmol) was dissolved in DCM (10ml) containing HOBT (115mg, 0.86mmol), DIPEA (331mg,2.57mmol) and ethyl (*S*)-5-(α-aminophenethyl)-1,3,4-oxadiazole-2-carboxylate trifluoroacetate (Method #16; 322mg, 0.86mmol). EDAC (205mg,1.07mmol) was added and the mixture stirred at ambient temperature for 16 hours. The reaction mixture was filtered and the filtrate washed

with dilute hydrochloric acid and water. After drying over magnesium sulphate and concentration the crude material was purified by bond elute silica column chromatography (eluent - DCM/Ethyl acetate gradient 0-20%) to give the title compound (104mg, 27%)
NMR 1.3(3H, t); 3.3-3.5(2H, m); 4.4(2H,q); 5.5-5.6(1H,m); 7.05(1H,s); 7.15(1H,s); 7.2-7.35(5H,m); 8.95(1H,d); 11.84(1H,s)
m/z 444.9

Example #129

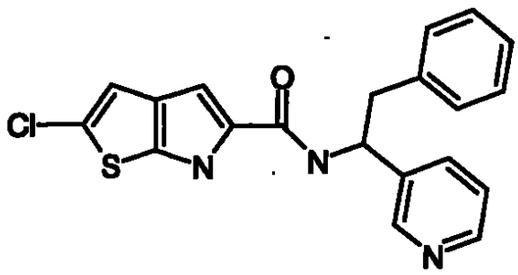
(*S*)-2-chloro-5-{*N*-[α-(4-methoxycarbonyloxazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10, 100mg, 0.5mmol) was dissolved in DCM (10ml) containing HOBT (68mg, 0.5mmol), DIPEA (193mg, 1.5mmol) and methyl (*S*)-5-(α-aminophenethyl)oxazole-4-carboxylate trifluoroacetate (Method #32, 230mg, 0.5mmol). EDAC (143mg, 0.75mmol) was added and the mixture stirred at ambient temperature for 4 hours. The reaction mixture was diluted with ethyl acetate (75ml) washed with dilute citric acid, water and brine, dried over magnesium sulphate and concentrated. The crude material was purified by bond elute silica column chromatography (eluent - DCM/Ethyl acetate gradient 0-50%) to give the title compound (147mg, 34%).
NMR 3.05-3.15(1H,m); 3.2-3.25(1H,m); 3.8(3H,s); 5.85-5.95(1H,m); 7.1(1H,s); 7.15(1H,s); 7.15-7.25(5H,m); 7.75(1H,d) 8.4(1H,s); 11.74(1H,s); m/z 429

Example #130

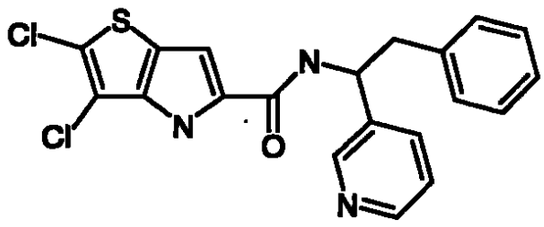
2-Chloro-5-{*N*-[α-(3-pyridyl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*] pyrrole (Method #10, 100mg, 0.5mmol) was dissolved in DCM (10ml) containing HOBT (68mg, 0.5mmol), DIPEA (193mg,1.5mmol) and α-(3-pyridyl)phenethylamine dihydrochloride (J. Am. Chem. Soc., 1950, 72, 1988; 135mg, 0.5mmol). EDAC (143mg,0.75mmol) was added and the mixture stirred at ambient temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (50ml), water (20ml) was added and the pH adjusted to 7 with dilute hydrochloric acid. The organic fraction was separated washed with water and brine, dried over magnesium sulphate and concentrated. The crude material was purified by bond elute silica column chromatography (eluent - Ethyl acetate) to give the title compound as a solid (128mg, 67%).
NMR 3.0-3.2(2H,m); 5.2-5.3(1H,m); 7.05(1H,s); 7.1-7.2(2H,m); 7.2-7.4(5H,m); 7.8(1H,d); 8.4(1H,d); 8.55-8.65(2H,m); 11.71(1H,s); m/z 381

Example #131

2,3-dichloro-5-{*N*-[α-(3-pyridyl)phenethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

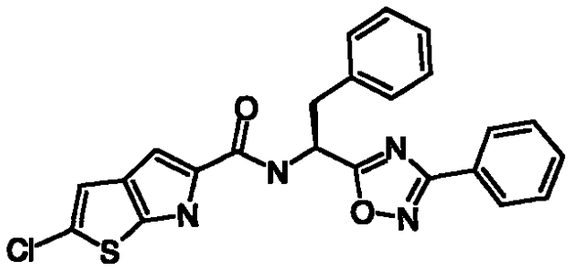


5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 118mg, 0.5mmol) was dissolved in DCM (10ml) containing HOBT (68mg, 0.5mmol), DIPEA (193mg,1.5mmol), α-(3-pyridyl)phenethyl)amine dihydrochloride (J. Am. Chem. Soc., 1950, 72, 1988; 135mg, 0.5mmol). EDAC (143mg,0.75mmol) was added and the mixture stirred at ambient temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (100ml), water (20ml) was added and the pH adjusted to 7 with dilute hydrochloric acid. The organic fraction was separated washed with water and brine, dried over magnesium sulphate and concentrated.

The crude material was purified by bond elute silica column chromatography (eluent - Ethyl acetate) to give the title compound as a solid (72mg, 34%)
NMR 3.0-3.3(2H,m); 5.2-5.3(1H,m); 7.1-7.2(2H,m); 7.2-7.4(5H,m); 7.85(1H,dt); 8.4(1H,dd); 8.6(1H,s); 8.75(1H,d); 12.28(1H,s); m/z 417

Example #132

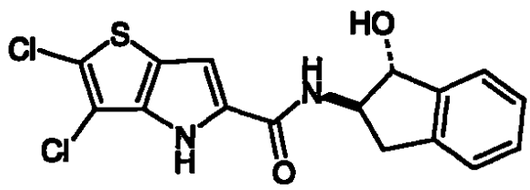
(*S*)-2-Chloro-5-{*N*-[α-(3-phenyl-1,2,4-oxadiazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*] pyrrole (Method #10, 201mg, 1mmol) was dissolved in DCM (15ml) containing HOBT (148mg, 1.1mmol), DIPEA (387mg,3mmol) and (S)-5 (α-aminophenethyl)-3-phenyl-1,2,4-oxadiazole trifluoroacetate (Method #18, 379mg, 1mmol). EDAC (238mg,1.25mmol) was added and the mixture stirred at ambient temperature for 16 hours. The reaction mixture was filtered and the filtrate diluted with DCM (50ml) washed with dilute hydrochloric acid and water. After drying over magnesium sulphate and concentration the crude material was purified by bond elute silica column chromatography (eluent - DCM/Ethyl acetate gradient 0-20%) to give the title compound (120mg, 26%);
NMR 3.3-3.6(2H,m); 5.5-5.7(1H,m); 7.1(1H,s); 7.15-7.4(6H,m); 7.55-7.65(3H,m); 8.05(2H,d); 9.05(1H,d); 11.9(1H,s); m/z 449

Example #133

2,3-Dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

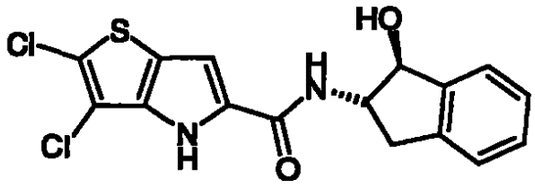


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 329 mg, 1.4 mmol) was dissolved in DCM (20 ml) containing HOBT (189 mg, 1.4 mmol), DIPEA (0.5 ml, 2.8 mmol) and 2-aminoindan-1-ol (Method #36, 250 mg, 1.4 mmol). The reaction mixture was stirred for one minute and EDAC (306 mg, 1.6 mmol) was added. The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20 ml) and the aqueous layer extracted with DCM (2 x 20 ml). The organic extracts were combined, dried over magnesium sulphate and concentrated under reduced pressure to give the title compound as a white solid (70 mg, 14%).

NMR: 2.8(1H,dd), 3.2(1H,dd), 4.4(1H,quin), 5.1(1H,d), 7.1(1H,s), 7.2-7.4(4H,m), 8.7(1H,d), 12.4(1H,s); m/z 366 (M-H)

Example #134

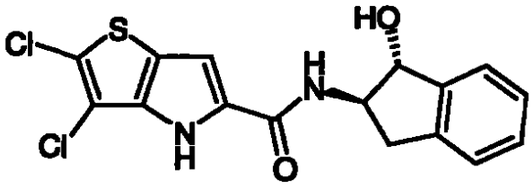
2,3-Dichloro-5-[*N*-((*1S,2S*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



and

Example #135

2,3-Dichloro-5-[*N*-((*1R,2R*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



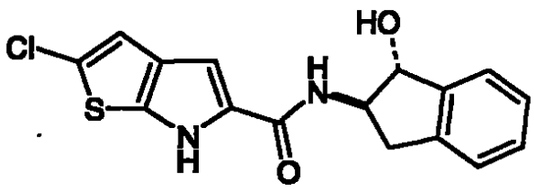
2,3-Dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole (Example #133) was subject to preparative HPLC under the following conditions to give 2,3-dichloro-5-[*N*-((*1S,2S*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole as a white solid (9 mg) and 2,3-dichloro-5-[*N*-((*1R,2R*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole as a white solid (12 mg).

Instrument	P.E Series 200 system 1

Column	Chiralpak AD (250mm x 4.6 mm) No.ADOOCE-AJ052
Eluent	MeOH
Oven Temperature	Ambient
Flow	1ml/min
Wavelength	254 nm
Sample concentration	1mg/ml in EtOH + sonication

Example #136

2-Chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole

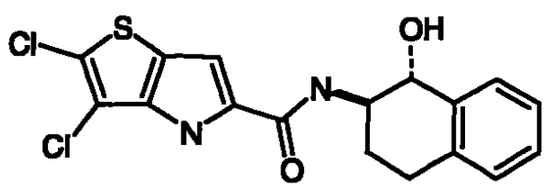


5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 280 mg, 1.4 mmol) was dissolved in DCM (20 ml) containing HOBT (189 mg, 1.4 mmol), DIPEA (0.5 ml, 2.8 mmol) and 2-aminoindan-1-ol (Method #36, 250 mg, 1.4 mmol). The reaction mixture was stirred for one minute and EDAC (306 mg, 1.6 mmol) was added. The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20 ml) and the aqueous layer extracted with DCM (2 x 20 ml). The organic extracts were combined, dried over magnesium sulphate and concentrated under reduced pressure to give the title compound as a white solid (78 mg, 17%).

NMR: 2.8(1H,dd), 3.2(1H,dd), 4.4(1H,quin), 5.1(1H,t), 5.6(1H,d), 7.1(1H,s), 7.2-7.4(5H,m), 8.4(1H,d), 11.8(1H,s); m/z 331 (M-H)

Example #137

2,3-Dichloro-5-[*N*-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

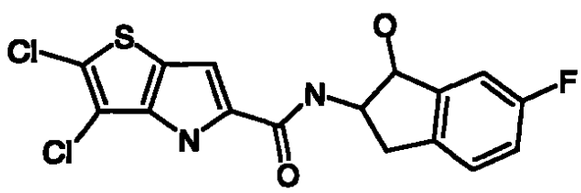


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 216 mg, 0.9 mmol) was dissolved in DCM (15 ml) containing HOBT (122 mg, 0.9 mmol), DIPEA (0.3 ml, 1.8 mmol)

and 2-amino-1,2,3,4-tetrahydronaphth-1-ol (Method #39, 150 mg, 0.9 mmol). The reaction mixture was stirred for one minute and EDAC (206 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20 ml) and the aqueous layer extracted with DCM (2x20 ml). The organic fractions were combined and concentrated under reduced pressure to give the title compound as a white solid (70 mg, 14%). NMR 1.8(1H,m), 2.0(1H,qd), 2.9(1H,m), 3.3(1H,qd), 4.4(1H,quin), 4.9(1H,m), 5.2(1H,s), 5.8(1H,brs), 6.8(1H,s), 7.0(1H,dd), 7.1(1H,d), 7.2(1H,s), 7.5(1H,d) 10.1(1H,brs).
m/Z 380 (M-H).

Example #138

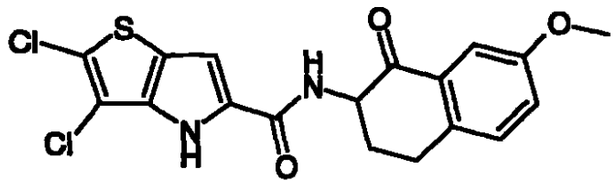
2,3-Dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 141 mg, 0.6 mmol) was dissolved in DCM (10 ml) containing HOBT (81 mg, 0.6 mmol), DIPEA (0.2 ml, 1.2 mmol) and 2-amino-6-fluoro-1-indanol (Method #38, 100 mg, 0.6 mmol). The reaction mixture was stirred for one minute and EDAC (138 mg, 0.7 mmol) was added. The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20 ml) and the aqueous layer extracted with DCM (2x20 ml). The organic fractions were combined and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (Isohexane:ethyl acetate 1:1) gave the title compound as a white solid (70 mg, 14%). NMR 3.0(1H,dd), 3.3(1H,m), 4.6(1H,q), 4.9(1H,t), 5.5(1H,d), 4.9(1H,m), 6.9-7.2(4H,m), 8.1(1H,d), 12.4(1H,brs); m/Z 383 (M-H)

Example #139

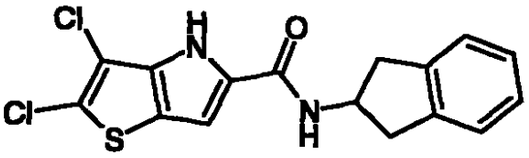
2,3-Dichloro-5-[*N*-(7-methoxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 216 mg, 0.9 mmol) was dissolved in DCM (20 ml) containing HOBT (122 mg, 0.9 mmol), DIPEA (0.3 ml, 1.8 mmol) and 2-amino-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene ((Farmaco, Ed. Sci.(1985), 40(6) , 422-428), 204 mg, 0.9 mmol). The reaction mixture was stirred for one minute and EDAC (206 mg, 1.0 mmol) was added. The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20 ml) and the aqueous layer extracted with DCM (2x20 ml). The organic fractions were combined and concentrated under reduced pressure to give the title compound as a brown solid (100 mg, 27%). NMR 3.0(1H,dd), 3.1(1H,dd), 3.3(2H,m), 4.8(1H,q), 5.8(1H,s), 6.9-7.2(4H,m), 8.6(1H,d), 12.2(1H,brs); m/z 408 (M-H).

Example #140

2,3-Dichloro-5-[*N*-(2-indanyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



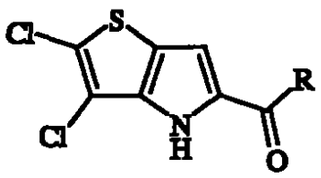
5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 45 mg, 0.19 mmol) was dissolved in DMF (10 ml) with 2-aminoindan (28 mg, 0.21 mmol), di-isopropylethylamine (0.1 ml, 0.57 mmol) and HATU (80 mg, 0.21 mmol). The mixtures were stirred at ambient temperature for approximately 16 hours. The mixture was partitioned between water and ethyl acetate and was washed with water (x 5). The aqueous phase was dried, filtered and concentrated, and the residue purified by silica bond-elut chromatography using a gradient of ethyl acetate in iso-hexane (0-50%) as eluent to give the title compound, m/z 351.

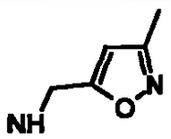
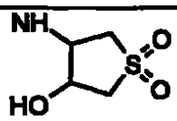
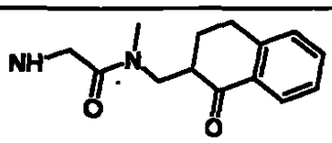
Following a similar procedure to the process of Example #140 the following examples were prepared:

Example #141: 2,3-Dichloro-5-[*N*-(3-methylisoxazol-5-yl)methyl]carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #142: 2,3-Dichloro-5-[*N*-(4-hydroxy-1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

Example #143: 2,3-dichloro-5-(*N*-{*N*-methyl-*N*-[(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

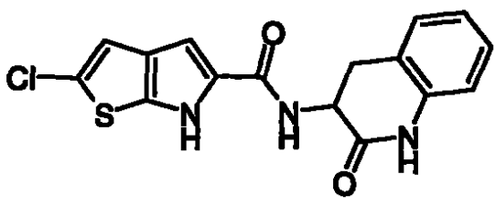


Example	R	M/z
#141		329
#142		365
#143 [1]		491

[1] Amine: Method #37

Example #144

2-Chloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole

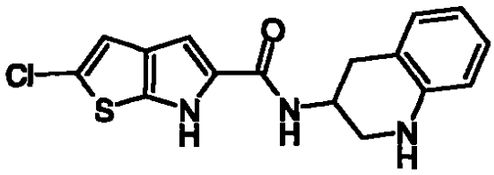


5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 101 mg, 0.5 mmol) was dissolved in DMF (2.5 ml) containing 3-amino-3,4-dihydro-2(1*H*)-quinolinone [J Med Chem (1986) 29 (12) 2427-32] (99 mg,0.5 mmol), HOBT (68 mg, 0.5 mmol) and Et_3N (55 mg, 0.5 mmol). The mixture was stirred for 1 minute before the addition of EDAC (96 mg, 0.5 mmol).

The mixture was stirred at ambient temperature for approximately 18 hours before being poured into water (50 ml), stirred vigorously and filtered. The recovered solid was washed with water, ether and dried to give the title compound as a amorphous solid.(161 mg). NMR ($DMSOd_6$): 11.96 (1H, s), 10.36 (1H, s), 8.50 (1H, d), 7.20 (2H, m), 7.19 (1H, s), 7.09 (1H, s), 6.96 (1H, m), 6.91 (1H,m), 4.72 (1H, m), 3.08 (2H, m); MH^+ 346.14.

Example #145

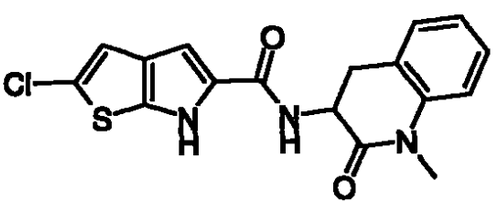
2-Chloro-5-[*N*-(1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 157 mg, 0.78 mmol) was dissolved in DMF (4 ml) containing 3-amino-1,2,3,4-tetrahydroquinoline [J Med Chem (1982) 25 (1) 68-70] (115 mg, 0.78 mmol) and HOBT (105 mg, 0.78 mmol). The mixture was stirred for 1 minute before the addition of EDAC (149 mg, 0.78 mmol). The mixture was stirred at ambient temperature for approximately 64 hours before being partitioned between water and EtOAc. The organics were washed with water, saturated aqueous $NaHCO_3$, water, saturated brine and dried. The organics were filtered, concentrated and chromatographed on Fluorochem silica 40-63µ 60A (eluent 40:60 EtOAc/isohexane) to afford the title compound as an amorphous solid (44 mg). NMR ($DMSOd_6$): 11.94 (1H, s), 8.04 (1H, d), 7.16 (1H, s), 7.06 (1H, s), 6.90 (2H, m), 6.48 (2H, m), 5.8 (1H, br), 4.18 (1H, m), 3.05 (1H, t), 2.85 (2H, m); MH^+ 332.17.

Example #146

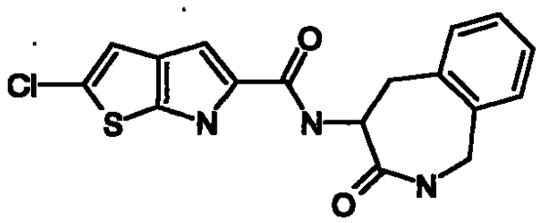
2-Chloro-5-[*N*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 80 mg, 0.4 mmol) was dissolved in DMF (2 ml) containing 3-amino-3,4-dihydro-1-carbostyril [JCS 1965 1080-1087] (71 mg, 0.4 mmol) and HOBT (54 mg, 0.4 mmol). The mixture was stirred for 1 minute before the addition of EDAC (77 mg, 0.4 mmol). The mixture was stirred at ambient temperature for approximately 18 hours before being partitioned between water and EtOAc. The organics were washed with water, saturated aqueous $NaHCO_3$, water, saturated brine and dried. The organics were filtered, concentrated and recrystalised from EtOAc to afford the title compound as an amorphous solid (66 mg). NMR 11.96 (1H, s), 8.54 (1H, d), 7.30 (2H, m), 7.17 (2H, m), 7.08 (2H, m), 4.68 (1H, m), 3.32 (3H, s), 3.14 (1H, m), 3.04 (1H, m); m/z (MH^+) 360.14

Example #147

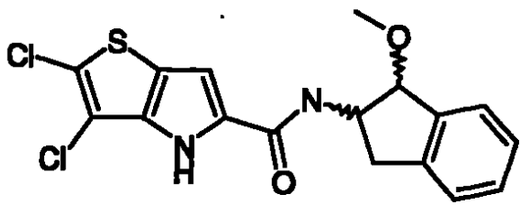
2-Chloro-5-[*N*-(3-oxo-2,3,4,5-tetrahydro-1*H*-benz[2]azepin-4-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole



5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole (Method #10; 101 mg, 0.5 mmol) was dissolved in DMF (2.5 ml) containing 4-amino-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one hydrochloride [CAS Reg No 148842-85-7] (107 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol) and Et_3N (101 mg, 1.0 mmol). The mixture was stirred for 1 minute before the addition of EDAC (96 mg, 0.5 mmol), then at ambient temperature for approximately 18 hours before being partitioned between water and EtOAc. The organics were washed with water, saturated aqueous $NaHCO_3$, water, saturated brine and dried; filtered and evaporated to afford the title compound as an amorphous solid (26 mg). NMR:11.92 (1H, s), 8.33 (1H, t), 8.29 (1H, d), 7.2 (6H, m), 5.30 (1H, m), 4.83 (1H, dd), 3.98 (1H, dd), 3.20 (2H, m); m/z (MH^+) 360.19.

Example #148

2,3-Dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole

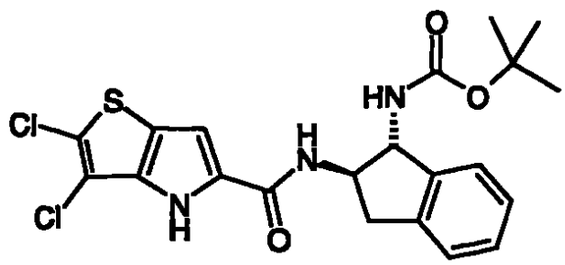


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 145mg, 0.613mmol), *trans*-2-amino-1-methoxyindan (Method #40, 100mg, 0.163mmol), DIPEA (0.105ml, 0.613mmol), and HOBT (83mg, 0.613mmol) was stirred in dichloromethane (5ml) for one minute. EDAC (147mg, 0.766mmol) was added and the mixture stirred at room temperature for 20 hours. The reaction mixture was evaporated, ethyl acetate (25ml) added and then washed with water. The organic solution was dried over magnesium sulphate and evaporated to give the title compound as a white powder (180mg, 77%).

NMR2.8(1H, dd), 3.3(1H, dd), 3.35(3H, s), 4.1-4.2(1H, m), 5.35-5.45(1H, m), 7.1-7.3(4H, m), 7.15(1H, s), 8.7(1H, d); m/z 380.9/382.9 (M+H).

Example #149

2,3-Dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole

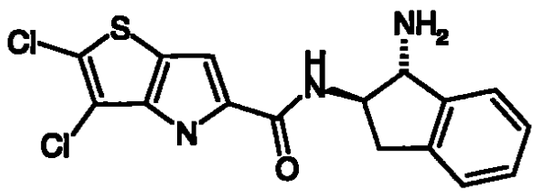


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 1.18g, 5.0mmol), (1*R*, 2*R*)-2-amino-1-[(1,1-dimethylethoxy)carbonylamino]indan (Method #43, 1.25g, 5.0mol), DIPEA (0.855ml, 5.0mmol), and HOBT (675mg, 5.0mmol) was stirred in dichloromethane (50ml) for one minute. EDAC (1.2g, 6.25mmol) was added and the mixture stirred at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (50ml), filtered and dried to give the title compound as a pale green powder (1.95g, 85%).

NMR1.4(9H, s), 2.8(1H, dd), 3.2(1H, dd), 4.5-4.7(1H, m), 5.1-5.2(1H, m), 7.05-7.3(5H, m), 7.4(1H, d), 8.6(1H, d), 12.4(1H, s).

Example #150

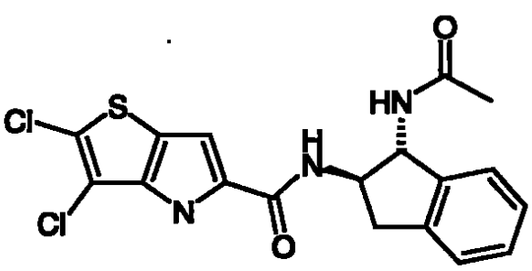
5-[*N*-(1-Aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



2,3-Dichloro-5-(*N*-{1-[(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole (Example #149, 1.0g, 2.15mmol) was dissolved in dichloromethane (20ml). Trifluoroacetic acid (2ml) was added and the mixture stirred at room temperature for 24 hours. The reaction was filtered and the isolated solid washed with dichloromethane to give the trifluoroacetic acid salt of the title compound as a pale green powder (800mg, 78%). NMR3.05(1H, dd), 3.4(1H, dd), 4.6-4.85(2H, m), 7.2(1H, d), 7.3-7.45(3H, m), 7.55(1H, d), 8.6(3H, broad s), 8.8(1H, d), 12.5(1H, s)

Example #151

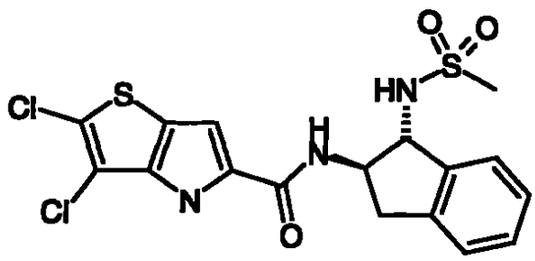
5-[*N*-(1-Acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



Triethylamine (101mg, 1.0mmol) was added to a suspension 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole trifluoroacetic acid salt (Example #150, 240mg, 0.5mmol) in dichloromethane (4ml), followed by acetyl chloride (47mg, 0.6mmol) dissolved in dichloromethane (1ml) and the reaction stirred at room temperature for 6 hours during which a white solid precipitated. The reaction was filtered and the crude material purified by silica chromatography with hexane : ethyl acetate to give the title compound as a white solid (50mg, 25%). NMR 1.87(3H, s), 2.82(1H, dd), 3.22(1H, dd), 4.45-4.62(1H, m), 5.38-5.5(1H, m), 7.02-7.27(4H, m), 7.1(1H, s), 8.35(1H, d), 8.59(1H, d), 12.36(1H, broad s); m/z 406.13/408.8 (M-H).

Example #152

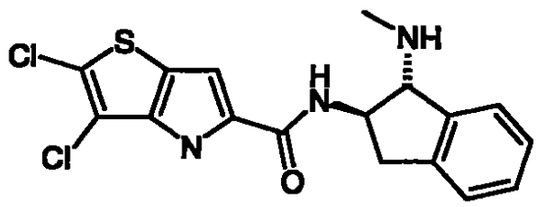
2,3-Dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 236mg, 1.0mmol), (1*R*,2*R*)-2-amino-1-methanesulphonamidoindan (Method #42, 226mg, 1.0mol), DIPEA (0.174ml, 1.0mmol), and HOBT (135mg, 1.0mmol) was stirred in dichloromethane (10ml) for one minute. EDAC (240mg, 1.25mmol) was added and the mixture stirred at room temperature for 20 hours. The mixture was diluted with ethyl acetate, washed with water (2 x 25ml), dried over magnesium sulphate and evaporated to give the title compound as a foam (400mg, 90%). NMR 2.84(1H, dd), 2.99(3H, s), 3.22(1H, dd), 4.44-4.64(1H, m), 4.89-5.0(1H, m), 7.14(1H, s), 7.16-7.36(4H, m), 7.84(1H, d), 8.64(1H, d), 12.43(1H, broad s); m/z 442.2/444.0 (M-H).

Example #153

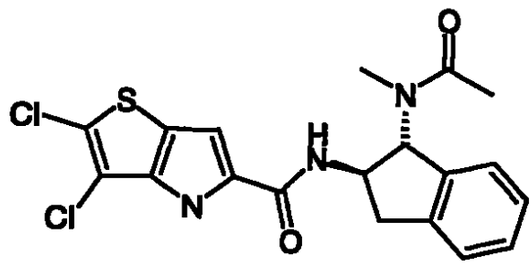
2,3-Dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



2,3-Dichloro-5-[*N*-(1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino}indan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole (Method #44, 900mg, 1.87mmol) in dichloromethane (20ml) treated with trifluoroacetic acid (2ml) at room temperature for 1 hour. Evaporation followed by co-evaporation with chloroform and drying gave the trifluoroacetic acid salt of the title compound as a pale brown foam (850mg, 92%). NMR 2.75(3H, s), 3.02(1H, dd), 3.5(1H, dd), 4.7-4.95(2H, m), 7.15(1H, s), 7.28-7.48(3H, m), 7.6(1H, d), 8.68(1H, d), 9.1(2H, broad s); m/z 380.4/382.4 (M+H).

Example #154

2,3-Dichloro-5-{*N*-[1-(*N*-methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



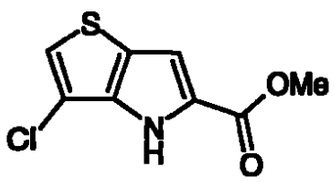
2,3-Dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole trifluoroacetic acid salt (Example #153, 390mg, 0.79mmol) in dichloromethane (5ml) at 5°C was treated with triethylamine (0.33ml, 2.37mmol) and acetyl chloride (68mg, 0.86mmol). After stirring at 5°C for 15 minutes the reaction was allowed to warm to room temperature and stirred for a further 2 hours. The mixture was diluted with ethyl acetate (25ml) and washed with saturated sodium bicarbonate and water. Drying over magnesium sulphate followed by evaporation gave the title compound as a pale brown foam (270mg, 80%). NMR: Indicates an approximate 1:1 ratio of rotamers of the title compound; 2.05(1.5H, s), 2.1(1.5H, s), 2.6(1.5H, s), 2.8(1.5H, s), 2.9-3.08(1H, m), 3.12-3.3(1H, m), 4.7-4.9(1H, m), 5.24(0.5H, d), 6.14(0.5H, d), 6.94-7.35(5H, m), 8.6(0.5H, d), 8.68(0.5H, d), 12.38(0.5H, broad s), 12.46(0.5H, broad s); m/z 421.9/423.9 (M+H)

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method #1

3-Chloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole

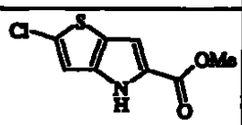
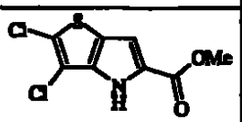
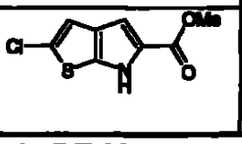


Methanolic sodium methoxide solution (28%) (5 ml, 25.9 mmol) was diluted with MeOH (5 ml) and was cooled to -25°C under nitrogen. A solution of 4-chloro-2-

thiophenecarboxaldehyde (J Heterocyclic Chem, 1976, 13, 393; 1.1 g, 7.5 mmol) and methyl azidoacetate (3.0 g, 26.1 mmol) in MeOH (20 ml) was added dropwise, maintaining the temperature at -25°C. On completion of addition the solution was allowed to warm to 5°C over a period of approximately 16 hours. The solution was added to saturated aqueous ammonium chloride (250 ml) and the mixture was extracted using DCM. The combined organic layers were concentrated at 0°C. The residue was taken up in xylene (30 ml) and this solution was added dropwise to xylene (120 ml) under reflux. The solution was heated under reflux for 30 minutes before being cooled and concentrated. The title compound was purified by a mixture of crystallisation (EtOAc/isohexane) and chromatography on a Bond Elut column eluting with a graduated solvent of 5-50% EtOAc in isohexane (640 mg, 40%). NMR ($CDCl_3$) 9.1 (1H, br), 7.1 (2H, s), 3.9 (3H, s); m/z 214.3.

Methods #2 - #4

The following compounds were made by the process of Method #1 using the appropriate starting materials

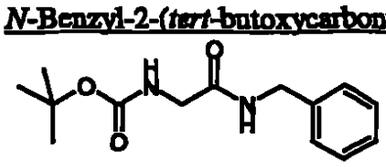
Meth	Compound	NMR ($CDCl_3$)	M/z
#2		9.1 (1H, br), 7.0 (1H, s), 6.9 (1H, s), 3.9 (3H, s)	214.2
#3 [1]		9.2 (1H, br), 7.0 (1H, s), 3.9 (3H, s)	248.2
#4 [2]		9.4-9.2 (1H, br), 7.0 (1H, s), 6.9(1H, s), 3.9 (3H, s)	214

1 Aldehyde: DE 2814798

2 Aldehyde: Aldehyde ref. Gronowitz *et al.* Tetrahedron Vol.32 1976 p.1403

Method #5

N-Benzyl-2-(*tert*-butoxycarbonylamino)acetamide

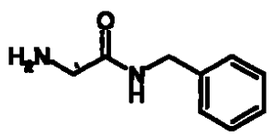


N-(*tert*-Butoxycarbonyl)glycine (875mg, 5mmol) was dissolved in DMF (7ml) containing DIPEA (3.5ml, 20mmol) and benzylamine (536mg, 5mmol). The mixture was allowed to stand for one minute before addition of *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (2.09g, 5.5mmol). The solution was allowed to stand for approximately 18 hours before being partitioned between ethyl acetate (50ml) and water (50ml). The layers were separated and the organic phase dried using magnesium sulphate, filtered, concentrated and purified using bond-elute silica column chromatography (eluent: dichloromethane-dichloromethane/methanol 5% gradient) to afford the *title compound* as an oil (1.32g, quantitative).

NMR: ($CDCl_3$): 7.2 (5H, m), 6.3(1H, br), 5.0(1H, br), 4.4(2H, d), 3.8(2H, d), 1.4(9H, s); m/z 265.4

Method #6

2-Amino-*N*-benzylacetamide

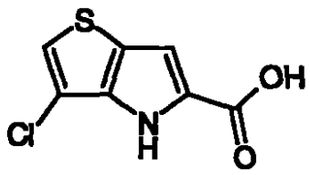


To a solution of *N*-benzyl-2-(*tert*-butoxycarbonylamino)acetamide (Method #5 , 1.18g, 4.47mmol) in dichloromethane (6ml) at 0°C was added dropwise, trifluoroacetic acid (2.4ml) and the resulting solution allowed to stir warming to room temperature overnight. The reaction mixture was neutralised by addition of saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic phases were dried over magnesium sulphate, filtered, concentrated and purified by bond-elute SCX column chromatography (eluent: methanol/dichloromethane (1:1) then methanol/dichloromethane (1:1)/ammonia5%) to afford the *title compound* as an oil (215mg, 29%).

NMR: ($CDCl_3$): 7.2(6H, m), 4.4(1.4H,d), 4.3(0.6H,d), 3.4(2H, br); m/z 165.17

Method #7

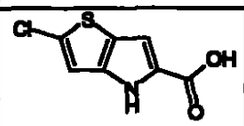
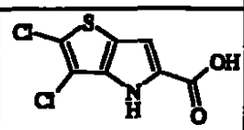
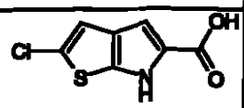
5-Carboxy-3-chloro-4*H*-thieno[3,2-*b*]pyrrole



3-Chloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole (Method #1; 0.61 g, 2.83 mmol) was taken up in MeOH (10 ml) and was heated under reflux. Aqueous lithium hydroxide (2.0 M, 3.0 ml, 6.0 mmol) was added portionwise over 45 minutes. The mixture was heated under reflux for 30 minutes before being cooled and concentrated. Water (20 ml) was added and the solution was neutralised using aqueous hydrochloric acid (2.0 M, 3.0 ml). The solution was extracted using EtOAc, and the combined organic layers were concentrated to afford the title compound as a yellow solid (0.57 g, 100%). NMR: 12.4 (1H, br), 7.4 (1H, s), 7.0 (1H, s); m/z 200.3.

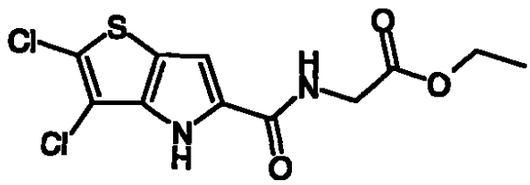
Methods #8 - #10

The following compounds were made by the process of Method #7 using the appropriate starting materials.

Meth	Compound	NMR	M/z	SM
#8		11.9 (1H, br), 7.0 (1H, s), 6.9 (1H, s)	200.1	Method #2
#9		7.0 (1H, s)	234.2	Method #3
#10		NMR 12.6-12.7 (1H, b), 12.0-12.1 (1H, b), 7.15(1H, s), 6.9(1H, s)	183	Method #4

Method #11

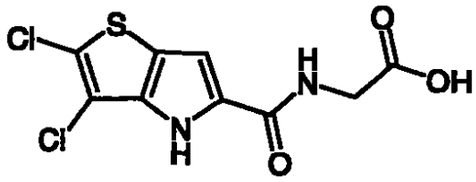
2,3-Dichloro-5-[*N*-(ethoxycarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 4.0g 16.95mmol) was added to a solution of glycine ethyl ester hydrochloride (2.60g, 18.64mmol) and DIPEA in dichloromethane (200ml) followed by HOBT (2.29g, 16.95mmol). The solution was stirred under nitrogen for 15 minutes before the addition of EDAC (3.89g, 22.03mmol). The mixture was stirred at ambient temperature for approximately 16 hours. The resultant white precipitate was isolated by filtration, washed with water and ether and dried. (4.79g, 88%).
NMR: 12.45 (1H,br), 8.75 (1H, t), 7.1 (1H, s), 4.1 (2H, q), 4.0 (2H, d), 1.2 (3H, t); m/z 321.2

Method #12

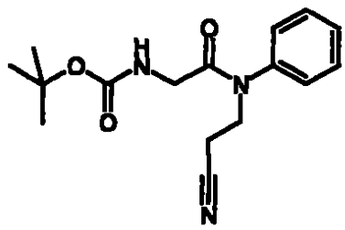
5-(*N*-Carboxymethylcarbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole



2N Sodium hydroxide solution (14.3ml, 28.7mmol) was added to a suspension of 2,3-dichloro-5-[*N*-(ethoxycarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole (Method #11, 4.60g, 14.33mmol) in tetrahydrofuran (THF) (100ml). The resultant solution was stirred at room temperature for one hour. The reaction mixture was concentrated '*in vacuo*', the residue diluted with water (250ml), the solution adjusted to pH=2 by addition of 2N Hydrochloric acid, and then extracted with ethyl acetate (3x150ml). The organic extracts were combined, dried over sodium sulphate then filtered and concentrated to give a white powder (3.34g, 80%); NMR: 12.6 (1H,br), 12.4 (1H, br), 8.6 (1H, t), 7.1 (1H, s), 3.9 (2H, d); m/z 291.17

Method #13

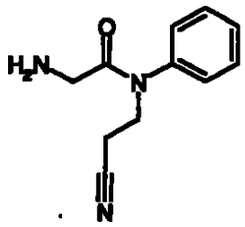
N-(2-Cyanoethyl)-*N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide



By a similar procedure to Method #5 the *title compound* was prepared using anilinopropionitrile to give a clear oil (598mg, 39%); NMR: ($CDCl_3$): 7.4(3H, m), 7.2(2H, m), 5.2(1H, br), 3.9(2H, t), 3.6(2H, d), 2.6(2H, t), 1.3(9H, s); m/z 304.51

Method #14

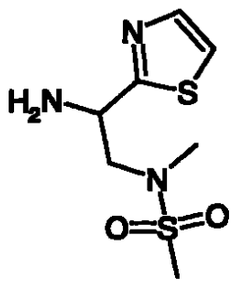
2-Amino-*N*-(2-cyanoethyl)-*N*-phenylacetamide



By a similar procedure to Method #6 the *title compound* was prepared using *N*-(2-cyanoethyl)- *N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide (Method #13) to give a clear oil (222mg, 60%); NMR: ($CDCl_3$): 7.4(3H, m), 7.2(1H, d), 7.1(1H, d), 3.9(2H, t), 3.1(1.33H, s), 3.0(0.67H, s), 2.65(1.33H, t), (0.67H, t); m/z 204.31

Method #15

N-[(2-Amino-2-(2-thiazolyl)]ethyl-*N*-methylmethanesulphonamide

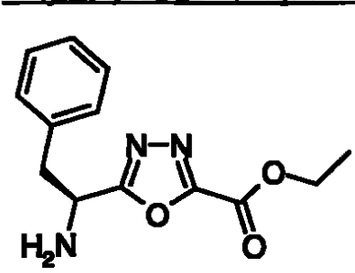


2-Bromothiazole (6.9 g, 42.0 mmol) was dissolved in dry diethyl ether (15 ml) and was added dropwise to butyl lithium (1.6 M, 29.7 ml, 47.5 mmol) in diethyl ether (40 ml) at -70°C. The mixture was stirred at -70°C for 30 minutes before the addition of a cold solution of ethyl 2-(*N*-methylmethanesulphonamido)acetate (Ger Offen, 1976, 27pp; 7.6 g, 39.0

mmol) in dry THF (70 ml). The solution was stirred for a further 30 minutes at -70°C before being allowed to warm to ambient temperature. Aqueous ammonium chloride (10%, 200 ml) was added and the solution was extracted using diethyl ether. The aqueous layer was acidified and re-extracted using diethyl ether. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue (5.30 g, 22.6 mmol) was dissolved in ethanol (100 ml) containing pyridine (18 ml) and hydroxylamine hydrochloride (1.88 g, 27.1 mmol). The mixture was heated under reflux in an inert atmosphere for 2.5 hours before being cooled and concentrated under reduced pressure. The residue was suspended in water and cooled to 0°C. The mixture was acidified to pH 4 using aqueous hydrochloric acid (2.0 M). A solid precipitated out of solution and was filtered off and washed with water. The product was dried under reduced pressure in the presence of phosphorous pentoxide. The dry solid (4.34 g, 17.4 mmol) was dissolved in acetic acid and 5% rhodium on carbon (40% *w/w*, 1.7 g) was added. The solution was agitated under an atmosphere of hydrogen at 5 bar for 48 hours. The reaction vessel was flushed free of hydrogen using inert gas and the solution was filtered through celite. The filtrate was concentrated under reduced pressure. The residue was suspended in ethanol and cooled to 0 °C. Aqueous hydrochloric acid (5.0 M) and ethanol (50 ml, 1:1) was added and the mixture was stirred for 30 minutes. A white precipitate was filtered off to afford the title compound (3.16 g) as the hydrochloride salt.

Method #16

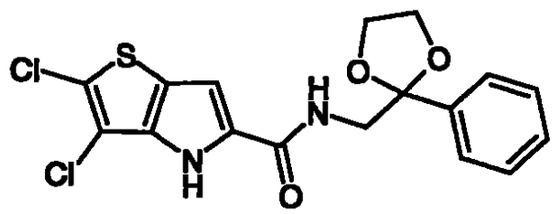
Ethyl (*S*)-5-(□-aminophenethyl)-1,3,4-oxadiazole-2-carboxylate trifluoroacetate



Ethyl (*S*)-5-[□-[(*tert*-butoxycarbonylamino)phenethyl]-1,3,4-oxadiazole-2-carboxylate, (Borg et al. J. Org. Chem. 1995, 60, 3112; 350mg) was dissolved in trifluoroacetic acid (5ml.) and allowed to stand at ambient temperature for 1 hour. The reaction mixture was concentrated and dried under vacuum to give a glassy solid (322mg) NMR 1.75(3H,t); 3.2-3.4(2H,m); 4.4(2H,q); 5.2(1H,t); 7.1-7.4(5H,m); 8.8-9.2(3H,bs)

Method #17

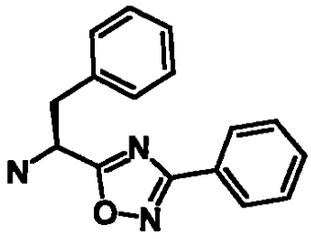
2,3-Dichloro-5-{*N*-[(2-phenyl-1,3-dioxolan-2-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



2-Phenyl-1,3-dioxolan-2-ylmethylamine hydrochloride (65 mg, 0.3 mmol) and 5-carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9; 71 mg, 0.3 mmol) were dissolved in DCM (10 ml) containing DIPEA (175 ml, 1.0 mmol) and HOBT (40 mg, 0.3 mmol). The mixture was stirred for one minute before the addition of EDAC (75 mg, 0.39 mmol). The solution was stirred at room temperature for approximately 18 hours. The mixture was concentrated and chromatographed on a Bond Elut column eluting with 20% - 40% EtOAc in isohexane. The title compound was isolated as a white solid (100 mg). NMR: 12.4 (1H, s), 8.2 (1H, s), 7.2 (1H, s), 4.0 (2H, m), 3.7 (2H, m), 3.6 (2H, d); m/z 395.2.

Method #18

(*S*)-5-(□-Aminophenethyl)-3-phenyl-1,2,4-oxadiazole trifluoroacetate



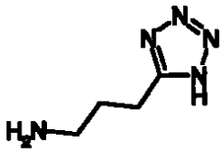
BOC-Phenylalanine (614mg, 2.32mmol) was dissolved in DCM (20ml) cooled with ice/water and dicyclohexyl carbodiimide (239mg, 1.16mmol) added. After stirring at 0-5°C for 1 hour the reaction mixture was filtered and concentrated in vacuo. Phenylamidoxime (104mg,0.77mmol) and pyridine (10ml) were added and the mixture heated to reflux for 2 hours. The reaction mixture was then evaporated to small volume, dissolved in ethyl acetate, washed with dilute citric acid, saturated sodium bicarbonate, water and brine, dried with magnesium sulphate and evaporated to give a crude product which was purified by chromatography on silica gel (eluted with Hexane/ ethyl acetate 4:1) to (S)-5-[□-(*tert*-butoxycarbonylamino)phenethyl]-3-phenyl-1,2,4-oxadiazole (274mg).

NMR 1.2-1.4 (9H,s), 3.1-3.3 (2H,m); 5.1-5.2(1H,m); 7.2-7.3(5H,m); 7.5-7.6(3H,m); 7.8(1H,d); 7.95-8.05(2H,m); m/z 364

(*S*)-5-[□-(*tert*-Butoxycarbonylamino)phenethyl]-3-phenyl-1,2,4-oxadiazole (274mg) was dissolved in trifluoroacetic acid (5ml) and stirred at ambient temperature for 2 hours. After evaporation and drying under vacuum the title compound was obtained as a pale yellow solid (232mg). NMR 3.2-3.5(2H,m); 5.15(1H,t); 7.1-7.3(5H,m); 7.4-7.6(3H,m); 7.9(2H,d); 9.0(3H,s); m/z 266

Method #19

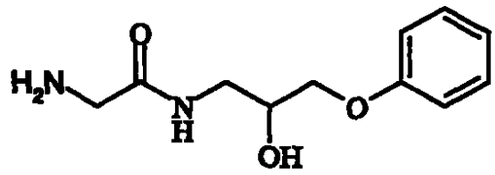
3-(1*H*-Tetrazol-5-yl)propylamine



4-{[(Phenylacetyl)oxy]amino}butanamide (*J. Biol. Chem.*, 1971, **246**, 6683) (16 g) was dissolved in dry pyridine (150 ml) and the solution was cooled to -10°C. A solution of $POCl_3$ (8.1 ml) in DCM (16.5 ml) was added dropwise over 30 minutes. The mixture was stirred at ambient temperature for 1 hour before being diluted with water until the pH reached 5. The solution was extracted using EtOAc. The combined organic layers were washed with dilute aqueous hydrochloric acid and water before being dried, filtered and concentrated. The resulting solid (9.2 g, 42.8 mmol) was dissolved in dry DMF (30 ml) and the solution was heated on a steam bath for 2 hours. Ammonium chloride (2.22 g, 41.5 mmol) was added to the hot solution along with sodium azide (2.68 g, 56.3 mmol). The mixture was cooled and left to stir for over 48 hours. The solution was filtered and basified to pH 8 using aqueous potassium bicarbonate. The aqueous layer was washed using EtOAc before being acidified using dilute aqueous hydrochloric acid. A white solid was filtered off. This solid (3.0 g, 11.5 mmol) was dissolved in acetic acid (50 ml) and water 5 ml. Palladium on charcoal (5%, 400 mg) was added and the solution was shaken under an atmosphere of hydrogen for 6.5 hours. The suspension was filtered and washed with acetic acid. The filtrate was concentrated and dried. The residue was treated with iso-propanol and the title compound was filtered off as a white solid (1.37 g, 94%).

Method #20

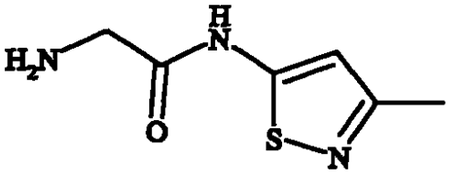
2-Amino-*N*-(2-hydroxy-3-phenoxypropyl)acetamide



N-Benzyloxycarbonylglycine (2.09 g) was dissolved in toluene (40 ml) and DMF (5 drops). Oxalyl chloride (1.3 ml) was added and the mixture was stirred at ambient temperature for 2 hours. The solution was diluted with diethyl ether (25 ml) and was added dropwise to a solution of 1-amino-3-phenoxy-2-propanol (1.67 g) in diethyl ether (25 ml). Sodium hydroxide (0.4 g) was dissolved in water (1.5 ml) and was added to the mixture. The solution was stirred for greater than 48 hours before being filtered. The sticky solid isolated was added to saturated aqueous sodium bicarbonate (100 ml) and was stirred for 15 minutes before being filtered. The solid was recrystallized from an EtOAc/petrol mixture. This resulting compound (650 mg) was dissolved in MeOH (10 ml) and palladium on charcoal (5%, 50 mg) was added along with acetic acid (1 ml). The solution was stirred under an atmosphere of hydrogen for 4 hours before being filtered. The filtrate was concentrated to afford an oily residue. The residue was recrystallized from EtOH/diethyl ether mixture to afford the title compound (200 mg).

Method #21

2-Amino-*N*-(3-methylisothiazol-5-yl)acetamide

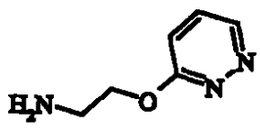


N-*t*-Butoxycarboylglycine (1.92 g, 1.1 mmol) was dissolved in dry EtOAc (20 ml) and the solution was cooled to -25°C. *N*-Methyl morpholine (1.1 g, 1.1 mmol) was added and the mixture was stirred for 2 minutes before the addition of ethyl chloroformate (1.08 g, 1.0 mmol). A white solid precipitated from solution. A suspension of 5-amino-3-methylisothiazole hydrochloride (1.5 g, 1.0 mmol) was added in triethylamine (1.01 g, 1.0 mmol) and dry EtOAc (10 ml). The mixture was stirred at ambient temperature for 17 hours before being filtered. The filtrate was concentrated and the residue was purified by flash column chromatography, using diethyl ether as eluent. The residue (271 mg, 0.1 mmol) was

dissolved in EtOAc (3 ml). Ethanolic HCl (1 ml) was added and the mixture was stirred at ambient temperature for 2.5 hours. The title compound precipitated as a white solid and was isolated by filtration (220 mg, 92%).

Method #22

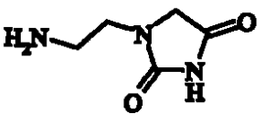
2-(Pyridazin-3-yloxy)ethylamine



Ethanolamine (6.0 ml) was suspended in dry xylene (100 ml) and the mixture was stirred at ambient temperature with sodium hydride (3 g). After 20 minutes the solution was cooled to 0°C. 3,6-Dichloropyridazine (15.0 g) was added. The solution was warmed to ambient temperature and was stirred for 15 hours before being extracted with chloroform. The chloroform was concentrated and the residue was taken up in EtOAc before being filtered. Ethanolic HCl was added and a white solid was filtered off. This compound (550 mg) was dissolved in MeOH (130 ml) and palladium on charcoal (5%, 200 mg) was added. The suspension was stirred under an atmosphere of hydrogen for 6 hours before being filtered. The filtrate was concentrated and the residue was triturated using diethyl ether. The title compound was isolated as a white solid (340 mg).

Method #23

1-(2-Aminoethyl)imidazolidine-2,4-dione

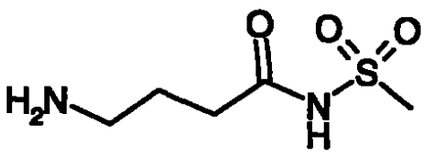


Ethylene diamine (30 ml) was dissolved in DCM (130 ml) with di-*t*-butyl dicarbonate (13.5 g). The mixture was stirred at ambient temperature for 30 minutes before the solvent was decanted off. The residue was washed with water and dried. The product (6.1 g) was dissolved in ethanol (15 ml). Chloroacetic acid (5.77 g) solution in aqueous sodium hydroxide (1 M, 61 ml) was added dropwise, followed by more aqueous sodium hydroxide (1 M, 31 ml). The mixture was stirred for 17 hours before being washed with diethyl ether. Benzyl chloroformate (5 g) was added to the aqueous phase and the mixture was stirred at ambient temperature for 4 hours. The solution was washed with diethyl ether and the aqueous layer

was acidified using aqueous citric acid (30%). The solution was extracted using EtOAc. The combined organic layers were washed with brine, then water before being dried, filtered and concentrated. The residue was triturated using diethyl ether/petrol mixture and the required intermediate was isolated as a white solid. Following repeated procedure on a larger scale, this solid (28 g) was dissolved in ethanol (250 ml) containing palladium on charcoal (10%, 4.6 g). The suspension was stirred under an atmosphere of hydrogen until the reaction was complete. The mixture was filtered and the filtrate was concentrated. The residue (3 g, was treated with potassium cyanate (1.3 g) in water (30 ml) and the mixture was heated under reflux for 2 hours. An excess of concentrated hydrochloric acid was added and the mixture was heated for a short time before being concentrated. The residue was taken up in water (50 ml) and was loaded onto basic Amberlite® IRA resin. The resin was washed with water until the eluent was found to be neutral. Dilute aqueous hydrochloric acid was used to elute the crude product from the resin. The acidic fractions were concentrated and the residue was triturated with ethanol. The title compound was isolated as orange crystals (950 mg).

Method #24

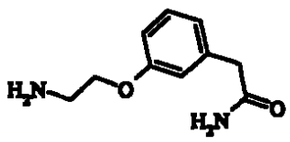
N-(4-Aminobutyryl)methanesulphonamide



4-Phthalimidobutyryl chloride (*J. Am. Chem. Soc.*, 1981, 103, 6750) (1.27 g) was heated with methane sulphonamide (480 mg) at 100°C for 15 min under argon. The mixture was cooled and left to stand for 17 hours. The residue was triturated with ethanol to afford the required intermediate. The solid (4 g) was treated with potassium hydroxide (75 g) in water (100 ml) at ambient temperature for 2 hours. Concentrated hydrochloric acid was added until the pH of the solution reached 9. The solution was extracted using EtOAc. The combined organic layers were concentrated and the residue was triturated using diethyl ether/petrol mixture and filtered. The residue (5.7 g) was taken up in water (150 ml) and dilute hydrochloric acid (1 M) was added until the pH reached 1. The mixture was heated on a steam bath for 1 hour before being cooled and extracted using EtOAc. The aqueous phase was concentrated and the residue was triturated using EtOAc/ethanol mixture to afford the title compound (1.5 g).

Method #25

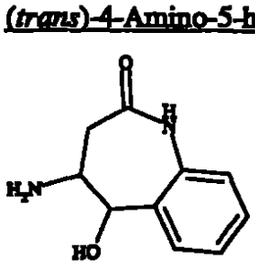
2-[3-(2-Aminoethoxy)phenyl]acetamide



3-Hydroxyphenylacetic acid (30.4 ml) was dissolved in MeOH (160 ml). Concentrated sulphuric acid (1.6 ml) was added and the mixture was heated under reflux for 6 hours. The mixture was concentrated to low bulk before the addition of toluene (120 ml). The mixture was washed with water, saturated aqueous sodium bicarbonate and brine. The combined organic layers were reduced in volume by one half before being stirred with ammonia solution (180 ml) for 16 hours. The mixture was concentrated and filtered. The solid was washed with water and was dried. The residue (24 g) was dissolved in MeOH (400 ml) with 1,2-dibromoethane (20 ml) and sodium hydroxide (6 g). The solution was heated under reflux for 36 hours before being concentrated. The residue was partitioned between water and EtOAc. The organic phase was separated and concentrated. This residue was purified by medium pressure liquid chromatography, using 5% MeOH in DCM as eluent. The purified intermediate (7.5 g) was dissolved in ethanol (300 ml) with ammonia solution (500 ml). The reaction vessel was sealed and the mixture was stirred at ambient temperature for 6 hours before being allowed to stand for 2.5 days. The solution was concentrated and the residue was purified using medium pressure liquid chromatography, using 25% MeOH in DCM as eluent, to afford the title compound (4.1 g).

Method #26

(*trans*)-4-Amino-5-hydroxy-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one

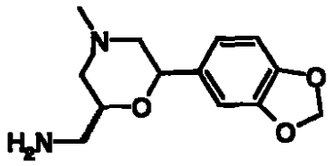


Anhydrous toluene (33 ml) and ethanol (2.2 ml) were heated with potassium (0.3 g) until all the metal has dissolved. 3,4-Dihydro-1*H*-1-benzazepine-2,5-dione (*J. Org. Chem.*, 1972, 37, 208) (11.6 g) was added and the mixture was heated under reflux for 2 minutes

before being cooled to ambient temperature. Butyl nitrite (1.7 ml) was added and the mixture was stirred for 4 hours before being left to stand for 3 days. The solvent was decanted and the residue was passed down a Fluorisil® column, using 5% MeOH in chloroform as eluent. The product (1.0 g) was dissolved in water (40 ml) and MeOH (14 ml) containing palladium on charcoal (5%, 500 mg). The mixture was stirred under an atmosphere of hydrogen for 1 hour. The mixture was filtered and the filtrate was concentrated. The residue was recrystallized using ethanol to afford the title compound.

Method #27

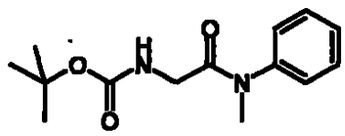
(2*R*,5*S*)- 2-Aminomethyl-5-(1,3-benzodioxol-5-yl)- 4-methylmorpholine



A solution of 1-(1,3-benzodioxol-5-yl)-2-(methylamino)ethanol (*Synthesis*, 1979, 423) (28.65 g) and oxirane-2-carboxamide (*Bull. Chem. Soc. Jpn.*, 1989, 62, 3202) (14.0 g) in ethanol (500 ml) was heated under reflux for 1.5 hours. The solution was concentrated and the residue was triturated using diethyl ether. A white powder was filtered off. This product (3.0 g) was added portionwise to trifluoroacetic acid (30 ml) at ambient temperature. The solution was stirred for 45 minutes before being concentrated. The residue was basified using saturated aqueous sodium bicarbonate. The mixture was filtered and the filtrate was concentrated. The residual oil was purified by flash column chromatography, using a gradient of MeOH in EtOAc as eluent, to afford both *cis*- and *trans*- isomers of the required intermediate. The *trans*- isomer (1.6 g) was dissolved in dry diethyl ether (180 ml). The solution was heated under reflux using Soxhlet equipment with lithium aluminium hydride (2.0 g) for 16 hours. The solution was cooled and water (2 ml) was added with sodium hydroxide solution (3 M, 2 ml), followed by more water (6 ml). The metal residues were removed by filtration and the filtrate was extracted using DCM. The combined organic layers were dried, filtered and concentrated. The residue was triturated using ethanol to afford the title compound as a white solid.

Method #28

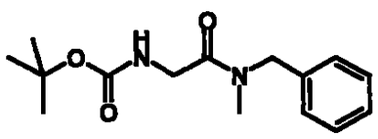
N-Methyl-*N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide



By a similar procedure to Method #5 the *title compound* was prepared using *N*-methylaniline to give a pale orange oil (771mg, 58%); NMR: ($CDCl_3$): 7.4 (3H, m), 7.1(2H, m), 5.3(1H, br), 3.6(2H, br), 3.2(3H, s), 1.4(9H, s); m/z 265.42

Method #29

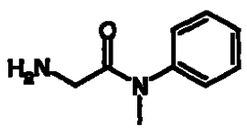
N-Benzyl-*N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide



By a similar procedure to Method #5 the *title compound* was prepared using *N*-benzylmethylamine to give a yellow oil (670mg, 48%); NMR: ($CDCl_3$): 7.2 (5H, m), 5.5(1H, br), 4.6 (1.33H, s), 4.4(0.67H, s), 3.9(2H, br), 2.9(1H, s), 2.8(2H, s), 1.4(9H, s); m/z 279.50

Method #30

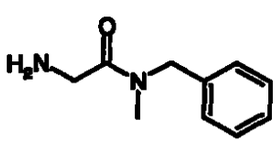
2-Amino-*N*-methyl-*N*-phenylacetamide



By a similar procedure to Method #6 using *N*-methyl-*N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide (Method #28) the *title compound* was prepared to give the *title compound* as a clear oil (231mg, 56%); NMR: ($CDCl_3$): 7.3(3H, m), 7.1(2H, d), 3.2(3H, s), (2H, br); m/z 165.17

Method #31

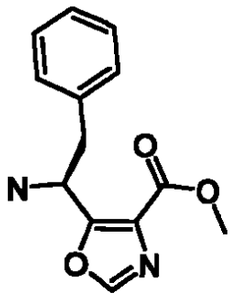
2-Amino-*N*-methyl-*N*-benzylacetamide



By a similar procedure to Method #6 using *N*-benzyl-*N*-phenyl-2-(*tert*-butoxycarbonylamino)acetamide (Method #29) the *title compound* was prepared to give the *title compound* as a clear oil (256mg, 73%); NMR: ($CDCl_3$): 7.3(5H, m), 4.6(1.33H, s), 4.4(0.67H, s), 3.4(2H, br), 2.95(1.33H, s), 2.8(2.34H, s), (1.33H, s); m/z 179.23

Method #32

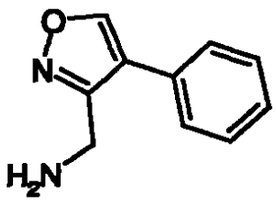
Methyl (*S*)-5-(□-aminophenethyl)oxazole-4-carboxylate trifluoroacetate



Methyl (*S*)-5-[□-(*tert*-butoxycarbonylamino)phenethyl]-oxazole-4-carboxylate, (Tett. Lett., 1982, 23, 235; 417mg) was dissolved in trifluoroacetic acid (3ml) and stood at ambient temperature for 1 hour and concentrated to give an oil. Trituration with diethyl ether gave the title compound as a white solid. (281mg); NMR 3.1-3.25(1H,m); 3.3-3.4(1H,m); 3.7(3H,s); 5.2-5.3(1H,m); 7.05(2H,d); 7.2-7.3(3H,m); 8.7(1H,s); 8.75-8.85(3H,bs)

Method #33

3-Aminomethyl-4-phenylisoxazole



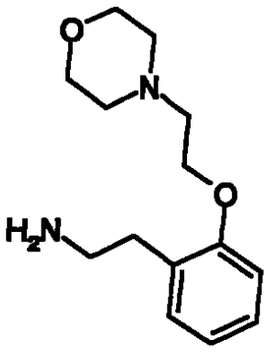
4-Phenylisoxazole-3-carboxylic acid ethyl ester (JOC 50 13 2372 1983; 404mg, 1.86mmol) dissolved in THF 10ml under nitrogen was treated with 2M lithium borohydride in THF (1.86ml, 3.72mmol). The resultant mixture was stirred at 0C for 5hours, then allowed to warm to room temperature overnight. 1M acetic acid was added dropwise till effervesence ceased, a further 20 ml of water was added and the resultant solution extracted with ethyl acetate (3x20 ml), the organic extracts were washed with saturated sodium bicarbonate solution (10ml) and saturated brine (10ml), dried with anhydrous magnesium sulphate and

evaporated to dryness under reduced pressure to give 3-hydroxymethyl-4-phenylisoxazole (295mg); NMR (CDCl3) : 4.9(2H,d), 7.3-7.5(5H,m), 8.5(1H,s)
m/z 176 (M+H)

3-Hydroxymethyl-4-phenylisoxazole (295mg,1.68mmol) was dissolved in THF 5ml under nitrogen together with phthalimide (292mg, 1.68mmol) and triphenylphosphine (440mg, 1.68mmol), the resultant stirred solution was cooled to 0C and treated with DIAD (330ul,1.68mmol) dropwise over 30 mins, then allowed to warm to room temperature overnight. After evaporation to dryness the mixture was purified by chromatography on a 20g Bond Elute silica column eluting with 1:1 DCM:hexane to give 4-phenyl-3-phthalimidomethylisoxazole (316mg): m/z 305 (M+H). This was dissolved in methanol 3ml, treated with hydrazine hydrate (114ul, 2.4mmol) and refluxed for 30 mins. The resultant suspension was filtered, the solid washed with ethanol (2x5ml) and the filtrate then evaporated to dryness, this residue was taken up in 2N HCl and any insoluble material again removed by filtration. The filtrate was basified with saturated sodium bicarbonate and extracted with ethyl acetate (3x10ml), the combined organic extracts were washed with water (5ml) and saturated brine (5ml), then dried over magnesium sulphate and evaporated under reduced pressure to give 3-aminomethyl-4-phenylisoxazole (130mg); NMR (CDCl3) : 4.1(2H,s), 7.3-7.5(5H,m), 8.4(1H,s); m/z 175 (M+H)

Method #34

2-[2-(2-morpholinoethoxy)phenyl]ethylamine



2-(2-Hydroxyphenyl)ethylamine (1.73g, 10mmol) dissolved in DCM 60ml was treated with a solution of sodium bicarbonate (1.68g, 20mmol) in water, the emulsion was stirred

vigorously in an ice bath and benzyl chloroformate (1.785g, 10.5mmol) was added dropwise over 10 mins and the mixture was stirred overnght at room temperature.
The DCM phase was removed and the aqueous phase extracted with DCM (2x20ml). The combined organics were then dried over magnesium sulphate and evaporated under reduced pressure, the product was purified by chromatography on 20g silica bond elute, eluting with DCM to give *N*-(benzyloxycarbonyl)-2-(2-hydroxyphenyl)ethylamine (1.4g); NMR (CDCl3) : 2.8(2H,q), 3.4(2H,q), 5.1(3H,m), 6.4(1H,s), 6.8(2H,m), 7.1(2H,m), 7.3-7.4(5H,m)

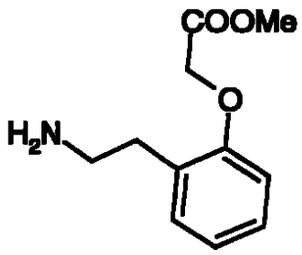
N-(Benzyloxycarbonyl)-2-(2-hydroxyphenyl)ethylamine (542mg, 2mmol) dissolved in DMF 5ml was treated with potassium carbonate (325 mesh, 350mg, 2.5mmol) and 2-chloroethyl p-toluenesulphonate (484ul,2.6mmol) and the mixture was stirred at 60C overnight. After cooling, water 10ml was added and the mixture extracted with diethyl ether (3x20ml) dried over magnesium sulphate and evaporated under reduced pressure, the product was purified by chromatography on 20g silica bond elute, eluting with DCM to give *N*-(benzyloxycarbonyl)-2-[2-(2-chloroethoxy)phenyl]ethylamine(450mg); NMR (CDCl3) : 2.9(2H,q), 3.5(2H,m), 3.8(2H,m), 4.2(2H,m), 4.9(1H,b), 5.1(2H,s), 6.8(1H,d), 6.9(1H,t), 7.1(2H,m), 7.3-7.4(5H,m) HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 4.98min

N-(Benzyloxycarbonyl)-2-[2-(2-chloroethoxy)phenyl]ethylamine (110mg, 0.33mmol) dissolved in NMP 3ml was heated with morpholine (174ul, 2mmol) at 80C overnight. Water (5ml) was added and the mixture extracted with ethyl acetate (30ml), the organic phase was washed with water (2x5ml) dried over magnesium sulphate and evaporated under reduced pressure to give *N*-(benzyloxycarbonyl)-2-[2-(2-morpholinoethoxy)phenyl]ethylamine (143mg); NMR (CDCl3) : 2.5(4H,q), 2.8(4H,m), 3.4(2H,q), 3.7(4H,q), 4.1(2H,t), 5.0(2H,s), 5.3(1H,b), 6.8(2H,m), 7.1(1H,d), 7.2(1H,t), 7.3-7.4(5H,m) HPLC Hichrome C18 column Acetonitrile/water/0.1%TFA 5-95% over 7.5 min Rt 3.73min m/z 385 (M+H)

N-(Benzyloxycarbonyl)-2-[2-(2-morpholinoethoxy)phenyl]ethylamine (143mg) dissolved in methanol was treated with 10% palladium on carbon and hydrogenated for 2 hours. The solid was removed by filtration, washed with methanol (2x2ml), the filtrate evaporated under reduced pressure and azeotroped twice with toluene to give the title compound (83mg) m/z 251 (M+H), which was used directly in the next step.

Method #35

Methyl 2-[2-(2-aminoethyl)phenoxy]acetate

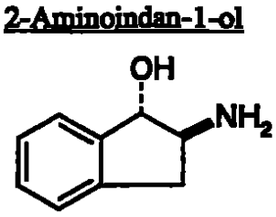


N-(Benzyloxycarbonyl)-2-(2-hydroxyphenyl)ethylamine (see Method #34: 718mg, 2.65mmol) dissolved in DMF 6ml was treated with potassium carbonate (-325 mesh, 397mg, 4.0mmol) methyl bromoacetate (362ul, 3.7mmol) and the mixture was stirred overnight at room temperature. After cooling, water 10ml was added and the mixture extracted with diethyl ether (3x20ml) dried over magnesium sulphate and evaporated under reduced pressure to give methyl 2-{2-[2-(benzyloxycarbonyl(amino)ethyl)]phenoxy}acetate (847mg); NMR (CDCl3) : 2.8(2H,q), 3.5(2H,m), 3.8(3H,s), 4.6(2H,s), 5.1(3H,m), 6.7(1H,d), 6.9(1H,t), 7.1-7.4(7H,m)

Methyl 2-{2-[2-(benzyloxycarbonylamino)ethyl]phenoxy}acetate (343mg, 1mmol) dissolved in methanol together with p-toluenesulphonic acid (190mg,1mmol) was treated with 10% palladium on carbon and hydrogenated for 2 hours. The solid was removed by filtration, washed with methanol (2x2ml), the filtrate evaporated under reduced pressure and azeotroped twice with toluene to give methyl 2-[2-(2-aminoethyl)phenoxy]acetate (403mg), m/z 210 (M+H) which was used without further purification.

Method #36

2-Aminoindan-1-ol



Isoamyl nitrite (15 ml, 108 mmol) was added to a solution of indan-1,2-dione (12 g, 90 mmol) in methanol (380 ml) at 45°C followed by concentrated HCl (12 ml) dropwise over 5 minutes. The reaction mixture was stirred for 3 hours at room temperature. Excess isoamyl

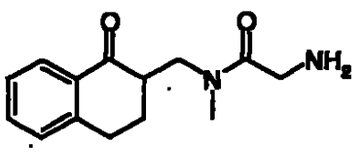
nitrite (1 ml) and concentrated HCl (1 ml) was added and the suspension stirred for a further 15 minutes. On cooling to room temperature a white precipitate formed. The precipitate was filtered off and washed with cold methanol (40 ml) followed by diethyl ether (40 ml) to afford indan-1,2-dione-2-oxime as a white solid (6.2 g, 43%).

NMR: 3.8(2H,s), 7.4(1H,t), 7.6(1H,d), 7.7(2H,t); m/z 162 (M+H)

A solution of indan-1,2-dione-2-oxime (6.2 g, 39 mmol) in ethanol (470 ml) and 4MHCl/Dioxane (36 ml) was hydrogenated at room temperature and 40 psi. The reaction mixture was filtered through celite, washed with ethanol (30 ml) and concentrated under reduced pressure to give 10 g of an off-white solid which was recrystallised from ethanol to give the title compound as a white solid (5 g, 86%). NMR: 2.8(1H,dd), 3.2(1H,dd), 3.7(1H,q), 5.1(1H,t), 6.0(1H,d), 7.1-7.3(4H,m), 8.6(2H,s)

Method #37

2-Amino-*N*-methyl-*N*-(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methylacetamide



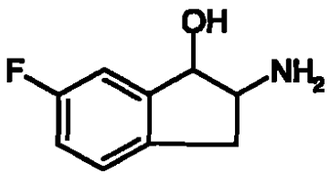
Tetralone (1 eq, 100 mmol, 15 g) and methylamine hydrochloride (2.5 eq, 250 mmol, 15 g) and paraformaldehyde (1 eq, 100 mmol, 3 g) in ethanol (100 ml) were heated under reflux for 16 hours. The reaction mixture was cooled and filtered to afford 2-(methylaminomethyl)-3,4,dihydro-1-(2H)-naphthalenone as a solid (14 g).

2-(Methylaminomethyl)-3,4,dihydro-1-(2*H*)-naphthalenone (1 eq, 20 mmol, 4.5 g), HOBT (1 eq, 20 mmol, 2.7 g), *N*-benzyloxycarbonylglycine (1 eq, 20 mmol, 4.18 g), triethylamine (1.25 eq, 25 mmol, 3 ml) and dicyclohexylcarbodi-imide (1 eq, 20 mmol, 4.12 g) were dissolved in dichloromethane (130 ml) and were stirred at ambient temperature for 18 hours before being cooled to 0 °C and filtered. The filtrate was concentrated and the residue was taken up in ethyl acetate before being washed with aqueous sodium bicarbonate, dried, filtered and concentrated. The residue was left to stand in a solution of hydrogen bromide in acetic acid for 30 minutes. The mixture was triturated with diethyl ether and the solvent was decanted off. The residue was treated with ammonia solution and this was extracted with

chloroform. The chloroform was concentrated and the residue was recrystallised from ethanol to afford the title compound.

Method #38

2-Amino-6-fluoro-1-indanol



To a solution of sodium carbonate (0.8 g, 7.2 mmol) in water (13 ml) was added 4-fluorophenylalanine (1.3 g, 7.2 mmol) followed by a solution of *N*-ethoxycarbonylphthalamide (1.6 g, 7.2 mmol) in ethyl acetate (10 ml). The two-phase reaction mixture was stirred for 24 hours at room temperature. The organic phase was separated and discarded and the aqueous phase was acidified with concentrated HCl to pH 2. The aqueous phase was then extracted with ethyl acetate (3 x 20 ml) and the combined extracts dried over magnesium sulphate then concentrated under reduced pressure to give 3-(4-fluorophenyl)-2-phthalimidopropanoic acid as a white solid (2g, 89%); NMR 3.3(1H,dd), 3.5(1H,dd), 5.1(1H,dd), 6.3(1H,brs), 7.0(2H,t), 7.1(2H,dd), 7.8(4H,s).

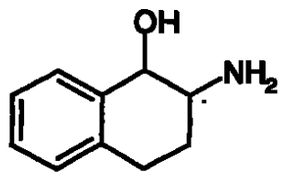
To a solution of 3-(4-fluorophenyl)-2-phthalimidopropanoic acid (2.0 g, 6.4 mmol) in DCM (20 ml) was added thionylchloride (0.6 ml, 6.4 mmol) and 1 drop of DMF. The reaction mixture was stirred at room temperature for 1 hour. Aluminium chloride (2.6 g, 19.2 mmol) was added and the reaction mixture stirred for 3 hours at room temperature. The resulting mixture was poured into ice and concentrated HCl (20 ml) and stirred for 10 minutes. This mixture was extracted with DCM (3 x 20 ml) and the combined organic extracts were washed with water (2 x 20 ml), saturated sodium hydrogen carbonate (1 x 20 ml) and water (1 x 20 ml). The organic phase was then dried over magnesium sulphate and concentrated under reduced pressure to give 6-fluoro-2-phthalamido-indan-1-one as a white solid (1g, 53%). NMR 3.3(1H,dd), 3.5(1H,dd), 5.1(1H,dd), 6.8(1H,t), 7.0(1H,dd), 7.7-8.0(5H,m); m/z 296 (M+H)

Sodium borohydride (512 mg, 14 mmol) was added to a solution 6-fluoro-2-phthalamido-indan-1-one (800 mg, 2.7 mmol) in isopropanol/water (6:1, 10.5 ml) and the

solution stirred at room temperature for 24 hours. Excess acetic acid was then added to the reaction mixture and the resulting solution heated at 60°C for 6 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a white solid which was purified by ion-exchange chromatography using Dowex 50wx2 (water:methanol 1:1 containing 3% ammonia) to give the title compound as a white solid (141 mg, 31 %); NMR 3.3(1H,dd), 3.5(1H,dd), 4.8(1H,m), 4.9(1H,d), 6.8-7.4(3H,m); m/Z 168 (M+H)

Method #39

2-Amino-1,2,3,4-tetrahydronaphth-1-ol



To a solution of sodium carbonate (0.8 g, 7.2 mmol) in water (13 ml) was added homophenylalanine (1.3 g, 7.2 mmol) followed by a solution of *N*-ethoxycarbonylphthalamide (1.6 g, 7.2 mmol) in ethyl acetate (10 ml). The two-phase reaction mixture was stirred for 24 hours at room temperature. The organic phase was separated and discarded and the aqueous phase was acidified with concentrated HCl to pH 2. The aqueous phase was then extracted with ethyl acetate (3 x 20 ml) and the combined extracts dried over magnesium sulphate then concentrated under reduced pressure to give 4-phenyl-2-phthalimidobutanoic acid as a white solid (1.5 g, 67%); m/z 308 (M-H).

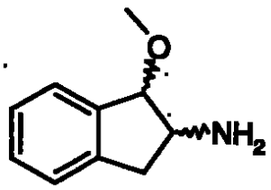
To a solution of 4-phenyl-2-phthalimidobutanoic acid (1.5 g, 4.9 mmol) in DCM (20 ml) was added thionylchloride (0.4 ml, 4.9 mmol) and 1 drop of DMF. The reaction mixture was stirred at room temperature for 1 hour. Aluminium chloride (2.0 g, 14.7 mmol) was added and the reaction mixture stirred for 3 hours at room temperature. The resulting mixture was poured into ice and concentrated HCl (20 ml) and stirred for 10 minutes. This mixture was extracted with DCM (3 x 20 ml) and the combined organic extracts were washed with water (2 x 20 ml), saturated sodium hydrogen carbonate (1 x 20 ml) and water (1 x 20 ml). The organic phase was then dried over magnesium sulphate and concentrated under reduced pressure to give 2-phthalamido-3,4-dihydro-(2*H*)-naphthalen-1-one as a white solid (880 mg,

62%). NMR 2.3(1H,m), 2.7(1H,m), 3.1(1H,dt), 3.3(1H,m), 5.2(1H,dd), 7.3-8.0(8H,m); m/z 292 (M+H)

To a solution of 2-phthalamido-3,4-dihydro-(2*H*)-naphthalen-1-one (880 mg, 3 mmol) in isopropanol/water (6:1, 11.5 ml) was added sodium borohydride (567 mg, 15 mmol) and the solution stirred at room temperature for 24 hours. Excess acetic acid was then added to the reaction mixture and the resulting solution heated at 60°C for 6 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a white solid which was purified by ion-exchange chromatography using Dowex 50wx2 (water:methanol 1:1 containing 3% ammonia) to give the title compound as a white solid (150 mg, 30 %). NMR 2.8(1H,dd), 3.0(1H,dd), 3.3(1H,m), 3.5(1H,m), 4.5(1H,m), 4.8(1H,d), 7.1-7.4(4H,m); m/z 164 (M+H)

Method #40

(+/-) *Trans*-2-Amino-1-methoxyindan



A solution of (+/-) *trans*-2-bromo-1-hydroxyindan (21.0g, 0.1mol) and potassium phthalimide (42.0g, 0.22 mol) in dry DMF (120ml) was heated at 100°C for 5 hours. The reaction mixture was cooled and evaporated to an oil which was triturated with ethyl acetate and filtered. The filtrates were evaporated and purified by chromatography on silica with 2:1 *iso*- hexane:ethyl acetate as eluent to give (+/-)-*trans* -1-hydroxy-2-phthalimido indan as a pale yellow amorphous powder (17.7g, 63%). NMR 2.8(1H, dd), 3.15(1Hdd), 4.8-5.0(1H, m), 5.4(1H, d), 5.45(1H, d), 7.0-7.3(4H, m), 7.75-8.95(4H, m).

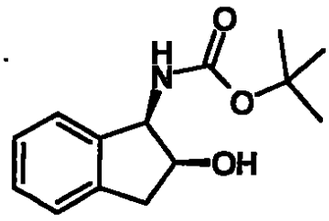
To a solution of (+/-) *trans*-1-hydroxy-2-phthalimidoindan (1.4g, 5.0mmol) in dry tetrahydrofuran (20ml) was added 60% sodium hydride (300mg, 7.5mmol). The mixture was stirred at room temperature for 2 hours and then methyl iodide (0.62ml, 10.0mmol) added. The mixture was stirred for a further 2 hours and then 5% water in tetrahydrofuran (10ml) and ethyl acetate (75ml) added. The solution was washed with water, dried over magnesium

sulphate and evaporated to give (+/-)-*trans*-1-methoxy-2-phthalimidoindan as a white solid (1.2g, 82%). NMR 2.85(1H, dd), 3.25(3H, s), 3.5(1H, dd), 4.5-4.65(1H, m), 5.55(1H, d), 7.05-7.3(4H, m), 7.85(4H, s).

A mixture of (+/-)-*trans*-1-methoxy-2-phthalimidoindan (850mg, 2.9mmol) and hydrazine hydrate (5ml) in ethanol was stirred at room temperature for 24 hours. The mixture was evaporated and purified by ion exchange chromatography (Dowex 50W X2 H^+ form) and the title compound eluted with 50% aqueous methanol containing 3% ammonium hydroxide to give the title compound a pale yellow solid (400mg, 85%). NMR 2.8(1H, dd), 3.35(3H, s), 3.38(1H, dd),4.05-4.15(1H, m), 4.5-4.6(1H, m), 7.2-7.35(3H, m), 7.45-7.55(1H, m); m/z 164 (M+H).

Method #41

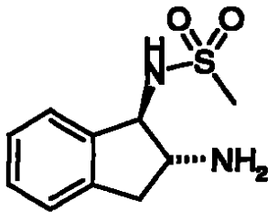
(1*R*,2*S*)- 1-[(1,1-dimethylethoxy)carbonylamino]-2 hydroxyindan



(1*R*,2*S*)-1-Amino-2-hydroxyindan (10.0g, 67.1mmol) was dissolved in dichloromethane (550ml) and triethylamine (18.7ml, 134.2mmol). Di-*tert*-butyl dicarbonate (18.3g, 83,9mmol) in dichloromethane (50ml) was added and the mixture stirred at room temperature for 20 hours then evaporated. Ethyl acetate (200ml) was added, the solution washed with water, dried over magnesium sulphate and evaporated. The crude product was purified by chromatography on silica with 4:1 *iso*-hexane:ethyl acetate as eluent to give the title compound as a white solid (16.1g, 96%); NMR 1.42(9H, s), 2.78(1H, dd), 3.0(1H, dd), 4.3-4.42(1H, m), 4.78-4.9(1H, m), 4.9-5.0(1H, m), 6.3(1H, d), 7.0-7.25(4H, m).

Method #42

(1*R*,2*R*)-2-Amino-1-methanesulphonamidoindan

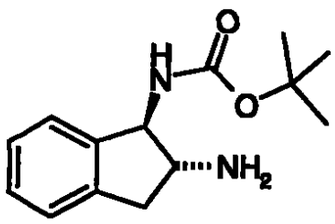


(1*R*,2*S*)-1-Amino-2-hydroxyindan (3.0g, 20mmol) was dissolved in dry tetrahydrofuran (40ml) and triethylamine (8.4ml, 60.0mmol) at 10°C. Methane sulphonyl chloride (5.0g, 44.0mmol) dissolved in tetrahydrofuran (10ml) was added at such a rate that the internal temperature remained below 15°C. Following the addition the mixture was stirred at room temperature for 20hours and then evaporated. To the residue was added ethyl acetate (100ml) and the mixture washed with saturated aqueous sodium bicarbonate and then water. The organic solution was dried over magnesium sulphate and evaporated to give (1*R*,2*S*)-1-methanesulphonamido-2-methylsulphonyloxyindan as a pale yellow solid (5.7g, 93%). NMR: 3.0-3.35(2H, m), 3.1(3H, s), 3.25(3H, s), 5.05-5.2(1H, m), 5.3-5.4(1H, m), 7.2-7.4(4H, m), 7.85-8.0(1H, m).
m/z 304.2 (M-H).

(1*R*,2*S*)-1-Methanesulphonamido-2-methylsulphonyloxyindan (2.0g, 6.56mmol) was dissolved in dry dimethyl acetamide (20ml). Sodium azide (1.7g, 26.2mmol) was added and the mixture heated to 90°C for 1 hour. The reaction was cooled, diluted with ethyl acetate (100ml), washed with water (6 x 50ml), dried over magnesium sulphate and filtered. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 3 hours. Filtration through celite followed by evaporation gave the title compound as a pale green solid (1.25g, 83%). NMR ($CDCl_3$): 1.68(2H, broad s), 2.67(1H, dd), 3.2(3H, s), 3.23(1H, dd), 4.5-4.6(1H, m), 4.6-4.8(1H, m), 7.15-7.35(4H, m); m/z 227.4 (M+H).

Method #43

(1*R*,2*R*)-2-Amino-1-[(1,1-dimethylethoxy)carbonylamino]indan

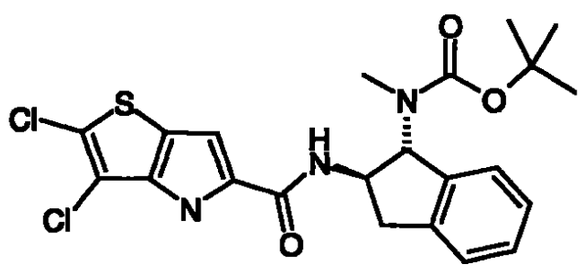


(1*R*,2*S*)-1-[(1,1-Dimethylethoxy)carbonylamino]-2-hydroxyindan (Method #41, 7.5g, 30.1mmol) was dissolved in dry tetrahydrofuran (90ml) and triethylamine (6.3ml, 45.0mmol). Methanesulfonyl chloride (3.78g, 33.0mmol) dissolved in dry tetrahydrofuran (10ml) was added and the mixture stirred at room temperature for 20 hours. The mixture was evaporated and ethyl acetate (250ml) added. After washing with water and drying over magnesium sulphate the organic solution was evaporated to (1*R*,2*S*)-1-[(1,1-dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan as white solid (9.7g, 98%). NMR1.45(9H, s), 3.05-3.35(2H, m), 3.18(3H, s), 5.15-5.25(1H, m), 5.28-5.38(1H, m), 7.15-7.22(4H, m), 7.45(1H, d).

(1*R*,2*S*)-1-[(1,1-Dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan (3.5g, 10.7mmol) was dissolved in dry dimethyl acetamide (50ml). Sodium azide (3.5g; 53.9mmol) was added and the mixture heated to 90°C for 3 hours. The reaction was cooled, diluted with ethyl acetate (150ml), washed with water (6 x 50ml) and dried over magnesium sulphate. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 4 hours. Filtration through celite followed by evaporation gave the title compound as a white solid (2.6g, 98%). NMR: 1.45(9H, s), 2.5(1H, dd), 3.0(1H, dd), 3.2-3.45(3H, m), 4.5-4.6(1H, m), 7.0-7.25(5H, m).

Method #44

2,3-Dichloro-5-[*N*-(1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino}indan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole



To a solution of (1*R*,2*S*)-1-[(1,1-dimethylethoxy)carbonylamino]-2-hydroxyindan (Method #41, 7.0g, 28.1mmol) in dichloromethane (50ml) was added 3,4-dihydro-2*H*-pyran (4.7g, 56.2mmol) and pyridinium toluene-4-sulphonate (100mg). The mixture was stirred for 4 hours, diluted with ethyl acetate (200ml), washed with water (2 x 50ml), dried over magnesium sulphate and evaporated to give (1*R*,2*S*)-1-[(1,1-dimethylethoxy)carbonylamino]-2-[(tetrahydropyran-2-yl)oxy]indan as a white solid (8.9g, 96%). NMR1.25-1.85(6H, m), 1.45(9H, d), 2.85-3.1(2H, m), 3.35-3.5(1H, m), 3.68-3.9(1H, m), 4.35-5.1(3H, m), 6.8(1H, dd), 7.1-7.3(4H, m).

(1*R*,2*S*)-1-[(1,1-Dimethylethoxy)carbonylamino]-2-[(tetrahydropyran-2-yl)oxy]indan (4.0g, 12.0mmol) was dissolved in dry DMA (25ml) at 10°C and 60% sodium hydride (575mg, 14.4mmol) added. The mixture was stirred at room temperature for 30 minutes and then methyl iodide (2.0g, 14.4mmol) added after which the reaction was stirred for a further 3 hours at room temperature. The mixture was diluted with ethyl acetate (50ml), washed with water (6 x 50ml), dried over magnesium sulphate and evaporated to give (1*R*,2*S*)-1-{*N*-[(1,1-dimethylethoxy)]carbonyl-*N*-methyl-amino}-2-(tetrahydropyran-2-yl)oxyindan as an oil (4.1g, 98%). NMR 1.4-1.9(6H, m), 1.5(9H, d), 2.7(3H, dd), 2.85-3.3(2H, m), 3.47-3.6(1H, m), 3.72-4.0(1H, m), 4.7-5.0(2H, m), 5.5-5.84(1H, m), 7.15-7.35(4H, m); m/z 348.6 (M+H).

To a solution of (1*R*,2*S*)-1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino}-2-(tetrahydropyran-2-yl)oxyindan (4.0g, 11.5mmol) in methanol (50ml) was added toluene-4-sulphonic acid (100mg) and the mixture stirred at room temperature for 2 hours. Saturated aqueous sodium bicarbonate (50ml) and water (10ml) was added and the mixture extracted with ethyl acetate. The organic extract was washed with water, dried over magnesium sulphate and evaporated to give (1*R*,2*S*)-1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino}-2-hydroxyindan as an oil (3.0g, 100%). NMR 1.45(9H, s), 2.6(3H, s), 2.75(1H, dd), 3.05(1H, dd), 4.4-4.57(1H,m), 5.0-5.12(1H, m), 5.34(1H, dd), 7.03-7.33(4H, m).

To a solution give (1*R*,2*S*)-1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino}-2-hydroxyindan (3.0g, 11.4mmol) in dry tetrahydrofuran (40mmol) was added triethylamine (2.4ml, 17.1mmol) and methane sulphonyl chloride (1.44g, 12.55mmol). The mixture was stirred at room temperature for 1 hour, evaporated and diluted with ethyl acetate (100ml). The organic solution was washed with saturated aqueous sodium bicarbonate and then water, dried

over magnesium sulphate and evaporated to give a pale yellow syrup. The crude material was purified by silica chromatography with 4:1 *iso*-hexane:ethyl acetate as eluent to (1*R*,2*S*)-1-{*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methyl-amino}-2-methanesulphonyloxyindan as a clear colourless syrup (3.1g, 80%). NMR ($CDCl_3$): 1.54(9H, s), 2.7(3H, d), 3.0(3H, s), 3.16-3.42(2H, m), 5.35-5.51(1H, m), 5.78(1H, dd), 7.2-7.35(4H, m); m/z 342.5 (M+H).

(1*R*,2*S*)-1-{*N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-methyl-amino}-2-methanesulphonyloxyindan (3.0g, 8.8mmol) was dissolved in dry DMA (30ml) and sodium azide (2.3g, 35.2mmol) added. The mixture was heated to 90°C for 6 hours, cooled and diluted with ethyl acetate (100ml). The solution was washed with water (6 x 50ml), dried over magnesium sulphate and filtered. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 4 hours. The mixture was filtered, evaporated and purified by silica chromatography with 10% methanol in dichloromethane to give (1*R*,2*S*)-2-amino-1-{*N*-[(1,1-dimethylethoxy)]carbonyl-*N*-methyl-amino}indan as an oil (1.2g, 55%). NMR 1.36-1.56(9H, m), 2.6(3H, s), 2.7-2.87(1H, m), 3.2-3.35(1H, m), 4.37-4.54(1H, m), 5.4-5.7(1H, m), 6.93-7.1(1H, m), 7.12-7.5(4H, m); m/z 263.48 (M+H).

5-Carboxy-2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method #9, 472mg, 2.0 mmol), (1*R*,2*S*)-2-amino-1-{*N*-[(1,1-dimethylethoxy)]carbonyl-*N*-methyl-amino}indan (524mg, 2.0mmol), DIPEA (0.348ml, 2.0mmol) and HOBT (270mg, 2.0mmol) was stirred in dichloromethane (10ml) at room temperature for 2 minutes. EDAC (480mg, 2.5mmol) was added and the mixture stirred at room temperature for 20 hours. The reaction was evaporated, ethyl acetate (50ml) added and washed with water. The organic phase was dried over magnesium sulphate and evaporated to give the title compound as a pale brown foam (900mg, 94%). NMR 1.2-1.45(9H, m), 2.77(3H, s), 2.9-3.26(2H, m), 4.7-4.94(1H, m), 5.5-5.8(1H, m), 6.9-7.34(5H, m), 8.55-8.73(1H, m), 12.25(1H, broad s); m/z 480.3/482.1 (M+H).

Example 155

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

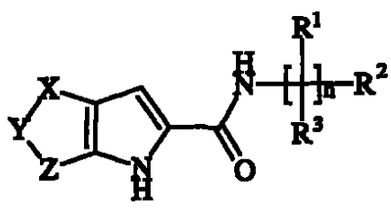
(g): Injection III	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

1. A compound of formula (I):



(I)

wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5-, -CR^4=CR^5-S-, -O-CR^4=CR^5-, -CR^4=CR^5-O-, -N=CR^4-S-, -S-CR^4=N-, -NR^6-CR^4=CR^5- and -CR^4=CR^5-NR^6-;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

R^6 is hydrogen or C_{1-6}alkyl;

R^1 is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto,

sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO$_2$-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^{a}C(O)-, -C(O)NR^a-, -SO$_2$NR^a-, -NR^{a}SO$_2$-, -NR^{a}C(O)NR^b-, -OC(O)NR^a-, -NR^{a}C(O)O-, -NR^{a}SO$_2$NR^b-, -SO$_2$NR^{a}C(O)- and -C(O)NR^{a}SO$_2$-; wherein R^a and R^b are independently selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V ;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

R^3 is hydrogen or C_{1-6}alkyl;

n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

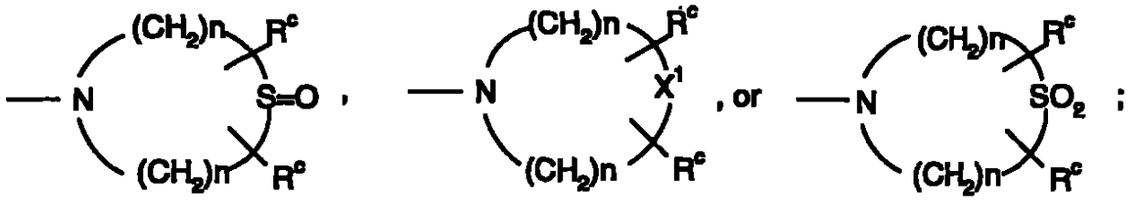
with the provisos:

i) when -X-Y-Z- is -S-CH=CH-, R^2-(CR^1R^3)$_n$- cannot be amino, 1-phenyl-5-methyl-1H-1,5-benzodiazepine-2,4(3H,5H)dion-3-yl, 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl, 2-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)ethyl, 3-(4-phenyl-1,2,5,6-tetrahydropyrid-1-yl)propyl, 2-(4-phenylpiperazin-1-yl)ethyl, 2-(*N*-methylamino)ethyl, 2-morpholinoethyl or 2-(*N*-methyl-*N*-benzylamino)ethyl;

ii) when -X-Y-Z- is -CH=CH-S-, R^2-(CR^1R^3)$_n$- cannot be amino or 1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-benzo(E)(1,4)diazepin-3-yl;

iii) when -X-Y-Z- is -CH=C(SO_2NH_2)-S-, R^2-(CR^1R^3)$_n$- cannot be methyl or isobutyl; and

iv) when -X-Y-Z- is as initially defined, n is 1, R^1 is arylmethyl, substituted arylmethyl, (heterocyclic group)methyl and substituted (heterocyclic group)methyl and R^3 is hydrogen then R^2 is not a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, -$NR^aCH_2CH_2OR^a$, or



each R^a and R^b is independently hydrogen or $-C_1$-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3, and

X^1 is NR^a, $-CH_2-$, O or S.

2. A compound of formula (I) according to claim1 wherein:

-X-Y-Z- is selected from $-S-CR^4=CR^5-$ or $-CR^4=CR^5-S-$;

wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

n is 0;

R^2 is a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is a C_{3-12}cycloalkyl which is optionally fused to a benz ring wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl,

N,N-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic groups; wherein S may be optionally substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino , morpholinocarbonyl , *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I) as claimed in claim 1wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

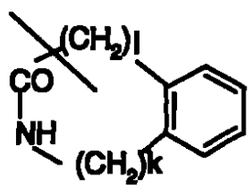
wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

n is 0;

R^2 is a group -E-F-G-H;

wherein E, F and G are each a direct bond; and

H is a cyclic amide of formula



in which k is 0, 1, 2 or 3 and l is 0, 1, 2 or 3 such that the sum of k and l is 2 or 3 and wherein one of the carbon atoms governed by k or l may be replaced by sulphur and wherein H is optionally substituted on carbon by one or more groups selected from S and may be independently optionally substituted on nitrogen by a group selected from T;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-6}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4. A compound of formula (I) as claimed in claim 1wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

wherein R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

n is 1;

R^1 is hydrogen or arylC_{1-6}alkyl;

R^2 is selected from a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is an unsaturated five membered heterocyclic group containing at least one nitrogen atom and one or two ring atoms selected from oxygen and sulphur and wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-6}cycloalkyl and aryl groups;

R^3 is hydrogen or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

5. A compound of formula (I) as claimed in claim 1 wherein:

-X-Y-Z- is selected from -S-CR^4=CR^5- or -CR^4=CR^5-S-;

wherein R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

n is 0;

R^2 is a group -E-F-G-H;

wherein E is a direct bond;

F is methylene;

wherein G is -C(O)NR^a-, wherein R^a is selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V ;

H is aryl which may be optionally substituted on carbon by one or more groups selected from S;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino,

C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V ;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl , and 4-hydroxypiperidinocarbonyl;

or a pharmaceutically acceptable salt thereof.

6. A compound selected from

2,3-dichloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(benzoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-{*N*-[2-(1-phenylmethanesulphonamido)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

3-chloro-5-[*N*-(4-oxo-2,3,4,5-tetrahydrobenz[1,5]thiazepin-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(benzoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-phenyl-1-cyclopropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-(*N*-{2-[(2-pyridyl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(2-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-phenoxyethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(2-thienyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(4-fluorophenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(*N*-methylmethanesulphonamido)-1-(thiazol-2-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[2-(thiomorpholino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-sulphamoylphenylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-hydroxy-1-phenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[3-(5-tetrazolyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(5-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benz[*b*]azepin-4-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-{*N*-[3-(benzyloxycarbonylamino)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(4-dimethylaminophenyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-benzyl-2-hydroxyethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(phenylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-*(R)*-hydroxy-α-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-hydroxyphenethyl)carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-hydroxyphenyl)ethyl]carbamoyl}4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(benzimidazol-2-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-chlorophenyl)-2-hydroxy-1-(methoxycarbonyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(imidazo[1,2-*a*]pyrid-2-yl)carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[(benzthiazol-2-yl)methyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(6-trifluoromethylpyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(2-pyridazinyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxy-3-phenoxypropyl)carbamoylmethyl] carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-methylisothiazol-5-yl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(pyridazin-3-yloxy)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-(*N*-{2-[(3-trifluoromethylpyrid-2-yl)amino]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(4-sulphamoylphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-pyridyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[1-hydroxymethyl-2-(4-imidazolyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-(2-[(3-quinolyl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[3-(4-acetamidophenoxy)-2-hydroxypropyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[3-(*N*-methylsulphonylcarbamoyl)propyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-{[2-(guanidino)thiazol-4-yl]methylthio}ethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2,4-dioxoimidazolidin-1-yl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

5-{*N*-[2-benzylthio-1-(hydroxymethyl)ethyl]carbamoyl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(dimethyaminosulphonylamino)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(6-methoxypyrid-3-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(S)-2,3-dichloro-5-{*N*-[(2-oxo-3-phenyl-2,3,4,5-tetrahydrooxazol-5-yl)methyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[3-(carbamoylmethyl)phenoxy]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{[6-(benzo[1,3]dioxol-5-yl)-4-methylmorpholin-2-yl]methyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-benzylcarbamoyl)- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-phenethylcarbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(3-phenylpropyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(2-hydroxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(α,α-dimethylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-phenylcyclobutyl)methyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(β-methylphenethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(*N*-benzylcarbamoylmethyl)carbamoyl]- 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(*N*-benzyl-*N*-methylcarbamoylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-phenylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-methoxyphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-fluorophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-nitrophenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,6-dimethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(4-methylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-methyl-*N*-(3-methylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-chlorophenyl) *N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-phenylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(1,1-dimethyl-2-hydroxyethyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)-*N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-hydroxyethyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-hydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxybutyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-[bis(hydroxymethyl)methyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,3-dihydroxypropyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxymethylphenyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(5-isoquinolyl)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(3-hydroxymethy)lphenyl]carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-[4-(2-hydroxyethyl)phenyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2,4-difluorophenyl)-*N*-methyl-carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(1,2,3,4-tetrahydro-1-quinolyl)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(2-cyanoethyl)-*N*-methylcarbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[*N*-(4-hydroxypiperidino)carbamoylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*- cyclopentylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-isopropylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(*N*-isopropyl-*N*-methylcarbamoylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(thiomorpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(morpholinocarbonylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[(1,1-dioxothiomorpholino)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2*b*]-pyrrole;

2,3-dichloro-5-{*N*-[(1-oxothiomorpholino)carbonylmethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-indanyl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

5-[*N*-(benz[1,2]oxazol-3-ylmethyl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(hydroxymethyl)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-phenylisoxazol-3-ylmethyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(2-morpholinoethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(methoxycarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(carboxymethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[2-(3-methoxyphenyl)ethyl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(2-methoxyethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(carbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(*N*-methylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(*N*,*N*-dimethylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(morpholinocarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-(*N*-{2-[2-(*N*-benzylcarbamoylmethoxy)phenyl]ethyl}carbamoyl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{2-[2-(4-hydroxypiperidinocarbonylmethoxy)phenyl]ethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(5-ethoxycarbonyl-1,3,4-oxadiazol-2-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(4-methoxycarbonyloxazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-{*N*-[α-(3-pyridyl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-{*N*-[α-(3-pyridyl)phenethyl)]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(*S*)-2-chloro-5-{*N*-[α-(3-phenyl-1,2,4-oxadiazol-5-yl)phenethyl]carbamoyl}-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-((*1S,2S*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-((*1R,2R*)-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(7-methoxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(2-indanyl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(3-methylisoxazol-5-yl)methyl]carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-[*N*-(4-hydroxy-1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{*N*-methyl-*N*-[(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)methyl]carbamoylmethyl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

2-chloro-5-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2-chloro-5-[*N*-(3-oxo-2,3,4,5-tetrahydro-1*H*-benz[2]azepin-4-yl)carbamoyl]-6*H*-thieno[2,3-*b*]pyrrole;

2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole; and

2,3-dichloro-5-{*N*-[1-(*N*-methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in any one of claims 1-6, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

8. The use of a compound of the formula as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as a medicament.

9. The use of a compound of the formula as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a glycogen phosphorylase inhibitory effect in a warm-blooded animal such as man.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01880

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 495/04, C07D 491/04, C07D 513/04, C07D 487/04, A61K 31/407, A61P 3/10, A61P 9/10

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)

IPC7: C07D, A61P

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, 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.
X	WO 9639384 A1 (PFIZER, INC.), 12 December 1996 (12.12.96) —	1-9
X	EP 0846464 A2 (PFIZER INC.), 10 June 1998 (10.06.98) —	1-9
X	US 5998463 A (BERNARD HULIN ET AL), 7 December 1999 (07.12.99) —	1-9
E,A	EP 1088824 A2 (PFIZER PRODUCTS INC.), 4 April 2001 (04.04.01) —	1-9

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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
19 December 2001	03-01-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01880

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9946268 A1 (NOVO NORDISK A/S), 16 Sept 1999 (16.09.99)	1-9
A	ES 2081747 A1 (LABORATORIOS DEL DR. ESTEVE, S.A.), 1 March 1996 (01.03.96)	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/11/01

International application No.
PCT/SE 01/01880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639384 A1	12/12/96	AP 623 A	19/12/97
		AP 9600803 D	00/00/00
		AU 701465 B	28/01/99
		AU 5462696 A	19/12/96
		BG 100547 A	31/12/96
		BR 9602542 A	27/10/98
		CA 2224062 A	12/12/96
		CN 1140709 A	22/01/97
		CN 1142492 A	12/02/97
		CZ 9601573 A	12/03/97
		EP 0832065 A,B	01/04/98
		SE 0832065 T3	
		FI 974436 A	27/01/98
		HR 960244 A	31/12/97
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		JP 10511687 T	10/11/98
		LV 11613 A,B	20/12/96
		NO 306398 B	01/11/99
		NO 961664 A	09/12/96
		NZ 286460 A	24/09/98
		PL 314561 A	09/12/96
		SG 44947 A	19/12/97
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		US 6107329 A	22/08/00
EP 0846464 A2	10/06/98	AU 717547 B	30/03/00
		AU 4686997 A	11/06/98
		CA 2223317 A	05/06/98
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EP 1088824 A2	04/04/01	BR 0004582 A	17/04/01
		JP 2001131181 A	15/05/01
WO 9946268 A1	16/09/99	AU 2713999 A	27/09/99
		AU 2825899 A	27/09/99
		BR 9908723 A	21/11/00
		CN 1300279 T	20/06/01
		EP 1062218 A	27/12/00
		EP 1080068 A	07/03/01
		NO 20004526 A	08/11/00
		PL 342851 A	16/07/01
		WO 9946237 A	16/09/99

INTERNATIONAL SEARCH REPORT
Information on patent family members

06/11/01

International application No.
PCT/SE 01/01880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ES 2081747 A1	01/03/96	ES 1025262 U,Y	01/12/93

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01880

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01880

Claim 8 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

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CONSULADO GENERAL DE COLOMBIA
3RD FLOOR, 18-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 9883 • TELEFAX 020-7637 5804
E-MAIL consulco@consulco.demon.co.uk

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

CERTIFICA

Que, **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por **J. GARBRAH**, Oficial de del Ministerio de Relacione Exteriores Británico, firma que se encuentra registrada en este Consulado General.

Que, **AstraZeneca AB**, es una Sociedad constituída, organizada y existente en Sodertalje, Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese país.

Que, **DAVID ERIC GILES**, en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, Gran Bretaña.

El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los quince (15) días del mes de Noviembre de dos mil (2000).

Certificación No.11 /1722
Derechos: U$ 106,00 CANCELADOS

HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Res. 1878 Ministerio Justicia

JAIRO H. BERRIO VILLARREAL
Cónsul General

CONSULADO GENERAL DE COLOMBIA
LONDRES

Es la Novena Cuarenta de este círculo se copia la presente fotocopia que coincide con la fotocopia suministrada que se ha tenido a la vista
Fecha DIC. 2 2002
NOTARIO CUARENTA
Agustín Codazzi Zárate
Círculo de Bogotá D.C. Colombia

REPUBLICA DE COLOMBIA
Rosa Pulla Lahoud Notaria
Cuarenta y una (E)
Notaría Cuarenta y Seis de Bta.

BRIGARD & CASTRO

SANTAFE DE BOGOTA - COLOMBIA

PODER

Yo (nosotros) ASTRAZENECA AB

Domiciliado(s) en: S-151 85, Sodertalje, SUECIA

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales y extrajudiciales.

Otorgado y firmado en

hoy de

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We ASTRAZENECA AB

Domiciled in: S-151 85, Sodertalje SWEDEN

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. Furthermore, I (we) hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

This 10 NOV 2000 day

Signature

Name DAVID ERIC GILES
Title DIRECTOR IP SERVICES

JOSE NAVARRO ALVAREZ
INTERPRETE OFICIAL

5 DIC 2000

NOTARIO CUARENTA Y 3
Agencia Cesar Pinzon
Santafé de Bogotá, D.C. Colombia

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
Personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

De ASTRAZENECA AB

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 10 day of November of 2000
Personally appeared before me
DAVID ERIC GILES
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

DIRECTOR IP SERVICES

of ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of SWEDEN
under date of 3RD JANUARY 2000

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de
compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que antecede y que ha(n) declarado que otorga(n) el mismo para los fines y propósitos que en él se expresan.

15 DIC 2000

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

to me known and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

DIC. 2 2002

Notary Public (Seal)

LEGALIZACION ANTE CONSUL C LOMBIANO ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D644894**

Date **14 November, 2000**

This document bears the signature / seal of **J B Hodgson**

HUGO ... ALVAREZ
TRADUCTOR INTERPRETE OFICIAL
Res. 4416 Minjusticia 1998

Acting in the capacity of **Notary Public**

Signed by: J. Garbrah

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

En la Notaría Cuarenta de este círculo se cotejó la presente fotocopia que coincide con la fotocopia autenticada que se le puso a la vista
Fecha DIC. 2002
NOTARIO CUARENTA
Agustín Castillo Zárate
Santafé de Bogotá D.C. Colombia

COMO NOTARIO CUARENTA Y ESE DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA.
BOGOTA D.C. REPUBLICA DE COLOMBIA
15 DIC 2000
NOTARIO CUARENTA

REPUBLICA DE COLOMBIA
Rosa Falla Latorre
Notaria
Cuarenta y Seis

2424
244 2424

TRADUCCION OFICIAL No. 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado ASTRAZENECA AB, una compañía domiciliada en S-151 85. Sodertalje, SUECIA al doctor RAMIRO CASTRO y HECTOR GOMEZ, Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sella con el Sello del Traductor al mismo tiempo que la presente.-

++

ANEXOS: El Poder arriba mencionado, Certificación Notarial, Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres, Inglaterra, Certificación del Consulado General de Colombia en Londres, Inglaterra, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

++

Firma llegible (Firmado)
Notario Público
SELLO NOTARIAL EN RELIEVE.

++

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. D644894
Fecha...14 de Noviembre del año 2000.....
Este documento porta
la firma/sello de J. B. Hodgson
.....
actuando en la capacidad de
Notario Público
.....
Firmado por: J. Garbrah

Firma llegible (firmado)

COMO NOTARIO CUARENTA Y UNO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA.
BOGOTA D.C. REPUBLICA DE COLOMBIA
5 DIC 2000

En la Notaría Cuarenta de Bogotá se exhibió el presente fotocopia que coincide con la fotocopia que se ha tenido a la vista
Fecha DIC. 2 2002
NOTARIO CUARENTA
Agustín Castillo Zárate
Bogotá D.C., Colombia

HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Res. 1476 Min-Justicia 1995

215.

Por el Secretario de Estado Principal de Su Majestad para los Asuntos de la Comunidad y el Extranjero.

SELLO EN RELIEVE.

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

++

EN ESPAÑOL: La Certificación del Consulado General de Colombia en Londres, Inglaterra bajo el Número de Certificación 11/1722 de fecha 15 de Noviembre del año 2000; Autenticación Hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el Número 481834 de fecha 29 de Noviembre del año 2000.

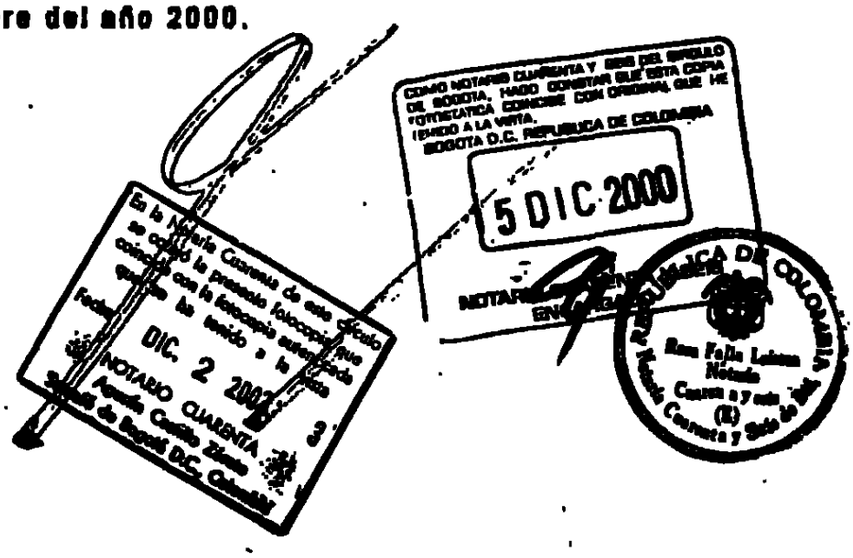
(Pagados Derechos por valor de $106.00 Dólares)

++

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
Res. 1870 Minjusticia 1999

Resolución Número 1876 del Ministerio de Justicia
Fecha: 4 de Diciembre del año 2000.



Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero

SELLO EN RELIEVE

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

++

EN ESPAÑOL: La Certificacion del Consulado General de Colombia en Londres, Inglaterra bajo el Numero de Certificacion 117122 de fecha 15 de Noviembre del año 2000; Autenticacion firmado por el Ministerio de Relaciones Exteriores de Colombia bajo el Numero 49124 de fecha 25 de Noviembre del año 2000.

(Pagados Derechos por valor de $108 00 Dolares)

++

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS

90.116

247

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 100168-1 WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/SE01/01880	31 August 2001 (31/08/01)	06 September 2000 (06/09/00)

Title of invention:

BICYCLIC PYRROLYL AMIDES AS GLUCOGEN PHOS PHORYLASE INHIBITORS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.: +46 8 553 260 00
Facsimile No.: +46 8 553 288 20
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SE	SE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BARTLETT, Julie B
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FREEMAN, Sue
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/SE01/01880

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KENNY, Peter
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MORLEY, Andrew
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WHITTAMORE, Paul
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/SE01/01880

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property
AstraZeneca AB
S-151 85 Sodertalje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** *Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.*

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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Sheet No. .4.

International application No.
PCT/SE01/01880

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

BILL, Kevin et al
Global Intellectual Property, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

EPO MUNICH 2 LCS

FAX: 0044 1625519178

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

AstraZeneca AB
GLOBAL INTELLECTUAL PROPERTY
S-151 85 Sodertalje
SUEDE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	07.06.2002
Applicant's or agent's file reference: 100166-1 WO	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/SE01/01880	31/08/2001	08/09/2000

Applicant
ASTRAZENECA AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the International application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the International application must be furnished to an elected Office, that translation must contain a translation of any annexes to the International preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

5. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Breil, S Tel.+49 89 2399-7271

Form PCT/IPEA/416 (July 1992)

EPO MUNICH 2 LCS

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100168-1 WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/SE01/01880	31/08/2001	08/09/2000
International Patent Classification (IPC) or national classification and IPC		
C07D495/04		
Applicant		
ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/09/2002	07.08.2003
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Friebel, F Telephone No. +49 89 2399 8552

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE01/01880

I. Basis of the report

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-119 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE01/01880

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

8. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8.

because:

☒ the said international application, or the said claims Nos. 8 - IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos..

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-9
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-7,9

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE01/01880

No: Claims

2. Citations and explanations
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/SE01/01880

point III:

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

point V:

The instant application claims bicyclic pyrrolyl amides which possess glycogen phosphorylase inhibitory activity and may be used in particular for the treatment of type 2 diabetes.

The characteristic structural featur of the compounds claimed is a pyrrolo-2-carboxamide core structure annelated with a heterocyclic 5-ring denoted in the generic formula (I) by the -X-Y-Z- substructure. The moiety attached to the amide nitrogen is defined very broad and preferably contains a cyclic moiety ⇒ the definition of R^2 = E-F-G-H and the specific meaning of H.

Compounds showing a combination of such structural features are already known from the prior art, however, in connection with a different indication; see for instance the document ES 2081747 briefly referred to on page 2 of the description. The compounds disclosed therein are said to be useful in the treatment of gastric secretion disorders.
Known compounds are excluded via various provisos at the end of Claim 1.
Novelty is therefore acknowledged; Art.33(2) PCT.

As concerns inventiv step reference is made to the documents WO 9639384 and EP 846464 which relate to the same field; viz. glycogen phosphorylase inhibition. The compounds disclosed therein are also bicyclic carboxamides however based on a 2-carboxy indole core structure in contrast to the annelated pyrroles according to the instant application. As there is no hint in the pior art which would motivate the art skilled person when looking for new phosphorylase inhibitors to replace the benzene part of the prior art indoles by a heterocyclic 5-ring substructure, inventive step is also acknowledged; Art.33(3) PCT.

For the assessment of the present claim 8 on the question whether it is industrially

applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

As concerns the document EP 1088824 the IPEA assumes that the present application is entitled to the priority date claimed.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 100166-1 WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No. +46 8 553 260 00

Facsimile No. +46 8 553 288 20

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BARTLETT, Julie B
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No. +46 8 553 260 00

Facsimile No. +46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FREEMAN, Sue
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KENNY, Peter
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MORLEY, Andrew
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WHITTAMORE, Paul
AstraZeneca R&D Alderley
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GH Ghana	☒ MX Mexico
☒ AG Antigua and Barbuda	☒ GM Gambia	☒ MZ Mozambique
☒ AL Albania	☒ HR Croatia	☒ NO Norway
☒ AM Armenia	☒ HU Hungary	☒ NZ New Zealand
☒ AT Austria	☒ ID Indonesia	☒ PL Poland
☒ AU Australia	☒ IL Israel	☒ PT Portugal
☒ AZ Azerbaijan	☒ IN India	☒ RO Romania
☒ BA Bosnia and Herzegovina	☒ IS Iceland	☒ RU Russian Federation
☒ BB Barbados	☒ JP Japan	
☒ BG Bulgaria	☒ KE Kenya	☒ SD Sudan
☒ BR Brazil	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BY Belarus	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BZ Belize	☒ KR Republic of Korea	☒ SI Slovenia
☒ CA Canada	☒ KZ Kazakhstan	☒ SK Slovakia
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ SL Sierra Leone
☒ CN China	☒ LK Sri Lanka	☒ TJ Tajikistan
☒ CO Colombia	☒ LR Liberia	☒ TM Turkmenistan
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	☒ TZ United Republic of Tanzania
☒ DE Germany	☒ LV Latvia	☒ UA Ukraine
☒ DK Denmark	☒ MA Morocco	☒ UG Uganda
☒ DM Dominica	☒ MD Republic of Moldova	☒ US United States of America
☒ DZ Algeria		
☒ EC Ecuador		
☒ EE Estonia	☒ MG Madagascar	☒ UZ Uzbekistan
☒ ES Spain	☒ MK The former Yugoslav Republic of Macedonia	☒ VN Viet Nam
☒ FI Finland		☒ YU Yugoslavia
☒ GB United Kingdom	☒ MN Mongolia	☒ ZA South Africa
☒ GD Grenada	☒ MW Malawi	☒ ZW Zimbabwe
☒ GE Georgia		

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ GQ Equatorial Guinea	☐	☐
☒ PH Philippines	☐	☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

	Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
			national application: country	regional application:* regional Office	international application: receiving Office
item (1)	06.09.2000 (06 Sep 2000)	0021831.3	United Kingdom (GB)		
item (2)					
item (3)					
item (4)					
item (5)					

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / SE .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐	Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	5
description (excluding sequence listing part)	:	119
claims	:	15
abstract	:	1
drawings	:	
Sub-total number of sheets	:	140
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	140

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☐ original separate power of attorney	:	
3. ☐ original general power of attorney	:	
4. ☒ copy of general power of attorney; reference number, if any: GF.1519/2001	:	1
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☐ other *(specify)*:	:	

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 31 August 2001

Thomas Miller

Thomas Miller
Global Intellectual Property, AstraZeneca AB

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
☐ received:
☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **MODELO DE UTILIDAD**	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable:

Fecha

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03018834 07230838 Folios: 262
Fecha (AMD): 2003-03-05 16:42:33
Tramite : 911 PCT-PATENT 379 PASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
ASTRAZENECA AB

Oficio Nº 05832

ASUNTO:	Radicación Nº	03-018834
	Solicitud internacional	PCT/SE01/01880
	Fecha inicio fase nacional	06/04/2003
	Trámite	011
	Evento	379
	Actuación	330
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).
- 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 Única 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 25 JUL. 2003.

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