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SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 04-87003

54. **TITULO** DERIVADOS DE AMIDA HETEROCICLICA CON ACTIVIDAD INHIBIDORA DE GLUCOGENO

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA

74. **APODERADO** RAMIRO CASTRO DUQUE

22. **SANTAFE DE BOGOTA, D.C.**

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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
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Título (54): DERIVADOS DE AMIDA HETEROCICLICA CON ACTIVIDAD INHIBIDORA DE GLUCÓGENO

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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- [x] Documento de cesión del Inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [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.
- [x] Otros Tarjeta de Propietarios

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.

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
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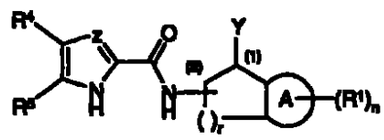
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(54) Title: HETEROCYCLIC AMIDE DERIVATIVES HAVING GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY



(1)

(57) Abstract: Heterocyclic amides of formula (1) wherein: Z is CH or nitrogen; R^4 and R^5 together are either -S-C(R^6)=C(R^7)- or -C(R^7)=C(R^6)-S- ; R^6 and R7 are selected from for example hydrogen, halo, C_{1-4}alkyl, and C_{1-4}alkanoyl; A is phenylene or heteroarylene; n is 0, 1 or 2; R^1 is selected from for example halo, nitro, cyano, hydroxy, carboxy; r is 1 or 2; Y is -NR^2R^3 or -OR^3; R^2 and R^3 are selected from for example hydrogen, hydroxy, aryl, heterocyclyl and C_{1-6}alkyl (optionally substituted by 1 or 2 R^8 groups); R^4 is selected from for example hydrogen, halo, nitro, cyano, hydroxy, C_{1-4}alkyl, and C_{1-4}alkanoyl; R^8 is selected from for example hydroxy, -COCOOR^9, -C(O)N(R^9)(R^{10}), -NHC(O)R^9 , (R^9)(R^{10})N- and -COOR^9 ; R^9 and R^{10} are selected from for example hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}); R^{13} is selected from hydroxy, halo, trihalomethyl and C_{1-4}alkoxy; or a pharmaceutically acceptable salt or pro-drug thereof; 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.

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HETEROCYCLIC AMIDE DERIVATIVES HAVING GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

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 of 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 DM.

It has been estimated that, after an overnight fast, 74% of HGO was 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.

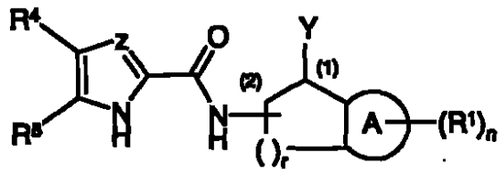
Liver glycogen phosphorylase a activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetalogia 43, 589-597).

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). Additionally, plasma glucose concentration is reduced, in a dose related manner, 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 following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physiol, 273: E868).

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.

According to one aspect of the present invention there is provided a compound of formula (1):



(1)

wherein:

Z is CH or nitrogen;

R^4 and R^5 together are either –S-C(R^6)=C(R^7)- or –C(R^7)=C(R^6)-S- ;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy and C_{1-4}alkanoyl;

A is phenylene or heteroarylene;

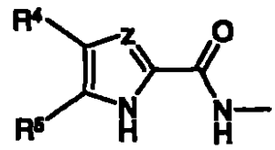
n is 0, 1 or 2;

R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl,

N-C_{1-4}alkylcarbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, -S(O)$_b$$C_{1-4}$alkyl (wherein b is 0,1,or 2), C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

or, when n is 2, the two R^1 groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

r is 1 or 2; and when r is 1 the group

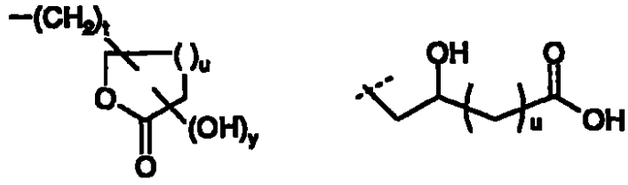


is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, carbamoyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, heterocyclyl, aryl, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$, $-SO_bR^8$ (wherein b is 0, 1 or 2) and

groups of the formulae B and B':



(B) (B')

wherein y is 0 or 1, t is 0, 1, 2 or 3 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen; or

wherein NR^2R^3 may form a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by –C(=O)-, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the

ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy and C_{1-4}alkylS(O)$_b$- (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, -CO_2C_{1-4}alkyl, aryl and aryl(C_{1-4})alkyl], halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, (heterocyclyl)C_{1-4}alkyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, C_{1-4}alkyl or -C(O)OC_{1-4}alkyl), C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkylS(O)$_b$- (wherein b is 0, 1 or 2), arylS(O)$_b$- (wherein b is 0, 1 or 2), heterocyclylS(O)$_b$- (wherein b is 0, 1 or 2), benzylS(O)$_b$- (wherein b is 0, 1 or 2), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -N(OH)CHO, -C(=N-OH)NH_2, -C(=N-OH)NHC_{1-4}alkyl, -C(=N-OH)N(C_{1-4}alkyl)$_2$, -C(=N-OH)NHC_{3-6}cycloalkyl, -C(=N-OH)N(C_{3-6}cycloalkyl)$_2$, -COCOOR^9, -C(O)N(R^9)(R^{10}), -NHC(O)R^9, -C(O)NHSO_2(C_{1-4}alkyl), -NHSO_2R^9, (R^9)(R^{10})NSO_2-, -COCH_2OR^{11}, (R^9)(R^{10})N- and -COOR^9, -CH_2OR^9, -CH_2COOR^9, -CH_2OCOR^9, -CH_2CH(CO_2R^9)OH, -CH_2C(O)NR^{9}R^{10}, -(CH_2)$_w$CH(NR^{9}R^{10})CO_2R$^{9'}$ (wherein w is 1, 2 or 3), and -(CH_2)$_w$CH(NR^{9}R^{10})CO(NR$^{9'}$R$^{10'}$) (wherein w is 1, 2 or 3);

R^9, R$^{9'}$, R^{10} and R$^{10'}$ are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, trihaloalkyl, aryl, heterocyclyl, heterocyclyl(C_{1-4}alkyl), and -C(=O)O(C_{1-4})alkyl; or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or R$^{9'}$ and R$^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, C_{1-4}alkoxy and heterocyclyl; or the ring may be optionally substituted on two adjacent carbons by –O-CH_2-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH_2-O- group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

R^{11} is independently selected from hydrogen, C_{1-4}alkyl, and hydroxyC_{1-4}alkyl;

or a pharmaceutically acceptable salt or pro-drug thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

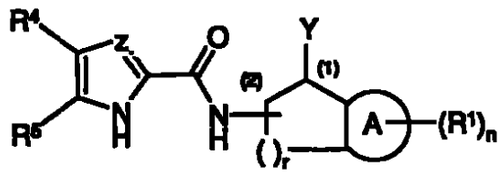
viii) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

ix) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

x) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

xi) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

According to another aspect of the present invention there is provided a compound of formula (1):



(1)

wherein:

Z is CH or nitrogen;

R^4 and R^5 together are either –S-C(R^6)=C(R^7)- or –C(R^7)=C(R^6)-S- ;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 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,

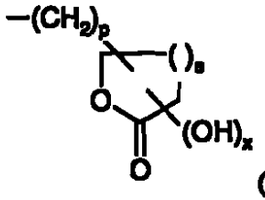
N-(C_{1-6}alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

A is phenylene or heteroarylene;

n is 0, 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, sulfino, sulfo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N*,*N*-(C_{1-4}alkyl)$_2$amino, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxy and

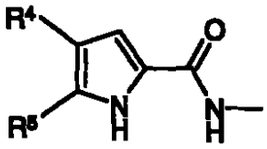
R^1 is of the formula A' or A'':



(A) $-CH_2CH(OH)(CH_2)_sCO_2H$ (A')

wherein x is 0 or 1, p is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

r is 1 or 2; and when r is 1 the group

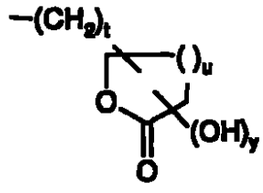


is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranylgroup, 1,1-dioxotetrahydrothiopyranyl, fluoromethylcarbonyl,

difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)], $-COR^8$, $-SO_bR^8$ (wherein b is 0, 1 or 2) and groups of the formulae B and B':



(B) $-CH_2CH(OH)(CH_2)_tCO_2H$ (B')

wherein y is 0 or 1, t is 0, 1, 2 or 3 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen);

{wherein R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 2,2-dimethyl-1,3-dioxolan-4-yl, heterocyclyl (optionally substituted on carbon or nitrogen by 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy and C_{1-4}alkyl), (heterocyclyl)C_{1-4}alkyl (wherein the heterocyclyl is optionally substituted on carbon or nitrogen by 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy and C_{1-4}alkyl), aryl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -N(OH)CHO, $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$ and $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, $-(CH_2)_uCH(NR^9R^{10})CO_2R^9$ (wherein u is 1, 2 or 3);

[wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranylgroup, 1,1-dioxotetrahydrothiopyranyl, 2,2-dimethyl-1,3-dioxolan-4-yl, aryl (optionally substituted by 1 or 2 substituents selected from hydrogen, nitro, halo, hydroxy and C_{1-4}alkyl) and C_{1-4}alkyl substituted by R^{13};

(wherein R^{13} is selected from hydroxy, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkyl$S(O)_d$ (wherein d is 0, 1 or 2)l, -N(OH)CHO, $(R^{11})(R^{12})NCO-$, $(R^{11})(R^{12})NSO_2-$, $-COCH_2OR^{11}$and $(R^{11})(R^{12})N-$;

{wherein R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl$S(O)_e$ (wherein e is 0, 1 or 2)}); and

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-$(C_{1-4})_2$alkylamino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkyl$S(O)_f(C_{1-4})$alkyl (wherein f is 0, 1 or 2), -N(OH)CHO, $(R^{11})(R^{12})NCO$-, $(R^{11})(R^{12})NSO_2$-, $-COCH_2OR^{11}$, $(R^{11})(R^{12})N$-;
wherein R^{11} and R^{12} are as defined above]};

provided that when R^1 is of the formula A' or A'' then R^2 and R^3 do not contain a group of the formula B or B' and when R^2 or R^3 is of the formula B or B' then R^1 does not contain a group of the formula A' or A'' such that a compound of formula (1) can contain only one of A', A'', B and B';

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

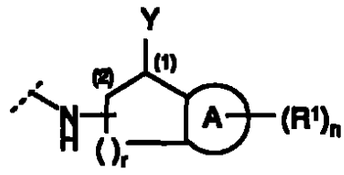
viii) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

ix) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

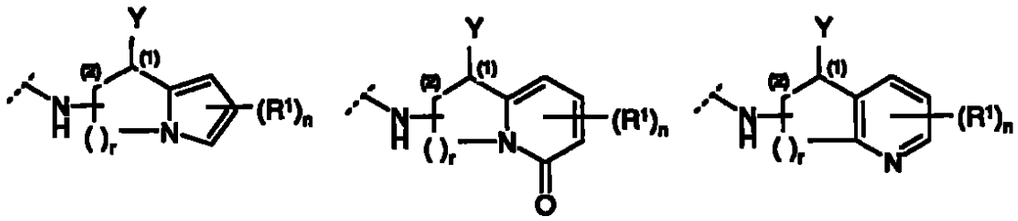
x) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

xi) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

It is to be understood that when A is heteroarylene, the bridgehead atoms joining ring A to the piperidinone ring may be heteroatoms. Therefore, for example, the definition of



when A is heteroarylene encompasses the structures:



It is to be understood that, where optional substitution on alkyl or cycloalkyl groups in R^3, R^9 and R^{10} (as defined hereinbefore or hereinafter) allows two hydroxy substituents on the alkyl or cycloalkyl group, or one hydroxy substituent and a second substituent linked by a heteroatom (for example alkoxy), then these two substituents are not substituents on the same carbon atom of the alkyl or cycloalkyl group.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are in-vivo hydrolysable esters of compounds of formula (1). Therefore in another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof 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 have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for

example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example. A pharmaceutically acceptable ester which is cleaved 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.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic 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/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and

2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hyrolysable esters include, for example, $R^A C(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_1-C_4)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-4}alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-4}alkyl"and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C_{2-6}alkenyl" include the examples of "C_{2-4}alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C_{2-4}alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of "C_{2-6}alkynyl"include the examples of "C_{2-4}alkynyl" and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term "hydroxyC_{1-4}alkyl" includes hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl and hydroxybutyl. The term "hydroxyethyl" includes 1-hydroxyethyl and 2-hydroxyethyl. The term "hydroxypropyl" includes 1-hydroxypropyl, 2-hydroxypropyl and 3-hydroxypropyl and an analogous convention applies to terms such as hydroxybutyl. The term "dihydroxyC_{1-4}alkyl" includes dihydroxyethyl, dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl. The term "dihydroxypropyl" includes 1,2-dihydroxypropyl and 1,3-dihydroxypropyl. An analogous convention applies to terms such as dihydroxyisopropyl and dihydroxybutyl.

The term "halo" refers to fluoro, chloro, bromo and iodo. The term "dihaloC_{1-4}alkyl" includes difluoromethyl and dichloromethyl. The term "trihaloC_{1-4}alkyl" includes trifluoromethyl.

Examples of "5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof" are:

1,3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl; 2,2-dimethyl-1,3-dioxan-4-yl; 2,2-dimethyl-1,3-dioxan-5-yl; 1,3-dioxan-2-yl.

Examples of "C_{1-4}alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C_{1-6}alkoxy" include the examples of "C_{1-4}alkoxy" and additionally butyloxy, *t*-butyloxy, pentoxy and 1,2-(methyl)$_2$propoxy. Examples of "C_{1-4}alkanoyl" include formyl, acetyl and propionyl. Examples of "C_{1-6}alkanoyl" include the example of "C_{1-4}alkanoyl" and additionally butanoyl, pentanoyl, hexanoyl and 1,2-(methyl)$_2$propionyl. Examples of "C_{1-4}alkanoyloxy" are formyloxy, acetoxy and propionoxy. Examples of "C_{1-6}alkanoyloxy" include the examples of "C_{1-4}alkanoyloxy" and additionally butanoyloxy, pentanoyloxy, hexanoyloxy and 1,2-(methyl)$_2$propionyloxy. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N*-(C_{1-6}alkyl)amino" include the examples of "*N*-(C_{1-4}alkyl)amino" and additionally pentylamino, hexylamino and 3-methylbutylamino. Examples of "*N,N*-(C_{1-4}alkyl)$_2$amino" include *N*-*N*-(methyl)$_2$amino, *N*-*N*-(ethyl)$_2$amino and *N*-ethyl-*N*-methylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include the example of "*N,N*-(C_{1-4}alkyl)$_2$amino" and additionally *N*-methyl-*N*-pentylamino and *N,N*-(pentyl)$_2$amino. Examples of "*N*-(C_{1-4}alkyl)carbamoyl" are methylcarbamoyl and ethylcarbamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are the examples of "*N*-(C_{1-4}alkyl)carbamoyl"and additionally pentylcarbamoyl, hexylcarbamoyl and 1,2-(methyl)$_2$propylcarbamoyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are *N,N*-(methyl)$_2$carbamoyl, *N,N*-(ethyl)$_2$carbamoyl and *N*-methyl-*N*-ethylcarbamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are the examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" and additionally *N,N*-(pentyl)$_2$carbamoyl, *N*-methyl-*N*-pentylcarbamoyl and *N*-ethyl-*N*-hexylcarbamoyl. Examples of "*N*-(C_{1-4}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are the examples of "*N*-(C_{1-4}alkyl)sulphamoyl" and additionally *N*-pentylsulphamoyl, *N*-hexylsulphamoyl and 1,2-(methyl)$_2$propylsulphamoyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(methyl)$_2$sulphamoyl, *N,N*-(ethyl)$_2$sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are the

examples of "*N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl" and additionally *N*,*N*-(pentyl)$_2$sulphamoyl, *N*-methyl-*N*-pentylsulphamoyl and *N*-ethyl-*N*-hexylsulphamoyl.

Examples of "cyano(C_{1-4})alkyl" are cyanomethyl, cyanoethyl and cyanopropyl. Examples of "C_{5-7}cycloalkyl" are cyclopentyl, cyclohexyl and cycloheptyl. Examples of "C_{3-8}cycloalkyl" and "C_{3-7}cycloalkyl" include "C_{5-7}cycloalkyl", cyclopropyl, cyclobutyl and cyclooctyl. Examples of "C_{3-6}cycloalkyl" includle cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "aminoC_{1-4}alkyl" includes aminomethyl, aminoethyl, aminopropyl, aminoisopropyl and aminobutyl. The term "aminoethyl" includes 1-aminoethyl and 2-aminoethyl. The term "aminopropyl" includes 1-aminopropyl, 2-aminopropyl and 3-aminopropyl and an analogous convention applies to terms such as aminoethyl and aminobutyl.

Examples of "C_{1-4}alkoxyC_{1-4}alkoxy" are methoxymethoxy, ethoxymethoxy, ethoxyethoxy and methoxyethoxy. Examples of "hydroxyC_{1-4}alkoxy" are hydroxyethoxy and hydroxypropoxy. Examples of "hydroxypropoxy" are 1-hydroxypropoxy, 2-hydroxypropoxy and 3-hydroxypropoxy.

Examples of "C_{1-4}alkylS(O)$_b$ (wherein b is 0,1 or 2)", "C_{1-4}alkylS(O)$_c$ (wherein c is 0 to 2)", "C_{1-4}alkylS(O)$_d$ (wherein d is 0 to 2)", "C_{1-4}alkylS(O)$_e$ (wherein e is 0 to 2)", and "C_{1-4}alkylS(O)$_f$ (wherein f is 0 to 2)" independently include methylthio, ethylthio, propylthio, methanesulphinyl, ethanesulphinyl, propanesulphinyl, mesyl, ethanesulphonyl, propanesulphonyl and isopropanesulphonyl.

Examples of "C_{3-6}cycloalkylS(O)$_b$ (wherein b is 0,1 or 2)" include cyclopropylthio, cyclopropylsulphinyl, cyclopropylsulphonyl, cyclobutylthio, cyclobutylsulphinyl, cyclobutylsulphonyl, cyclopentylthio, cyclopentylsulphinyl and cyclopentylsulphonyl.

Examples of "arylS(O)$_b$ (wherein b is 0,1 or 2)" include phenylthio, phenylsulphinyl and phenylsulfonyl. Examples of "benzylS(O)$_b$ (wherein b is 0,1 or 2)" inculde benzylthio, benzylsulfinyl and benzylsulfonyl. Examples of "heterocyclylS(O)$_b$ (wherein b is 0,1 or 2)" include pyridylthio, pyridylsulfinyl, pyridylsulfonyl, imidazolylthio, imidazolylsulfinyl, imidazolylsulfonyl, pyrimidinylthio, pyrimidinylsufinyl, pyrimidinylsulfonyl, piperidylthio, piperidylsulfinyl and piperidylsulfonyl.

Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" include methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. 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}alkylsulphonylamino" include methylsulphonylamino, ethylsulphonylamino and propylsulphonylamino. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino.

Where optional substituents are chosen from "0, 1, 2 or 3" 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. An analogous convention applies to substituents chose from "0, 1 or 2" groups and "1 or 2" groups.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, optionally substituted monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are 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 "heterocyclyl" are morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, dioxolanyl, thiadiazolyl, piperazinyl, isothiazolidinyl, triazolyl, tetrazolyl, pyrrolidinyl, 2-oxazolidinonyl, 5-isoxazolonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-5-yl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, and oxadiazolyl.

Suitably a "heterocyclyl" is morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl.

Conveniently "heterocyclyl" is oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, tetrazolyl, thizoyl, thiadiazolyl, pyridyl, imidazolyl, furyl, thienyl, morpholine, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, and piperazinyl.

Suitable optional substituents for "heterocyclyl" as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-}

$_{4}$alkoxy and C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2). Further suitable substituents for "heterocyclyl" as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Suitable optional susbtituents for "heterocyclyl" as an unsaturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2), *N*-(C_{1-4}alkyl)amino and *N,N*-(C_{1-4}alkyl)$_2$amino. Further suitable optional susbtituents for "heterocyclyl" as an unsaturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Examples of "(heterocyclyl)C_{1-4}alkyl" are morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, imidazolylmethyl, imidazolylethyl, oxazolylmethyl, oxazolylethyl, 1,3,4-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, pyrazinylethyl, piperazinylmethyl and piperazinylethyl.

Examples of "aryl" are optionally substituted phenyl and naphthyl.

Examples of "aryl(C_{1-4})alkyl" are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

Suitable optional substituents for "aryl" groups are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2), *N*-(C_{1-4}alkyl)amino and *N,N*-(C_{1-4}alkyl)$_2$amino. Further suitable optional susbtituents for "aryl" groups are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

"Heteroarylene" is a diradical of a heteroaryl group. A heteroaryl group is an aryl, monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen. Examples of heteroarylene are oxazolylene, oxadiazolylene, pyridylene, pyrimidinylene, imidazolylene, triazolylene, tetrazolylene, pyrazinylene, pyridazinylene, pyrrolylene, thienylene and furylene.

Suitable optional substituents for heteroaryl groups, unless otherwise defined, are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C_{1-4}alkyl,

C_{1-4}alkoxy, C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2), *N*-(C_{1-4}alkyl)amino and *N,N*-(C_{1-4}alkyl)$_2$amino. Further suitable optional substituents for "heteroaryl" groups are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Preferred values of A, Y, R^1, R^4, R^5, r and n are as follows. Such values may be used where appropriate with any of the definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

In one embodiment of the invention are provided compounds of formula (1), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (1), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (1).

Particular examples of in-vivo hydrolysable esters of compounds of the formula (1) are such esters of compounds of the formula (1) wherein Y comprises a group containing a carboxy group. Suitable esters are those hereinbefore described for carboxy groups.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein z is CH.

In another aspect of the invention Z is nitrogen.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein R^4 and R^5 are together –S-C(R^6)=C(R^7)-.

In another aspect of the invention R^4 and R^5 are together –C(R^7)=C(R^6)-S-.

In a further aspect of the invention, R^6 and R^7 are independently selected from hydrogen, halo or C_{1-6}alkyl.

Preferably R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl.

Particularly R^6 and R^7 are independently selected from hydrogen or chloro.

More particularly one of R^6 and R^7 is chloro.

In one embodiment, one of R^6 and R^7 is chloro and the other is hydrogen.

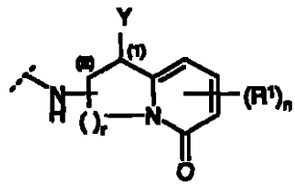
In another embodiment, both R^6 and R^7 are chloro.

In one aspect of the invention A is phenylene.

In another aspect of the invention A is heteroarylene.

Preferably A is selected from phenylene, pyridylene, pyrimidinylene, pyrrolylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, oxadiazolylene, thienylene and furylene.

In one embodiment, when A is heteroarylene, there is a nitrogen in a bridgehead position. In another embodiment, when A is heteroarylene, the heteroatoms are not in bridgehead positions. It will be appreciated that the preferred (more stable) bridgehead position is as shown below:



In one aspect of the invention n is 0 or 1.

In one aspect preferably n is 1.

In another aspect, preferably n is 0.

When n is 2, and the two R^1 groups, together with the carbon atoms of A to which they are attached, form a 4 to 7 membered ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, conveniently such a ring is a 5 or 6 membered ring containing two O atoms (ie a cyclic acetal). When the two R^1 groups together form such a cyclic acetal, preferably it is not substituted. Most preferably the two R^1 groups together are the group $-O-CH_2-O-$.

In another aspect of the present invention R^1 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl and C_{1-4}alkoxy.

In a further aspect R^1 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, $-S(O)_bC_{1-4}$alkyl (wherein b is 0, 1 or 2), C_{1-4}alkyl and C_{1-4}alkoxy.

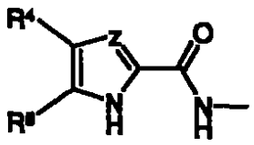
In a further aspect R^1 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, $-S(O)_bMe$ (wherein b is 0, 1 or 2), methyl and methoxy.

In a further aspect, R^1 is C_{1-4}alkyl.

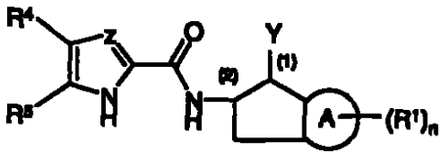
Preferably R^1 is selected from halo and C_{1-4}alkoxy.

In another embodiment preferably R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$.

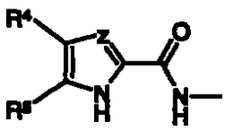
In one aspect of the invention r is 1 and when r is 1 the group



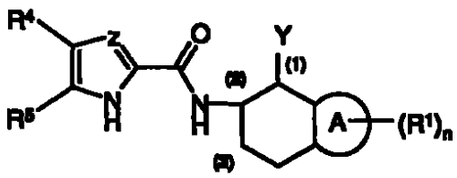
is a substituent on carbon (2) such that an example of when r is 1 is:



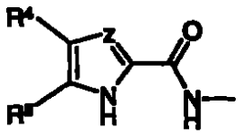
In another aspect of the invention r is 2 and when r is 2 the group



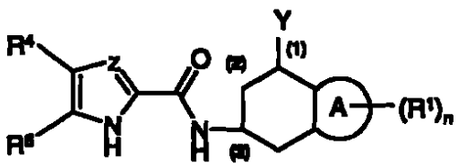
is a substituent on carbon (2) such that an example of when r is 2 is:



In another aspect of the invention r is 2 and when r is 2 the group



is a substituent on carbon (3) such that an example of when r is 2 is:



In one aspect of the invention Y is $-NR^2R^3$.

In another aspect of the invention Y is $-OR^3$.

Suitable values for R^2 and R^3 as heterocyclyl are morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl,

homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl.

More suitable values for R^2 and R^3 as heterocyclyl are pyridyl, pyrimidinyl and imidazolyl.

Further suitable values for R^2 and R^3 as heterocyclyl are tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl.

In one aspect of the invention, R^2 and R^3 are independently selected from groups of the formulae B and B' as hereinbefore described.

In one aspect of the invention R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0,.1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_b(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$,

$-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy.

In a further aspect of the invention R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2),

C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, –$COOR^9$, –CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, –$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ and –CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by –O-CH_2-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH_2-O- group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy.

In another aspect of the invention R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], -COR^8 and –SO_bR^8 (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, -CO_2C_{1-4}alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by -C(O)OC_{1-4}alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkylS(O)$_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkylS(O)$_b$- (wherein b is 0, 1 or 2), arylS(O)$_b$- (wherein b is 0, 1 or 2), heterocyclylS(O)$_b$- (wherein b is 0, 1 or 2 -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$,

$(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano).

In one aspect, one of R^9 and R^{10} is hydrogen and the other is selected from heterocyclyl and heterocyclyl(C_{1-4}alkyl). Conveniently R^9 or R^{10} as heterocyclyl and heterocyclyl(C_{1-4}alkyl) is selected from oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, tetrazolyl, thiazoyl, thiadiazolyl, pyridyl, imidazolyl, furyl, thienyl, morpholine, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, piperazinyl. morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, imidazolylmethyl, imidazolylethyl, oxazolylmethyl, oxazolylethyl, 1,3,4-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, pyrazinylethyl, piperazinylmethyl and piperazinylethyl;

wherein the heterocylic ring is optional substituted on any available atom by 1, 2 or 3 substituents independently selected from halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy and C_{1-4}alkyl$S(O)_b$ (wherein b is 0, 1 or 2), and additionally when the heterocyclyl ring is a heteroaryl ring, further suitable optional substituents are selected from nitro, amino, *N*-(C_{1-4}alkyl)amino and *N,N*-(C_{1-4}alkyl)$_2$amino, and/or wherein any heterocyclic ring is optionally oxidised such that a $-CH_2-$ group is replaced by a -C(O)-and/or a ring sulphur atom is oxidised to form the S-oxide(s).

In another aspect of the invention R^2 is selected from hydrogen, acetyl and C_{1-4}alkyl.

In a further aspect of the invention, Y is NR^2R^3 and NR^2R^3 forms a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by –C(=O)-, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy and C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2).

Suitable values for NR^2R^3 as a 4 to 7 membered ring are morpholino, 2,5-dioxomorpholino, piperidinyl, pyrrolidinyl, pyrazolyl, pyrrolyl, imidazolyl, piperazinyl and thiomorpholinyl.

In yet a further aspect of the inventions R^3 is selected from hydrogen, 1,3-dihydroxyisopropyl, 1,2-dihydroxypropyl, cyanomethyl, trifluoromethylcarbonyl, carboxyacetyl, carboxymethyl, formyl, acetyl, carbamoylacetyl, carbamoylmethyl, methoxyacetyl, methoxypropanoyl, acetoxyacetyl, methanesulfonyl, chloromethylsulfonyl, trifluoromethylsulfonyl, morpholinomethylcarbonyl, furylcarbonyl, thienylcarbonyl, nitrofurylcarbonyl, *N,N*-dimethylcarbamoyl, 4-methylpiperazinocarbonyl, *N*-ethylcarbamoyl, *N*-allylcarbamoyl, *N*-dinitrophenylcarbamoyl, pyridinylcarbonyl, tetrahydrofuran-2-on-5-ylcarbonyl, hydroxyphenylcarbonyl, acryloyl, 2-(tert-butoxycarbonyl)methylcarbonyl, aminoacetyl, 1-amino-1-carboxypropanoyl, chloroacetyl, hydroxyacetyl, carbamoylacetyl, carbamoylmethyl, methoxyacetyl, methoxypropanoyl, acetoxyacetyl, hydroxypiperidinoaminoacetyl, hydroxypyrrolidinylaminoacetyl, *N*-methyl-*N*-hydroxyethylaminoacetyl, *N*-benzyl-*N*-hydroxyethylaminoacetyl, *N*-(2,3-dihydroxypropyl)-*N*-methylaminoacetyl, *N,N*-bis(hydroxyethyl)aminoacetyl, *N,N*-bis(hydroxypropyl)aminoacetyl, (1-amino-1-carbonylamino)ethylcarbonyl, 1-hydroxy-1-carboxyethylcarbonyl, tert-butoxycarbonylmethyl, 1,3-dihydroxyisoprop-2-ylcarbonyl, 1-(tert-butoxycarbonylamino)-1-(carbamoyl)propanoyl, *N*-ethyl-*N*-(2-hydroxyethyl)aminoacetyl, thienylmethyl, tetrazolylmethyl, [2-(ethoxycarbonyl)cyclopropyl]methyl, *N*-(tert-butoxycarbonyl)aminoacetyl and *N*-(aminocarbonyl)-*N*-(tert-butoxycarbonyl)aminoacetyl.

In yet a further aspect of the inventions R^3 is selected from trifluoromethylcarbonyl, carboxyacetyl, formyl, acetyl, , methanesulfonyl, morpholinomethylcarbonyl, furylcarbonyl, thienylcarbonyl, nitrofurylcarbonyl, *N,N*-dimethylcarbamoyl, 4-methylpiperazinocarbonyl, *N*-ethylcarbamoyl, *N*-allylcarbamoyl, *N*-dinitrophenylcarbamoyl, pyridinylcarbonyl, tetrahydrofuran-2-on-5-ylcarbonyl, hydroxyphenylcarbonyl, acryloyl, 2-(tert-butoxycarbonyl)methylcarbonyl, aminoacetyl, 1-amino-1-carboxypropanoyl, chloroacetyl, hydroxyacetyl, carbamoylacetyl, carbamoylmethyl, methoxyacetyl, methoxypropanoyl, acetoxyacetyl, *N*-methyl-*N*-hydroxyethylaminoacetyl, *N*-benzyl-*N*-hydroxyethylaminoacetyl, *N*-(2,3-dihydroxypropyl)-*N*-methylaminoacetyl, *N,N*-bis(hydroxyethyl)aminoacetyl, *N,N*-bis(hydroxypropyl)aminoacetyl, (1-amino-1-carbonylamino)ethylcarbonyl, 1-hydroxy-1-carboxyethylcarbonyl, tert-butoxycarbonylmethyl, 1,3-dihydroxyisoprop-2-ylcarbonyl, 1-(tert-butoxycarbonylamino)-1-(carbamoyl)propanoyl and *N*-ethyl-*N*-(2-hydroxyethyl)aminoacetyl.

A preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is halo or hydrogen;

R^7 is halo or hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b-$ (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b-$ (wherein b is 0, 1 or 2), aryl$S(O)_b-$ (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b-$ (wherein b is 0, 1 or 2), benzyl$S(O)_b-$ (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), -

$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

viii) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

ix) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

x) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

Another preferred class of compounds is of formula (1) wherein:

Z is CH;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

R^6 is chloro;

R^7 is hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$,

$-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

Another preferred class of compound is of the formula (1) wherein:

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is chloro;

R^7 is hydrogen or chloro;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl,

-CO_2C_{1-4}alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by -C(O)OC_{1-4}alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole.

Another preferred class of compound is of the formula (1) wherein:

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is hydrogen or halo;

R^7 is hydrogen or halo;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-OR^3$;

R^3 is selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

wherein R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$,

$(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$ R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

ii) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

iii) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-[*N*-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

A further preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl,

$-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Another preferred class of compound is of the formula (1) wherein:

Z is CH;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S$-;

R^6 is hydrogen or halo;

R^7 is hydrogen or halo;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-OR^3$;

R^3 is selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

provided that the compound of formula (1) is not:

2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole.

A further preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0

r is 1;

Y is $-NR^2R^3$;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is selected from C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A further preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0;

r is 1;

Y is $-NR^2R^3$;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is selected from C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

provided that the compound of formula (1) is not:

(i) 2,3-dichloro-5-{*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

(iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

(iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

(v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

(vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

A preferred class of compound is of the formula (1) wherein;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is halo or hydrogen;

R^7 is halo or hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl,

pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

(i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

(ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

(iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

(iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

(v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

(vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

(vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

(viii) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

(ix) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

(x) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

Another preferred class of compounds is of formula (1) wherein:

Z is nitrogen;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

R^6 is chloro;

R^7 is hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-

oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

ii) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

Another preferred class of compound is of the formula (1) wherein:

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is chloro;

R^7 is hydrogen or chloro;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Another preferred class of compound is of the formula (1) wherein:

Z is nitrogen ;

R^4 and R^5 are together –S-C(R^6)=C(R^7)-;

R^6 is hydrogen or halo;

R^7 is hydrogen or halo;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, -SO_2Me and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is –OR^3;

R^3 is selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], -COR^8 and –SO_bR^8 (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, -CO_2C_{1-4}alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by -C(O)OC_{1-4}alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl),

pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkylS(O)$_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkylS(O)$_b$- (wherein b is 0, 1 or 2), arylS(O)$_b$- (wherein b is 0, 1 or 2), heterocyclylS(O)$_b$- (wherein b is 0, 1 or 2), benzylS(O)$_b$- (wherein b is 0, 1 or 2), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A further preferred class of compound is of the formula (1) wherein;

Z is nitrogen;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl,

dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Another preferred class of compound is of the formula (1) wherein:

Z is nitrogen;

R^4 and R^5 are together $-C(R^7)=C(R^6)$-S-;

R^6 is hydrogen or halo;

R^7 is hydrogen or halo;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-OR^3$;

R^3 is selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

A further preferred class of compound is of the formula (1) wherein;

Z is nitrogen;

R^4 and R^5 are together $-C(R^7)=C(R^6)$-S-;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0;

r is 1;

Y is $-NR^2R^3$;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is selected from C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A further preferred class of compound is of the formula (1) wherein;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$;

R^6 is halo;

R^7 is hydrogen;

A is phenylene;

n is 0

r is 1;

Y is $-NR^2R^3$;

R^2 is hydrogen or C_{1-4}alkyl;

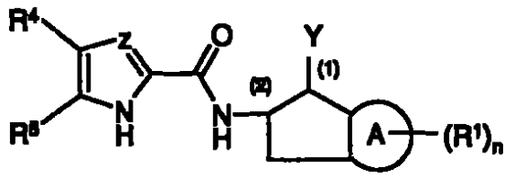
R^3 is selected from C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In a further preferred aspect of the invention is provided a compound of the formula (1A):



(1A)

wherein Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 is hydrogen or halo;

R^7 is hydrogen or halo;

A is phenylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

Y is $-NR^2R^3$ or OR^3;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is selected from C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$,

$(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A further preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 is halo or hydrogen;

R^7 is halo or hydrogen;

A is heteroarylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, cyano, nitro, hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, -SMe, -SOMe, $-SO_2Me$ and, (when n is 2) methylenedioxy;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl,

dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c(C_{1-4})$alkyl (wherein c is 0, 1 or 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ and -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), -C(=O)O^{t}Bu, C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl andC_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by -O-CH_2-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH_2-O- group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A preferred class of compound is of the formula (1) wherein;

Z is CH;

R^4 and R^5 are together -S-$C(R^6)$=$C(R^7)$-;

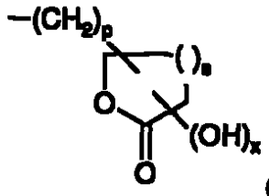
R^6 is halo or hydrogen;

R^7 is halo or hydrogen;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, cyano, nitro, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4}alkoxy and and R^1 is of the formula A' or A'':



(A) $-CH_2CH(OH)(CH_2)_rCO_2H$ (A')

wherein x is 0 or 1, p is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

{wherein R^8 is independently selected from hydrogen, hydroxy, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, morpholino, pyridyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, and $-CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

[wherein R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy

groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano) and C_{1-4}alkyl substituted by R^{13};

(wherein R^{13} is selected from C_{1-4}alkoxy, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, C_{1-4}alkyl$S(O)_d$(C_{1-4})alkyl (wherein d is 0, 1 or 2)); and

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-(C_{1-4})$_2$alkylamino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, and C_{1-4}alkyl$S(O)_f$(C_{1-4})alkyl (wherein f is 0, 1 or 2)]};

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

viii) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

ix) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

x) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

Another preferred class of compounds is of formula (1) wherein:

Z is CH;

R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$;

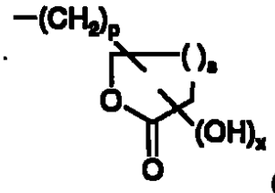
R^6 is chloro;

R^7 is hydrogen;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy and and R^1 is of the formula A' or A'':



(A) $-CH_2CH(OH)(CH_2)_rCO_2H$ (A')

wherein x is 0 or 1, p is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

r is 1 or 2;

Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

{wherein R^8 is independently selected from hydrogen, hydroxy, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon

by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$ and $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, $-CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

[wherein R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano) and C_{1-4}alkyl substituted by R^{13};

(wherein R^{13} is selected from C_{1-4}alkoxy, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, C_{1-4}alkyl$S(O)_d$(C_{1-4})alkyl (wherein d is 0, 1 or 2)); and

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N,N*-(C_{1-4})$_2$alkylamino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, and C_{1-4}alkyl$S(O)_f$(C_{1-4})alkyl (wherein f is 0, 1 or 2)]};

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof;

with the proviso that the compound of formula (1) is not:

i) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

In another aspect of the invention, preferred compounds of the invention are any one of:

2,3-dichloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*R*,2*R*)-1-{[(methyloxy)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-butoxycarbonylamino)-3-carbamoylpropanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(trifluoroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(furan-2-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(furan-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(3-thienylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(5-nitrofuran-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(pyridin-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-(acryloylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(3-hydroxyphenyl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-(acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(dimethylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(4-methylpiperazin-1-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(ethylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(prop-2-en-1-ylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*S*,2*S*)-1-({[(3,5-dinitrophenyl)amino]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*S*,2*S*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[((3R)-3-carboxy-3-hydroxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*, 2*S*)-1-[methyl(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[(tert-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(*1R*,2*R*)-1-[acetyl(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[*N*-(carboxymethyl)-*N*-(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-[(1*R*,2*R*)-1-({[(2*S*)-5-oxotetrahydrofuran-2-yl]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(methoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-[(1*R*,2*R*)-1-(acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-acetoxyacettyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-((1*S*,2*S*)-1-{[(2(*S*)-2-(*tert*-butoxycarbonylamino)-2-carbamoylacetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*S*,2*S*)-1-[(2-(*tert*-butoxycarbonylamino)acetylamino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[2-(tert-butoxycarbonyl)acetylamino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-{[3-hydroxy-2-(hydroxymethyl)propanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-[(1*R*,2*R*)-1-({[(2-hydroxyethyl)(phenylmethyl)amino]acetyl} amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-({[(2-hydroxyethyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-((1*R*,2*R*)-1-({[bis(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-({[ethyl(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihydroxypropyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-((1*R*,2*R*)-1-({[bis(2-hydroxypropyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-[(1*R*,2*R*)-1-[(tert-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetylamino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3*S*)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3S)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, further preferred compounds of the invention are any one of:

2-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetylamino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

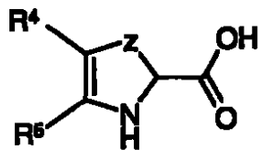
2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

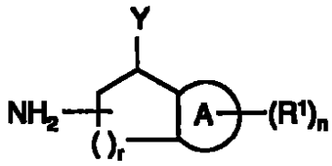
Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein A, Y, R^1, R^4, R^5, r and n are, unless otherwise specified, as defined in formula (1)) comprises of:

a) reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

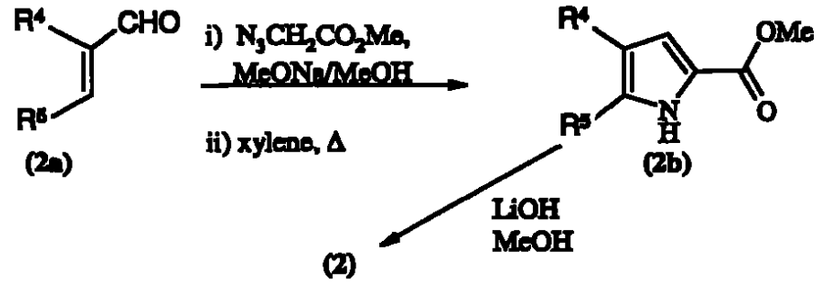
iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (2) and amines of formula (3) 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 (EDCI) and dicyclohexyl-carbodiimide (DCCI), 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.

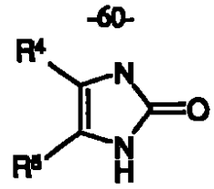
A compounds of formula (2) where Z is CH may be prepared according to Scheme 1:



Scheme 1

Compounds of formula (2a) are commercially available or they are known compounds or they are prepared by processes known in the art.

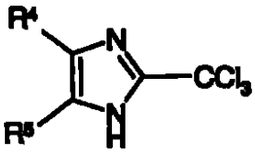
A compound of the formula (2) wherein X is nitrogen, can be prepared from a compound of the formula (4):



(4)

by firstly converting the oxo group to chlorine or bromine with a halogenating agent such as $POCl_3$ or $POBr_3$, in an inert organic solvent such as dichloromethane in a temperature range of ambient temperature to reflux (for example see *Nucleic Acid Chem.* 1991, 4, 24-6) , then displacing the chlorine or bromine group with cyanide using a cyanide salt such as potassium cyanide, in an inert organic solvent such as toluene, benzene or xylene, optionally in the presence of a catalyst such as 18-crown-6 (for example see *J. Heterocycl. Chem* 2000, 37(1), 119-126) and finally hydrolysing the cyano group to a carboxy group, with for example, an aqueous acid such as aqueous hydrogen chloride (for example see *Chem. Pharm. Bull.* 1986, 34(9), 3635-43).

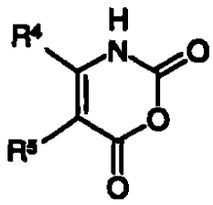
Alternatively, a compound of the formula (2) wherein X is nitrogen may be formed by reacting the compound of the formula (4) with $(Cl_3CCO)_2O$ and Cl_3CCO_2H in the presence of magnesium chloride using Cl_3CCO_2H as solvent, to form a compound of the formula (5):



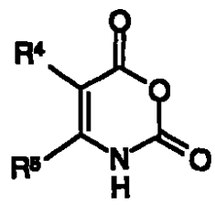
(5)

and then hydrolysing the compound of the formula (5), using, for example, aqueous sodium hydroxide, at a temperature range of ambient temperature to reflux (for example see *J Heterocycl. Chem.* 1980, 17(2), 381-2).

The compound of formula (4) may be prepared from a compound of formula (6) and (7) using conditions known for the Curtius rearrangement (*Tetrahedron* 1999, 55, 6167):

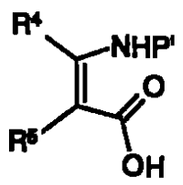


(6)

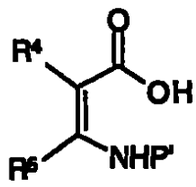


(7)

The compounds of the formula (8) and (9):



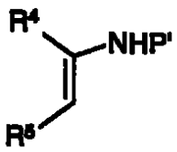
(8)



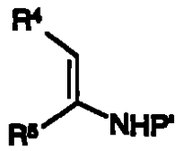
(9)

transform into compounds of the formula (6) and (7) respectively. This transformation either occurs spontaneously or may be induced with acid or base.

Compounds of the formula (8) and (9) may be prepared by introducing a carboxy group into a compound of the formula (10) or (11):



(10)



(11)

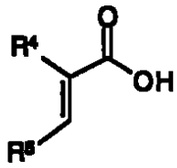
wherein P' is an amino protecting group such as butoxycarbonyl.

A carboxy group is introduced into the compound of the formula (10) or (11) by reacting an alkyl lithium reagent such as n-butyl lithium, in an inert organic solvent such as THF, at low temperature, for example in the range –10°C to –78°C and then forming the compound of the formula (8) or (9) as appropriate by either

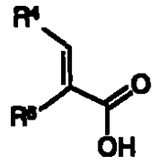
a) reacting the resulting compound with carbon dioxide; or

b) by reacting with DMF in the temperature range of –10°C to ambient temperature to form the corresponding aldehyde and oxidizing the aldehyde to carboxy with standard reagents to give the compound of the formula (8) or (9).

Compounds of the formula (10) and (11) may be prepared from a compound of the formula (12) and (13):



(12)

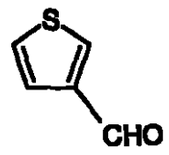


(12)

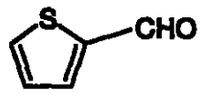
using conditions known for the Curtius reaction.

Compounds of the formula (12) and (13) may be prepared by oxidizing the corresponding aldehyde using standard oxidizing reagents such as potassium manganate or sodium periodate.

The aldehyde precursor of a compound of the formula (12) or (13) can be prepared using standard techniques known in the art. For example, many compounds of the formula (12) or (13) may be prepared by introducing the appropriate R^6 and R^7 into a compound of the formula (14) or (15) as appropriate:



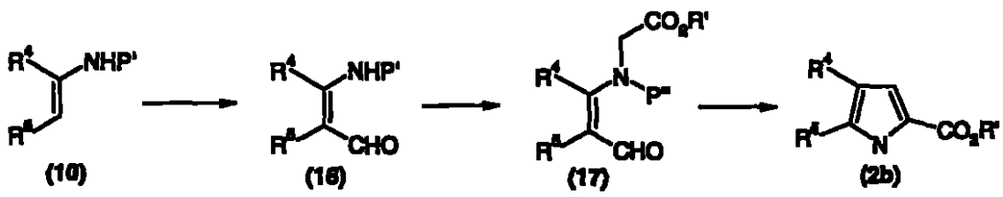
(14)



(15)

For example, when R^6 and R^7 are both chloro a compound of the formula (14) or (15) may be chlorinated with a chlorinating agent such as chlorine in the presence of aluminium chloride or iron (III) chloride, in an inert organic chlorinated solvent such as dichloromethane or 1,2-dichloroethane, followed by treatment with an aqueous base, such as, aqueous sodium hydroxide. The mono chlorinated compound can be formed in the same way.

Compounds of formula (2b) may also be prepared as illustrated in Scheme 2:

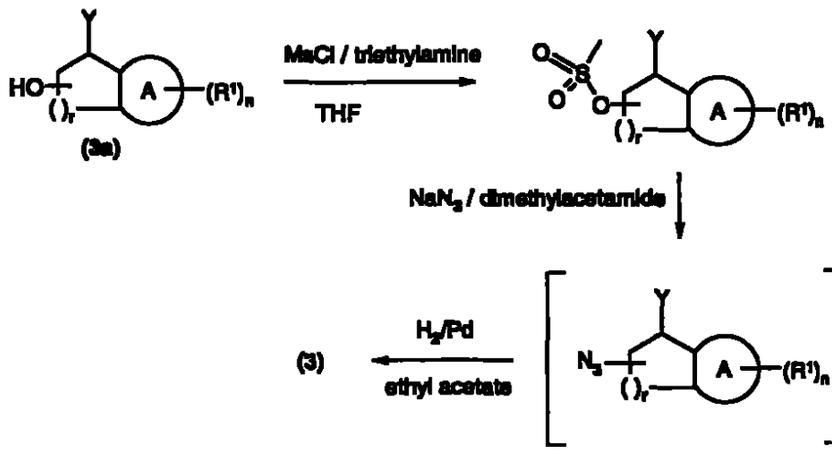


(10) (16) (17) (2b)

Scheme 2

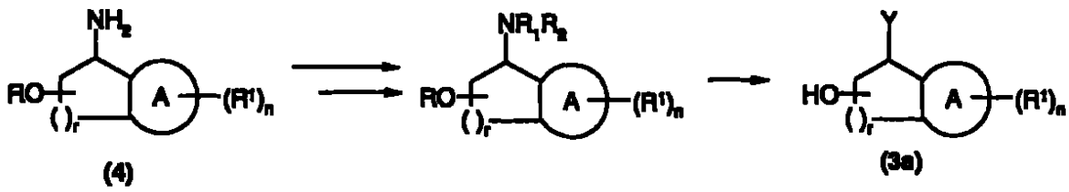
The conversion of compounds of formula (10) into compounds of formula (16) may be carried out by directed ortho lithiation reactions (J. Org. Chem, 2001, volume 66, 3662-3670), for example with n-butyl lithium and $(CHO)N(alkyl)_2$. The protecting group P' in compounds of formula (10) must be suitable directing group for this reaction and may be for example – CO_2tBu. Reaction of compounds of formula (16) with LCH_2CO_2R where L is a leaving group, and replacement of the protecting group P' with an alternative P'' (for example – COalkyl) according to standard processes, gives a compound of formula (17). This may be cyclised using a base, for example potassium carbonate or sodium methoxide.

Compounds of formula (3) where Y is OR^3 are commercially available or they are known compounds or they are prepared by processes known in the art. When Y is NR^2R^3, the amines of formula (3) may be prepared according to Scheme 3:

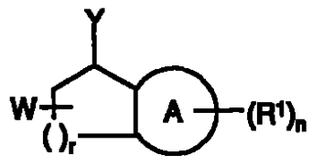


Scheme 3

Compounds of formula (3a) are commercially available or they are known compounds or they are prepared by processes known in the art. For example, starting from primary amines of formula (4), in which R is H or a suitable protecting group, one or both of R^1 and/or R^2 may be introduced by acylation, (for example reacting with acetoxyacetic acid and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride -EDAC), alkylation, reductive alkylation, sulphonation or related processes, followed by O-deprotection when appropriate. Alternatively, one or both of R^1 and/or R^2 may be obtained by modification of functionality in groups previously thus introduced, by reduction, oxidation, hydrolysis (for example the conversion of an acetoxy group to a hydroxy group), nucleophilic displacement, amidation, or a related process, or a combination of these processes, followed by O-deprotection when appropriate. It will be appreciated that such modifications may include modifications which convert one compound of the formula (1) into another compound of the formula (1).

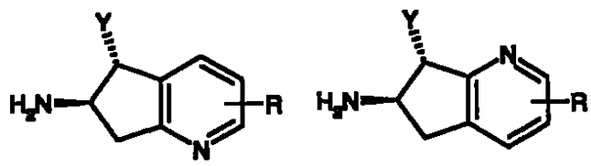


Amines of formula (3) may alternatively be obtained by applying the processes described for the preparation of compounds of formula (3a) to compounds of formula (20) in which W is NH_2 or a nitrogen atom with one or two suitable protecting groups.



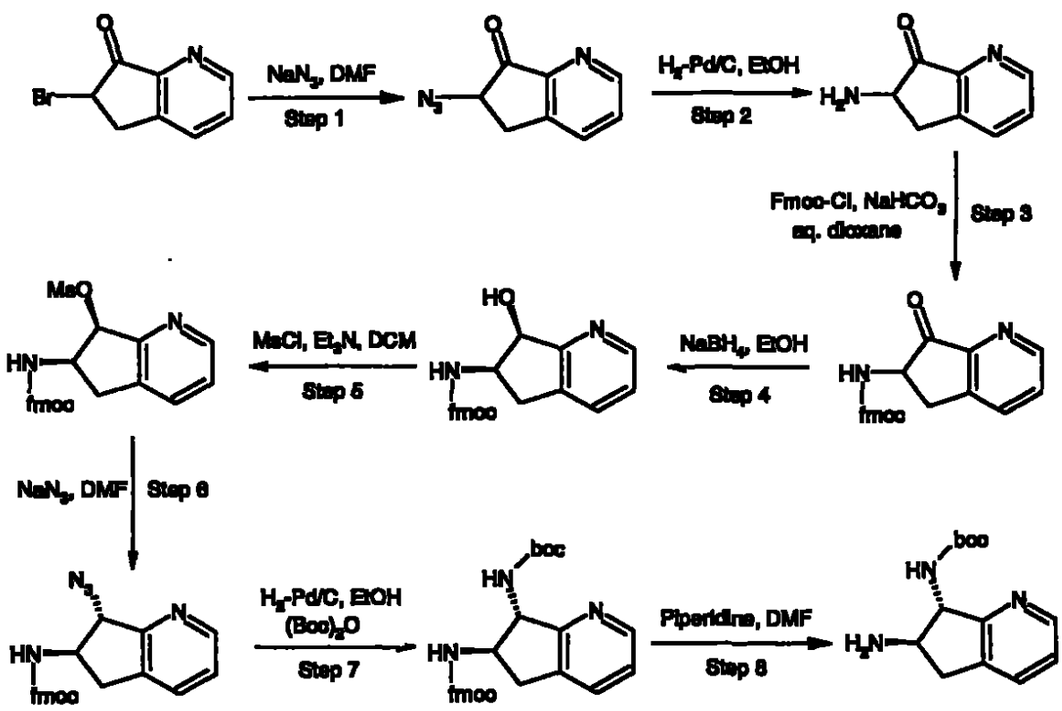
(20)

Compounds of the formula (3) where r = 1 and wherein A is heteroarylene can be prepared from suitably functionalised cycloalkyl fused heterocycles. For example, when A is pyridine,



(3b) (3c)

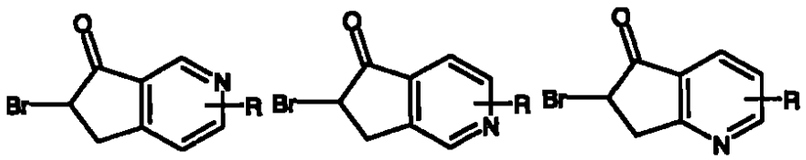
compounds of formula (3b) and (3c) may be prepared from the corresponding pyrindinone regioisomer according to Scheme 4 :-



Scheme 4

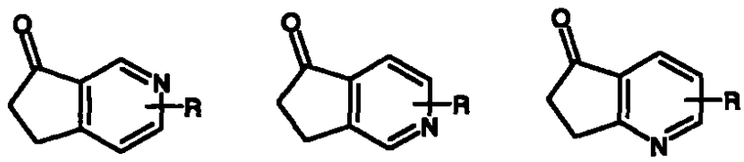
Step 1 is performed on a compound known in the literature (*Jpn. Kokai Tokkyo Koho*, 1995, 14. JP 07070136). Steps 2, 3, 4, 5, 6, 7 and 8 are performed using standard techniques known in the art.

It will be appreciated that the bromopyrindinone isomers (21a, 21b and 21c) could



(21a) (21b) (21c)

be converted to the corresponding heterocylic version of (3) by the means described in Scheme 4. The bromopyridinones can be prepared from the corresponding pyrindinone by standard techniques known in the art. The pyrindinones (22a, 22b, 22c) are known in the literature or they are prepared by processes known in the art.



(22a) (22b) (22c)

The process described above and shown in Scheme 4 may also be applied to other six membered heterocycles containing more than one nitrogen.

It will be appreciated that, in a similar manner, compounds of the formula (3) wherein A is heteroarylene containing a bridgehead nitrogen can be prepared from the appropriate suitably functionalised cycloalkyl fused heterocycles.

It will be appreciated that the processes described above for formation and modification of Y as NR^1R^2 may be applied similarly whether to make the compound of formula (3) before coupling to the acid of formula (2) or whether to the product of such a coupling.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention, for example R^1 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 may convert one compound of the formula (1) into another compound of the formula (1). 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 halogen 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.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

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.

<u>Assay</u>

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 (N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid);4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid), 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. For example, Example 10 was found to have an IC_{50} of 4.5µm.

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 (Dulbeco's Modified Eagle's Medium) with high level of glucose containing 10% foetal calf serum, NEAA (non essential amino acids), 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 (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation

products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compound of formula (1) 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.

The inhibition of glycogen phosphorylase activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
3) Insulin sensitising agents including PPARg agonists (for example pioglitazone and rosiglitazone);
4) Agents that suppress hepatic glucose output (for example metformin).
5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
6) Agents designed to treat the complications of prolonged hyperglycaemia;
7) Anti-obesity agents (for example sibutramine and orlistat);
8) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
9) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and

11) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to a further aspect of the present invention there is provided a compound of the formula (1), 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 (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament 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 (1), 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 (1), 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 (1).

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 (1).

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 (1).

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 (1) 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, 60μ, 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;

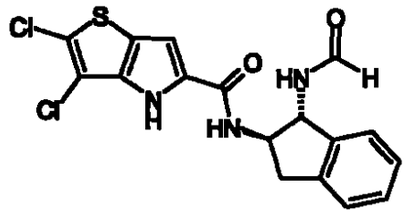
(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only 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;
EtOH	ethanol;
DCM	dichloromethane;
HOBT	1-hydroxybenzotriazole;
DIPEA	di-isopropylethylamine;
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride;
Et_2O	diethyl ether;

THF	tetrahydrofuran;
DMF	*N*, *N*-dimethylformamide;
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluroniumhexafluorophosphate
EDAC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
TFA	Trifluoroacetic acid
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DMA	N, N-dimethylacetamide

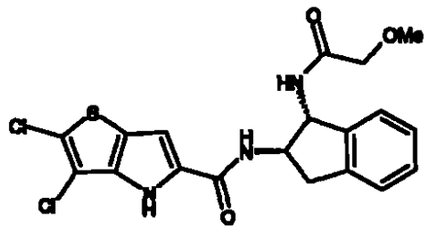
Example 1: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide trifluoroacetic acid salt (Method 8, 240 mg, 0.5 mmol), formic acid (50 µL, 1.4 mmol), DIPEA (174 µL, 1.0 mmol) and HOBT (67 mg, 0.5 mmol) were dissolved in DCM (5 ml), stirred for 5 mins, EDCI (120 mg, 0.625 mmol) added and the reaction stirred for 1hr. Formic acid (50 µL, 1.4 mmol) and EDCI (240 mg, 1.25 mmol) were added, the reaction stirred for 2 hours and the volatiles removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure. The residue was purified by column chromatography (2:1 EtOAc:Hexane) to afford the title compound (175mg, 89%) as a white foam.

^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 4.6 (m, 1H), 5.53 (m, 1H), 7.12 (m, 2H), 7.25 (m, 1H), 8.2 (s, 1H), 8.55 (d, 1H), 8.63 (d, 1H), 12.36 (s, 1H); MS m/z 394.

Example 2 2,3-Dichloro-*N*-((1*R*,2*R*)-1-{[(methyloxy)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



DIPEA (180 µL, 1.05 mmol), HOBT (68 mg, 0.5 mmol), methoxyacetic acid (0.5 mmol, 38 µL) and EDAC (120 mg, 0.63 mmol) were added to a suspension of *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 8, 240 mg, 0.5 mmol) in anhydrous DCM (7 mL). The reaction was stirred at ambient temperature for approximately 16 h. The volatiles were removed by evaporation under reduced preasure, the residue dissolved in EtOAc (10 mL), washed with water (2 x 10 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure and the residue was purified by flash column chromatography on SiO_2 (1:1 EtOAc:isohexane); the solvent removed by evaporation under reduced preassure and dried to give the title compound (44 mg, 20%) as a white solid.

^{1}H NMR 2.88 (dd, 1H), 3.26 (dd, 1H), 3.87 (dd, 2H), 4.73 (m 1H), 5.51 (t, 1H), 7.17 (m, 5H), 8.26 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H); MS m/z 439.

The following examples were made by the process similar to Example 2 using *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 8) and the appropriate commercially available carboxylic acid:

Example 3: *N*-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-Butoxycarbonylamino)-3-carbamoylpropanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 4: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

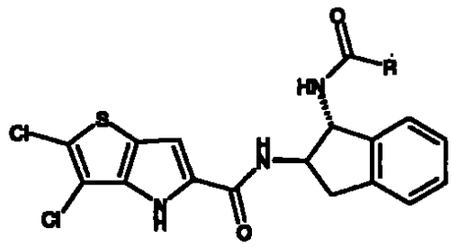
Example 5: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

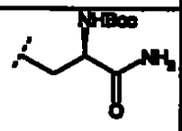
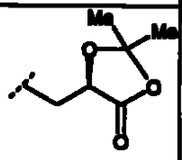
Example 6: *N*-[(1*R*,2*R*)-1-[(2-Acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 7: *N*-{(1*R*,2*R*)-1-[(2-Carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-carboxamide

Example 55: 2,3-Dichloro-*N*-{(1*R*,2*R*)-1-[(trifluoroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

5



Ex	R	NMR	M/z
3		(DMSO-d_6) 1.37 (s, 9H), 2.89 (dd, 1H), 3.23 (dd, 1H), 4.25 (m, 1H), 4.55 (m, 1H), 5.46 (t, 1H), 6.68 (d, 1H), 6.97 (s, 1H), 7.17 (m, 6H), 8.31 (d, 1H),	578
4			523
5	CH_2CH_2OMe	(DMSO-d_6) 2.33 (m, 2H), 2.84 (dd, 1H), 3.28 (s, 3H)3.24 (m, 1H), 3.56 (m, 2H), 4.57 (m, 1H), 5.47 (t, 1H), 7.17 (m, 5H), 8.35 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H)	452
6	CH_2OAc	-	466
7	$CH_2C(O)NH_2$	(DMSO-d_6) 2.86 (dd, 1H), 3.07 (m, 2H), 3.25 (m, 1H), 4.57 (m, 1H), 5.47 (m, 1H), 6.98 (s, 1H), 7.11 (s, 1H), 7.22 (m, 4H), 7.37 (s, 1H), 8.51 (d, 1H), 8.62 (d, 1H), 12.35 (s, 1H);	451
55	CF_3	-	462

The following examples were made by the process of Example 2 using *N*-[(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 9) and the appropriate commercially available carboxylic acid.

Example 8: 2,3-Dichloro-*N*-{(1*S*,2*S*)-1-[(furan-2-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 9: 2,3-Dichloro-*N*-{(1*S*,2*S*)-1-[(furan-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 10: 2,3-Dichloro-*N*-{(1*S*,2*S*)-1-[(3-thienylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 11: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-{[(5-nitrofuran-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

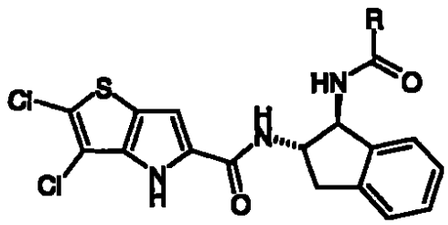
Example 12: 2,3-Dichloro-*N*-{(1*S*,2*S*)-1-[(pyridin-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

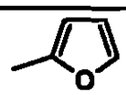
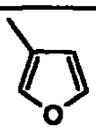
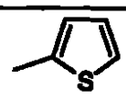
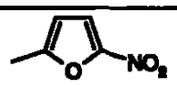
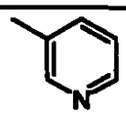
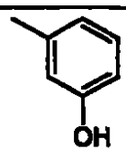
Example 13: *N*-[(1*S*,2*S*)-1-(Acryloylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 14: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-{[(3-hydroxyphenyl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 15: *N*-[(1*S*,2*S*)-1-(Acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

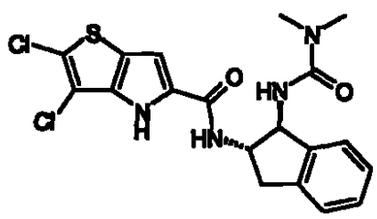
Example 16: *N*-[(1*S*,2*S*)-1-[(2-Carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Ex	R	NMR	M/z
8		-	458 $(M-H)^-$
9		-	458 $(M-H)^-$
10		-	476 $(M-H)^-$
11		-	503 $(M-H)^-$
12		-	471
13		-	417 $(M-H)^-$
14		-	484
15	CH_3	1.87 (s, 3H), 2.83 (m, 1H), 3.23 (m, 1H), 4.55 (m, 1H), 5.45 (m, 1H), 7.1 (s, 1H), 7.13 (m, 1H), 7.22 (m, 3H), 8.34 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H)	-
16	CH_2CO_2H	-	452

5

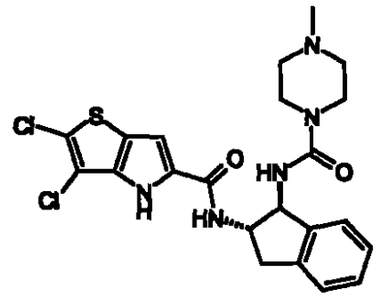
Example 17: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-[[(dimethylamino)carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



To a solution of *N*-[(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 9, 240 mg, 0.5 mmol) and Et_3N (101 mg, 1.0 mmol) in DCM (4 mL) was added a solution of dimethylcarbamoyl chloride (54 mg, 0.5 mmol) in DCM (1 mL). The reaction was stirred at ambient temperature for 2 hours, washed with saturated $NaHCO_3$ (1 mL), water (1 mL), brine (1 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (50 mg, 23%) as a foam.

^{1}H NMR 2.81 (s, 6H), 2.83 (m, 1H), 3.25 (m, 1H), 4.61 (m, 1H), 5.33 (m, 1H), 7.16 (m, 5H), 8.6 (d, 1H), 12.37 (s, 1H); MS m/z 437.

Example 18: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-[[(4-methylpiperazin-1-yl)carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



To a solution of *N*-[(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 9, 240 mg, 0.5 mmol) and Et_3N (101 mg, 1.0 mmol) in DCM (4 mL) was added a solution of 4-methyl-1-piperazine carbonyl chloride (100 mg, 0.5 mmol) in DCM (1 mL). The reaction was stirred at ambient temperature for 2 hours, washed with saturated $NaHCO_3$ (1 mL), water (1 mL), brine (1 mL) and dried ($MgSO_4$). The

volatiles were removed by evaporation under reduced pressure to give the title compound (110 mg, 45%) as a foam.

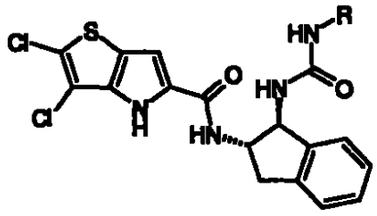
MS m/z $(M-H)^-$ 491.

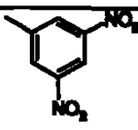
The following examples were made by the method below using *N*-[(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide trifluoroacetic acid salt (Method 9) and the appropriate commercially available isocyanate: *N*-[(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide trifluoroacetic acid salt (0.5 mmol) and Et_3N (1.0 mmol) were dissolved in dry THF (5 mL), the appropriate isocyanate (1.0 mmol) was added and the reaction stirred at ambient temperature for 20 hours. EtOAc (15 mL) was added and the mixture washed with water (2 x 5 mL) brine (5 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound as a foam.

Example 19: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-{[(ethylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

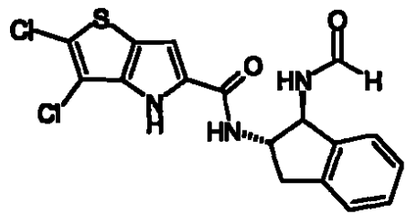
Example 20: 2,3-Dichloro-*N*-((1*S*,2*S*)-1-{[(prop-2-en-1-ylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 21: 2,3-Dichloro-*N*-[(1*S*,2*S*)-1-({[(3,5-dinitrophenyl)amino]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Ex	R	M/z
19	CH_2CH_3	437/439
20		449/451
21		364/366 ($-C_7H_3N_3O_5$)

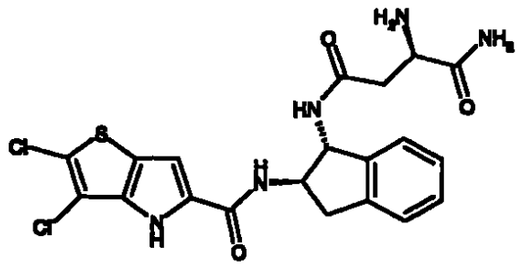
Example 22: 2,3-Dichloro-*N*-[(1*S*,2*S*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*S*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide trifluoroacetic acid salt (Method 9, 240 mg, 0.5mmol), formic acid (50 µL, 1.4 mmol), DIPEA (174 µL, 1.0 mmol) and HOBT (67 mg, 0.5 mmol) were dissolved in DCM (5 ml), stirred for 5 mins, EDCI (120 mg, 0.625 mmol) added and the reaction stirred for 1hr. Formic acid (50 µL, 1.4 mmol) and EDCI (240 mg, 1.25 mmol) were added, the reaction stirred for 2 hours and the volatiles removed by evaporation under reduced preasure. The residue was dissolved in EtOAc (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced preasure. The residue was purified by column chromatography (2:1 EtOAc:Hexane) to afford the title compound (180mg, 97%) as a white foam.

^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 4.6 (m, 1H), 5.53 (m, 1H), 7.12 (m, 2H), 7.25 (m, 1H), 8.2 (s, 1H), 8.55 (d, 1H), 8.63 (d, 1H), 12.36 (s, 1H); MS m/z 394.

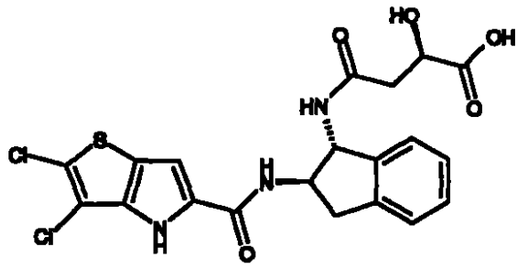
Example 23: *N*-[(1*R*,2*R*)-1-[[(3*R*)-3-Amino-3-carbamoylpropanoyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-Butoxycarbonylamino)-3-carbamoylpropanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example

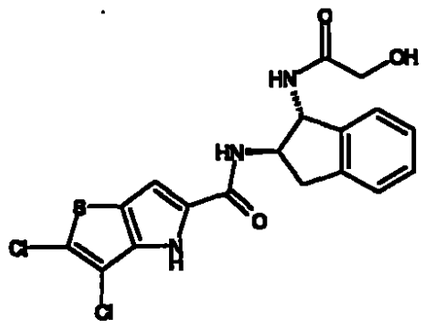
3; 290 mg, 0.5 mmol) was dissolved in TFA (3 mL) and the reaction stirred at ambient temperature for 1 hour. The volatiles were evaporated under reduced pressure and the crude material was azeotroped with chloroform (3 x 5 mL) to afford a gum. The gum was triturated with ether (5 mL), the solid collected by filtration, washed with ether (2 x 5 mL) and dried to give the trifluoroacetate salt of the title compound (270 mg, 91%) as a yellow solid.
^{1}H NMR 1.24 (m, 1H), 2.72 (m, 1H), 2.90 (dd, 1H), 3.26 (dd, 1H), 4.04 (m, 1H), 4.61 (m, 1H), 5.50 (t, 1H), 7.12 (s, 1H), 7.24 (m, 4H), 7.55 (s, 1H), 7.74 (s, 1H), 8.06 (br, 3H), 8.66 (d, 1H), 8.72 (d, 1H), 12.36 (s, 1H); MS m/z 502 $(M+Na)^+$.

Example 24: *N*-(1*R*,2*R*)-1-[((3R)-3-Carboxy-3-hydroxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



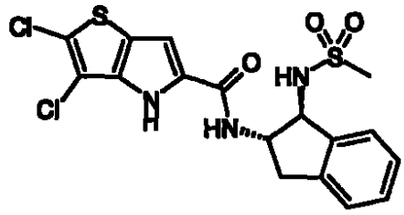
2,3-Dichloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 4; 200 mg, 0.4 mmole) was dissolved in THF (2 mL) and water (2 mL) and NaOH (100 mg) were added and the suspension stirred at ambient temperature for 48 hours. 2*N* HCl was added until *p*H 1 and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the reisdue was triturated with Et_2O, filtered and dried to give the title compound (133 mg, 69%) as a brown solid.
^{1}H NMR 2.45 (obs m, 2H), 2.87 (dd, 1H), 3.26 (obs dd, 1H), 4.39 (m, 1H), 4.57 (m, 1H), 5.52 (t, 1H), 7.18 (m, 5H), 8.43 (d, 1H), 6.63 (d, 1H), 12.39 (s, 1H); MS m/z 483.

Example 25: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-{(1*R*,2*R*)-1-[(2-Acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 6; 632 mg, 1.36 mmol) was dissolved in THF (10 mL), MeOH (10 mL) and K_2CO_3 (100 mg) were then added and the suspension stirred at ambient temperature for 16 hours. Water (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with water (2 x 50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed by evaporation under reduced pressure, the crude product was triturated (EtOAc:isohexane, 1:10), filtered, washed with isohexane (5 mL) and dried to give the title compound (428 mg, 74%) as a white solid. ^{1}H NMR 2.86 (dd, 1H), 3.25 (obs dd, 1H), 3.89 (m, 2H), 4.72 (m, 1H), 5.39 (t, 1H), 5.51 (t, 1H), 7.17 (m, 5H), 8.13 (d, 1H), 8.59 (d, 1H), 12.35 (s, 1H); MS m/z 424.

Example 26: 2,3-Dichloro-*N*-[(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

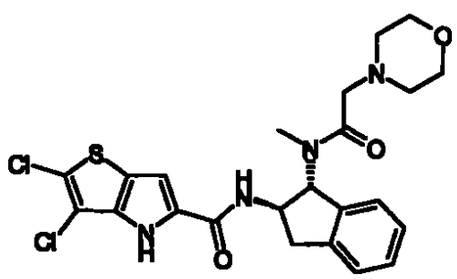


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method 4, 236 mg, 1.0 mmol), *N*-[(1*S*,2*S*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methanesulfonamide (226 mg, 1.0 mmol), DIPEA (174 µL, 1.0 mmol) and HOBT (135 mg, 1.0 mmol) were dissolved in DCM (10 mL) and stirred for approximately 5 mins. EDCI (240 mg, 1.25 mmol) was added and the reaction stirred for 20 hours. The volatiles were removed by evaporation, EtOAc (25mL) added, the

mixture washed with water (2 x 10 mL) and brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (430mg, 97%) as a foam.

^{1}H NMR 2.83 (m, 1H), 2.99 (s, 3H), 3.23 (m, 1H), 4.57 (m, 1H), 4.95 (m, 1H), 7.13 (s, 1H), 7.21-7.34 (m, 4H), 7.87 (d, 1H), 8.66 (d, 1H), 12.41 (s, 1H); MS m/z $(M-H)^-$ 442.

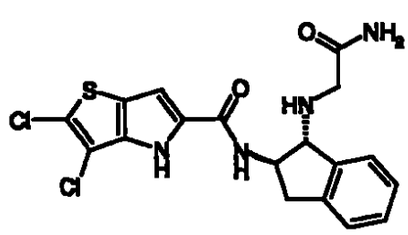
Example 27: 2,3-Dichloro-*N*-{(1*S*,2*S*)-1-[methyl(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



2,3-Dichloro-*N*-{(1*R*,2*R*)-1-[(chloroacetyl)(methyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 10, 100 mg, 0.22 mol) and morpholine (100 mg, 12.6 mmol) were dissolved in DCM, stirred at ambient temperature for 20hours and the volatiles removed by evaporation under reduced pressure. EtOAc (10 mL) was added and the mixture washed with water (2 x 5 mL), brine (5 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (60 mg, 54%) as a buff coloured powder.

^{1}H NMR 2.36 (m, 4H), 2.74 (d, 3H), 2.9-3.55 (m, 7H), 4.8 (m, 1H), 5.96 (dd, 1H), 7.0 (m, 1H), 7.09 (d, 1H), 7.26 (m, 3H), 8.62 (dd, 1H); MS m/z 507.

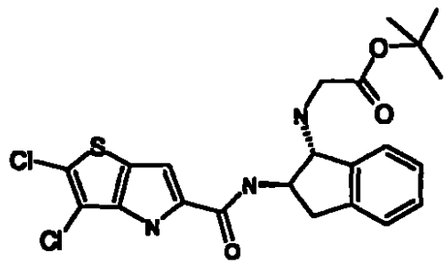
Example 28: *N*-[(1*R*,2*R*)-1-[(2-Amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Prepared in a similar manner to Example 29 using *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*- thieno[3,2-*b*]pyrrol-5-yl-2-carboxamide (Method 8) and bromoacetamide.

^{1}H NMR 2.69 (s, 1H), 2.8 (dd, 1H), 3.16 (m, 2H), 3.24 (m, 1H), 4.21 (m, 1H), 4.44 (m, 1H), 7.03 (s, 1H), 7.12 (s, 1H), 7.23 (m, 3H), 7.28 (s, 1H), 7.37 (s, 1H), 8.49 (d, 1H), 12.36 (s, 1H); MS m/z $(M-H)^-$ 422.

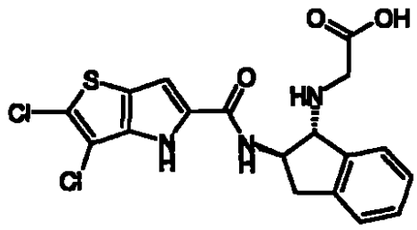
Example 29; *N*-(1*R*,2*R*)-1-[(tert-Butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



DIPEA (520 µL, 3.0 mmol) and *t*-butyl bromoacetate (150 µL, 1.0 mmol) were added to a solution of *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl-2-carboxamide (Method 8, 479 mg, 1.0 mmol) in CH_3CN (15 mL). The resulting suspension was stirred at 60°C for approximately 2 h. Upon cooling the volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (20 mL), washed with water (2 x 20 mL), brine (20 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure and the residue purified by column chromatography (EtOAc:isohexane 1:1) to afford the title compound (100 mg, 21%) as a white solid.

^{1}H NMR 1.49 (s, 9H), 1.87 (brs, 1H), 2.75 (dd, 1H), 3.62 (d, 2H), 3.65 (dd, 1H), 4.15 (d, 1H), 4.40 (m, 1H), 6.82 (s, 1H), 7.10 (d, 1H), 7.25 (s, 2H), 7.40 (d, 1H), 9.80 (s, 1H); MS m/z 480.

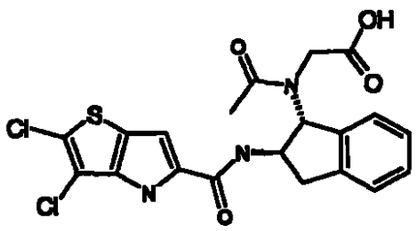
Example 30: *N*-[(1*R*,2*R*)-1-(Carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-(1*R*,2*R*)-1-[(*tert*-Butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 29; 100 mg, 0.21 mmol) dissolved in DCM (10 mL). TFA (1 mL) added and the reaction stirred at ambient temperature for 6 hours. Evaporation under reduced pressure, co-evaporation with $CHCl_3$ (2 x 10 mL) and drying gave the title compound (85mg, 36%) as a white powder.

^{1}H NMR 2.71 (dd, 1H), 3.16 (dd, 1H), 3.29 (m, 2H), 4.25 (m, 1H), 4.39 (m, 1H), 6.97 (m, 2H), 7.08 (m, 3H), 7.24 (m, 2H), 7.48 (d, 1H), 8.63 (d, 1H), 11.62 (s, 1H); MS m/z $(M-H)^-$ 422.

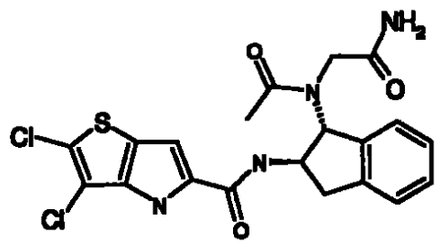
Example 31: *N*-(1*R*,2*R*)-1-[*N*-Acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



TFA (1 mL) was added to a solution of 1,1-dimethylethyl [acetyl((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (Method 18, 40 mg, 0.08 mmol) in DCM (5 mL) and the reaction was stirred at ambient temperature for 1 h. The volatiles were removed by evaporation under reduced pressure to afford the title compound (35 mg, 94%) as a white solid.

^{1}H NMR 2.49 (s, 3H), 2.97 (dd, 1H), 3.20 (dd, 1H), 3.90 (m, 2H), 4.70 (m, 1H), 5.50 (d, 1H), 7.25 (m, 5H), 8.60 (d, 1H), 12.43, (s, 1H); MS m/z 466, 349.

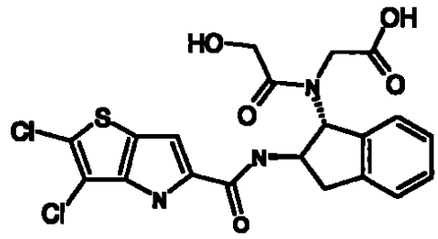
Example 32: *N*-{(1*R*,2*R*)-1-[Acetyl(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Acetyl chloride (17 µL, 0.24 mmol) was added to a solution of *N*-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 28, 100 mg, 0.24 mmol) in THF (10 mL). The reaction was stirred at ambient temperature for 1 h. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (50 mL), washed with water (2 x 10 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure and the residue purified by column chromatography (EtOAc:isohexane 1:2) to afford the title compound (50 mg, 45%) as a white solid.

^{1}H NMR 2.49 (s, 3H), 2.98 (dd, 1H), 3.20 (dd, 1H), 3.29 (brs, 2H), 4.0 (m, 2H), 4.65 (m, 1H), 5.70 (d, 1H), 7.25 (m, 5H), 8.30 (d, 1H), 12.10, (s, 1H); MS m/z 487.

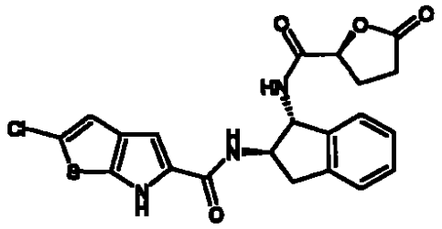
Example 33: *N*-{(1*R*,2*R*)-1-[*N*-(Carboxymethyl)-*N*-(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Potassium carbonate (20 mg) and MeOH (1 mL) were added to a solution of [[(acetyloxy)acetyl]((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetic acid (Method 19, 120 mg, 0.23 mmol) in THF (5 mL) and the reaction was stirred at ambient temperature for 24 h. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in water and acidified to pH 2.0 and then extracted into EtOAc (3 x 10 mL). The volatiles were removed by evaporation under reduced pressure to afford the title compound (110 mg, 100%) as a white solid.

^{1}H NMR 3.07 (dd, 1H), 3.18 (dd, 1H), 3.92 (d, 1H), 4.35 (d, 1H), 4.82 (m, 3H), 5.96 (d, 1H), 7.25 (m, 5H), 8.67 (d, 1H), 12.40 (s, 1H); MS m/z 482.

Example 34: 2-Chloro-*N*-[(1*R*,2*R*)-1-({[(2*S*)-5-oxotetrahydrofuran-2-yl]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



DIPEA (180 µL, 1.05 mmol), HOBT (68 mg, 0.5 mmol), (2*S*)-5-oxotetrahydrofuran-2-carboxylic acid (CAS Reg. No: [21461-84-7], 0.5 mmol, 65 mg) and EDAC (120 mg, 0.63 mmol) were added to a suspension of *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Method 21, 223 mg, 0.5 mmol) in anhydrous DCM (7 mL). The reaction was stirred at ambient temperature for approximately 16 h. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (5 mL), washed with water (2 x 5 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure and the residue triturated (EtOAc:hexane, 1:10), collected by filtration, washed with hexane (2 x 5 mL) and dried to give the title compound (112 mg, 56%) as a brown solid.

^{1}H NMR 2.15 (m, 1H), 2.43 (m, 3H), 2.91 (dd, 1H), 3.25 (dd, 1H), 4.70 (m, 1H), 4.92 (m, 1H), 5.46 (t, 1H), 7.03 (s, 1H), 7.13 (m, 1H), 7.18 (s, 1H), 7.25 (m, 3H), 8.55 (d, 1H), 8.75 (s, 1H), 11.85 (s, 1H); MS m/z 444, 446

The following examples were made by a similar process to Example 34 using *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Method 21) and the appropriate commercially available carboxylic acid:

Example 35: 2-Chloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 36: 2-Chloro-*N*-[(1*R*,2*R*)-1-[(methoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 37: *N*-[(1*R*,2*R*)-1-(Acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 38: 2-Chloro-*N*-[(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

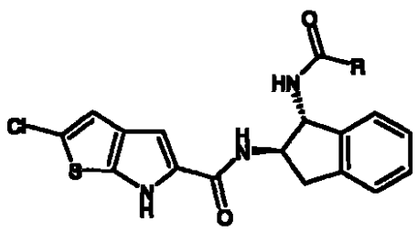
Example 39: *N*-[(1*R*,2*R*)-1-[(2-Acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

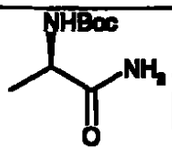
Example 40: *N*-((1*S*,2*S*)-1-[[(2(*S*)-2-(*tert*-Butoxycarbonylamino)-2-carbamoylacetyl]amino]-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

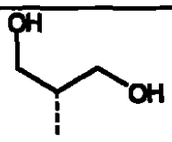
Example 41: *N*-[(1*S*,2*S*)-1-[(2-(*tert*-Butoxycarbonylamino)acetylamino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide Example 42: *N*-[(1*R*,2*R*)-1-[2-Carbamoylacetyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide

Example 56: *N*-[(1*R*,2*R*)-1-[2-(*tert*-Butoxycarbonyl]acetylamino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide

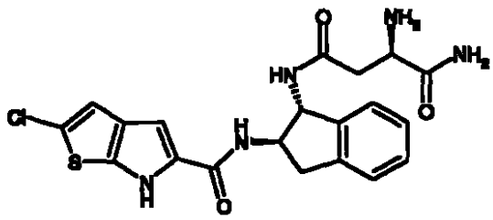
Example 57: 2-Chloro-*N*-((1*R*,2*R*)-1-[[3-hydroxy-2-(hydroxymethyl)propanoyl]amino]-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Ex	R	NMR	M/z
35	H	(DMSO-d_6) 2.88 (dd, 1H), 3.21 (dd, 1H), 4.58 (m, 1H), 5.51 (t, 1H), 7.00 (s, 1H), 7.18 (m ,5H), 8.19 (s, 1H), 8.53 (d ,2H), 11.82 (s, 1H)	358, 360
36	CH_2OMe	(DMSO-d_6) 2.88 (dd, 1H), 3.21 (dd, 1H), 3.30 (s, 3H), 3.86 (m, 2H), 4.71 (m ,1H), 5.51 (t, 1H), 6.99 (s, 1H), 7.15 (m, 5H), 8.23 (d, 1H), 8.50 (d, 1H), 11.82 (br s, 1H)	404, 406
37	Me	(DMSO-d_6) 1.88 (s, 3H), 2.84 (dd, 1H), 3.22 (dd, 1H), 4.53 (m, 1H), 5.44 (t, 1H), 6.99 (d, 1H), 7.17 (m, 5H), 8.32 (d, 1H), 8.51 (d, 1H), 11.82 (s, 1H);	374, 376
38	CH_2CH_2OMe	(DMSO-d_6) 2.38 (m, 2H), 2.84 (dd, 1H), 3.20 (m, 4H), 3.55 (m, 2H), 4.55 (m, 1H), 5.47 (t, 1H), 6.99 (d, 1H), 7.15 (m, 5H), 8.33 (d, 1H), 8.50 (d, 1H), 11.81 (s, 1H)	418, 420
39	CH_2OAc	(DMSO-d_6) 2.07 (s, 3H), 2.88 (dd, 1H), 3.23 (dd, 1H), 4.51 (q, 2H), 4.62 (m, 1H), 5.50 (t, 1H), 7.0 (d, 1H), 7.18 (m, 5H), 8.50 (t, 2H), 11.81 (s, 1H)	432, 434
40		(DMSO-d_6) 1.37 (s, 9H), 2.89 (dd, 1H), 3.05 (m, 2H), 3.57 (m, 1H), 4.24 (m, 1H), 5.53 (m, 1H), 5.46 (t, 1H), 6.70 (d, 1H), 6.98 (m, 2H), 7.18 (m, 5H), 8.28 (d, 1H), 8.52 (d, 1H), 11.82 (s, 1H)	568, 570
41	CH_2NHBoc	-	511, 513
42	$CH_2C(O)NH_2$	(DMSO-d_6) 2.86 (dd, 1H), 3.07 (m, 2H), 3.23 (dd, 1H), 4.55 (m, 1H), 5.47 (m, 1H), 6.98 (s, 1H), 7.0 (d, 1H), 7.19 (m, 5H), 7.38 (s, 1H), 8.49 (d, 1H), 8.53 (d, 1H), 11.82 (s, 1H).	417, 419
56	CH_2CO_2tBu	(DMSO-d_6) 1.36 (s, 9H), 2.83 (m, 1H), 3.19 (m, 3H), 4.57 (m, 1H), 5.45 (t, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.20 (m, 4H), 8.53 (t, 2H), 11.82 (s, 1H)	474, 476

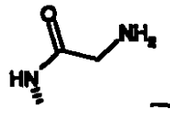
57		(DMSO-d_6) 2.85 (dd, 1H), 3.22 (dd, 1H), 3.45 (m, 1H), 3.57 (m, 4H), 4.51 (m, 3H), 5.48 (m, 1H), 7.0 (s, 1H), 7.18 (m, 5H), 8.25 (d, 1H), 8.5 (d, 1H), 11.80 (s, 1H)	433, 435 $(M-H)^-$

Example 43: *N*-[(1*R*,2*R*)-1-[(3*R*)-3-Amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



N-((1*S*,2*S*)-1-{[(2(*S*)-2-(*tert*-Butoxycarbonylamino)-2-carbamoylacetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Example 40, 251 mg, 0.46 mmol) was dissolved in trifluoroacetic acid (4 mL) and stirred at ambient temperature for 24 hours. The volatiles were evaporated under reduced pressure and the crude material was azeotroped with chloroform (3 x 5 mL) to afford a gum. The gum was triturated with ether (5 mL), the solid collected by filtration, washed with ether (2 x 5 mL) and dried to give the trifluoroacetate salt of the title compound (239 mg, 93%) as a brown solid.
^{1}H NMR 2.75 (m, 2H), 2.90 (dd, 1H), 3.23 (dd, 1H), 4.04 (m, 1H), 4.59 (m, 1H), 5.50 (t, 1H), 7.00 (s, 1H), 7.19 (m, 5H), 7.54 (s, 1H), 7.74 (s, 1H), 8.05 (br s, 3H), 8.56 (d, 1H), 8.70 (d, 1H), 11.83 (s, 1H); MS m/z 468, 469.

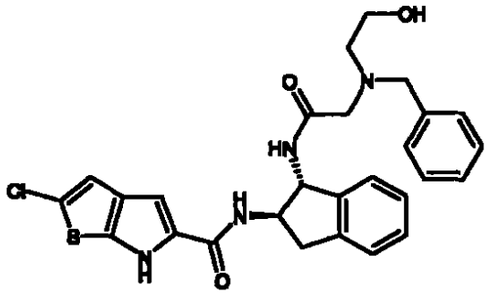
Example 44: *N*-[(1*R*,2*R*)-1-[(Aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



N-{(1*S*,2*S*)-1-[(2-(*tert*-Butoxycarbonylamino)acetylamino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Example 41; 366 mg, 0.75 mmol) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (0.5 mL) was added and the reaction stirred at ambient temperature for 7 hours. The volatiles were evaporated under reduced pressure and the crude solid was azeotroped with chloroform (3 x 5 mL), triturated with ether (5 mL), collected by filtration, washed with ether (2 x 5 mL) and dried to give the trifluoroacetate salt of the title compound (200 mg, 53%) as a brown solid.

^{1}H NMR 2.90 (dd, 1H), 3.21 (m, 1H), 3.65 (m, 2H), 4.59 (m, 1H), 5.51 (t, 1H), 6.99 (s, 1H), 7.19 (m, 5H), 8.08 (br, 3H), 8.58 (d, 1H), 8.84 (d, 1H); MS m/z 389, 391.

Example 45 : 2-Chloro-*N*-[(1*R*,2*R*)-1-({[(2-hydroxyethyl)(phenylmethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-(Benzylamino)ethanol (160 mg, 1.06 mmol) was added to a solution of 2-chloro-*N*-{(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Method 23; 216 mg, 0.53 mmol) and Et_3N (500 µL, 3.60 mmol) in anhydrous THF (5 mL) and the reaction stirred for approximately 16 hours at room temperature then for a further 16 h at 50 °C. The volatiles were removed under reduced pressure, the residue dissolved in EtOAc (10 mL), washed with H_2O (2 x 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, the residue triturated (EtOAc:isohexane, 1:5), collected by filtration, washed with isohexane (10 mL) and dried to give the title compound (100 mg, 36%) as a brown solid.

^{1}H NMR 2.58 (t, 2H), 2.90 (dd, 1H), 3.09 (dd, 2H), 3.18 (dd, 1H), 3.50 (dd, 2H), 3.68 (dd, 2H), 4.55 (t, 1H), 4.65 (m, 1H), 5.46 (t, 1H), 6.99 (s, 1H), 7.04 (d, 1H), 7.23 (m, 9H), 8.38 (d, 1H), 8.53 (d, 1H), 11.81 (s, 1H); MS m/z 523, 525

The following examples were made by the process of Example 45 using 2-chloro-*N*-{(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide and the appropriate commercially available amine:

Example 46: 2-Chloro-*N*-[(1*R*,2*R*)-1-[(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

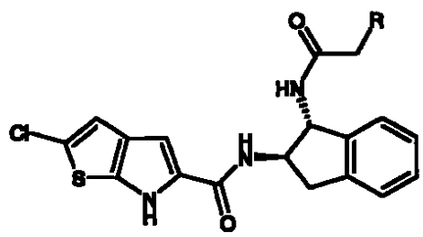
Example 47: 2-Chloro-*N*-((1*R*,2*R*)-1-({[(2-hydroxyethyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

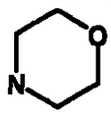
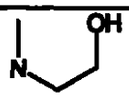
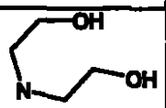
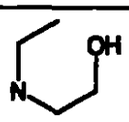
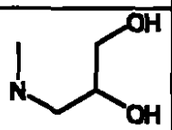
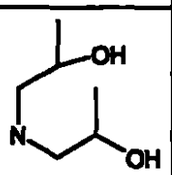
Example 48: *N*-((1*R*,2*R*)-1-({[Bis(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 49: 2-Chloro-*N*-((1*R*,2*R*)-1-({[ethyl(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 50: 2-Chloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihydroxypropyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

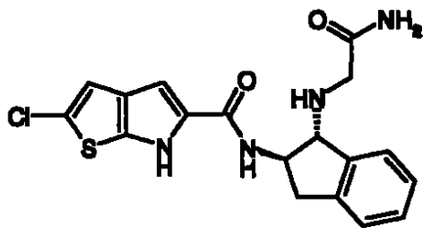
Example 51: *N*-((1*R*,2*R*)-1-({[Bis(2-hydroxypropyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Ex	R	NMR	M/z
46		(DMSO-d_6) 2.42 (m ,4H), 2.97 (m, 3H), 3.19 (dd, 1H), 3.55 (m, 4H), 4.69 (m, 1H), 5.44 (t, 1H), 6.98 (s, 1H), 7.09 (d, 1H), 7.14 (m, 4H), 8.13 (d, 1H), 8.50 (d, 1H), 11.80 (br s, 1H)	459, 461
47		(DMSO-d_6) 2.21 (s, 3H), 2.47 (m, 2H), 2.90 (dd, 1H), 3.03 (dd, 2H), 3.21 (dd, 1H), 3.44 (m, 2H), 4.43 (t, 1H), 4.66 (m, 1H), 5.49 (t, 1H), 6.99 (s, 1H), 7.19 (m, 5H), 8.25 (d, 1H), 8.52 (d, 1H), 11.81 (s, 1H)	447, 449
48		(DMSO-d_6) 2.59 (m, 4H), 2.91 (dd, 1H), 3.17 (m, 3H), 3.43 (m, 4H), 4.23 (t, 2H), 4.62 (m, 1H), 5.47 (t, 1H), 6.99 (s, 1H), 7.18 (m, 5H), 8.34 (d, 1H), 8.53 (d, 1H), 11.81 (br s, 1H)	477, 479
49		(DMSO-d_6) 0.92 (t, 3H), 2.54 (m, 4H), 2.90 (dd, 1H), 3.07 (dd, 2H), 3.21 (m, 1H), 3.37 (m, 2H), 4.45 (t, 1H), 4.63 (m, 1H), 5.46 (t, 1H), 6.98 (s, 1H), 7.16 (m ,5H), 8.25 (d, 1H), 8.51 (d, 1H), 11.80 (s, 1H)	461, 463
50		(DMSO-d_6) 2.22 (s, 3H), 2.42 (m, 2H), 2.99 (m, 3H), 3.25 (obs m, 3H), 3.56 (m, 1H), 4.43 (m, 1H), 4.54 (m, 1H), 4.66 (m, 1H), 5.50 (t, 1H), 6.99 (s, 1H), 7.17 (m, 5H), 8.34 (d, 1H), 8.51 (m, 1H), 11.80 (s, 1H)	477, 479
51		(DMSO-d_6) 0.96 (m, 6H), 2.35 (m, 4H), 2.88 (dd, 1H), 3.11 (dd, 1H), 3.67 (m, 2H), 4.49 (m, 2H), 4.60 (m, 1H), 5.47 (t, 1H), 6.99 (s, 1H), 7.17 (m, 5H), 8.69 8.49 (m, 2H), 11.77 (s, 1H)	505, 507

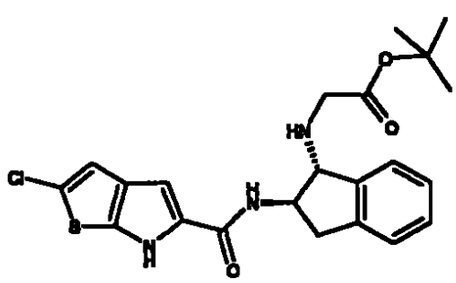
5

Example 52: *N*-[(1*R*,2*R*)-1-[(2-Amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



N-{(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-b]pyrrol-5-yl)-2-carboxamide trifluoroacetic acid salt (Method 21, 225 mg, 0.5 mmol), DIPEA (216 µL, 1.5 mmol) and bromoacetamide (70 mg, 0.5 mmol) heated in a microwave at 180°C for 3 mins. EtOAc (30 mL) was added and the mixture washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (EtOAc:MeOH 19:1) to afford the title compound (52 mg, 27%) as a white foam. ^{1}H NMR 2.68 (s, 1H), 2.79 (dd, 1H), 3.24 (m, 3H), 4.21 (m, 1H), 4.41 (m, 1H), 7.02 (m, 2H), 7.14 (s, 1H), 7.21 (m, 3H), 7.28 (m, 1H), 7.36 (m, 1H), 8.42 (d, 1H), 11.83 (s, 1H); MS m/z 389, 391.

Example 53: *N*-[(1*R*,2*R*)-1-[(*tert*-Butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

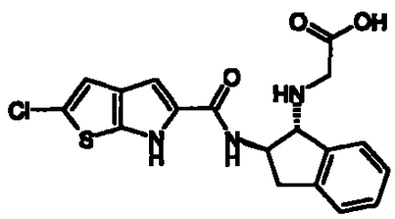


DIPEA (350 µL, 2.0 mmol) and *t*-butyl bromoacetate (90 µL, 0.7 mmol) were added to a solution of *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-b]pyrrol-5-yl)-2-carboxamide (Method 21, 300 mg, 0.7 mmol) in CH_3CN (10 mL). The resulting suspension was stirred at 60°C for approximately 2 h. Upon cooling the volatiles were removed by evaporation under reduced preasure, the residue dissolved in EtOAc (10 mL), washed with water (2 x 10 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced preasure and the residue purified by column

chromatography (EtOAc:isohexane 1:1) to afford the title compound (30 mg, 10%) as a white solid.

^{1}H NMR 1.45 (s, 9H), 2.11 (br s, 1H), 2.80 (dd, 1H), 3.60 (m, 3H), 4.27 (d, 1H), 4.46 (m, 1H), 6.8 (d, 2H), 7.10 (d, 1H), 7.30 (m, 4H), 11.35 (s, 1H); MS m/z 446, 448.

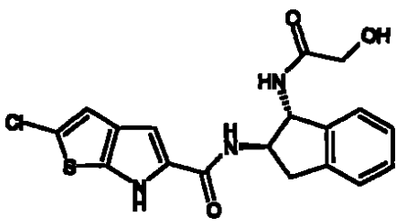
Example 54: *N*-{(1*R*,2*R*)-1-(Carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*R*,2*R*)-1-[(*tert*-Butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Example 53, 100 mg, 0.22 mmol), dissolved in DCM (5mL). TFA (1 mL) added and the reaction stirred at ambient temperature for 20 hours. Evaporation under reduced pressure, co-evaporation with $CHCl_3$ (2 x 10 mL) and drying gave the trifluoroacetic acid salt of the title compound (110 mg, 99%) as a grey powder.

^{1}H NMR 3.1 (dd, 1H), 3.52 (dd, 1H), 4.2 (m, 2H), 4.9 (m, 2H), 7.05 (s, 1H), 7.2 (s, 1H), 7.4 (m, 3H), 7.7 (d, 1H), 8.76 (d, 1H), 9.73 (s, 2H), 12.02 (s, 1H), 13.9 (s, 1H); MS m/z $(M-H)^-$ 388, 390.

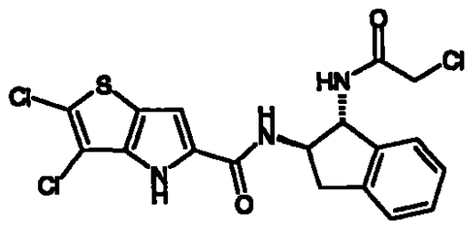
Example 58: 2-Chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetylamino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



N-{(1*R*,2*R*)-1-[(2-Acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Example 39; 393 mg, 0.92 mmol) was dissolved in THF (5 mL), MeOH (5 mL) and K_2CO_3 (50 mg) were then added and the suspension stirred at ambient temperature for 4 hours. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water

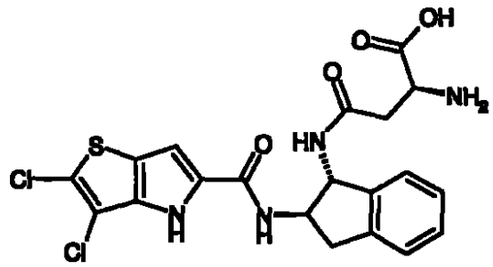
(50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed by evaporation under reduced pressure, the crude product was triturated (EtOAc:isohexane, 1:5), filtered, washed with isohexane (5 mL) and dried to give the title compound (257 mg, 72%) as a white solid. ^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 3.88 (dd, 2H), 4.70 (m, 1H), 5.39 (t, 1H), 5.50 (t, 1H), 7.00 (s, 1H), 7.18 (m, 5H), 8.10 (d, 1H), 8.51 (d, 1H), 11.81 (s, 1H); MS m/z 391, 393.

Example 59: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 8, 602 mg, 1.6 mmol) was dissolved in dichloromethane (30 mL), to this was added triethylamine (0.25 mL, 1.8 mmol) and chloroacetyl chloride (0.14 mL, 1.8 mmol). The solution was stirred at ambient temperature for 16 hours, after which triethylamine (0.25ml, 1.8mmol) and chloroacetyl chloride (0.14ml, 1.8mmol) were added before stirring for 1 hour. To the resulting slurry, water (15 mL) was added before filtering to give the title product (532 mg, 73%) as a cream solid.
^{1}H NMR 2.88 (m, 1H), 3.25 (m, 1H), 4.11 (s, 2H), 4.63 (m, 1H), 5.47 (t, 1H), 7.13 (m, 2H), 7.23 (m, 3H), 8.63 (d, 1H), 8.73 (d, 1H), 12.38 (s, 1H); MS m/z 442.

Example 60: *N*-[(1*R*,2*R*)-1-[((3*S*)-3-Amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

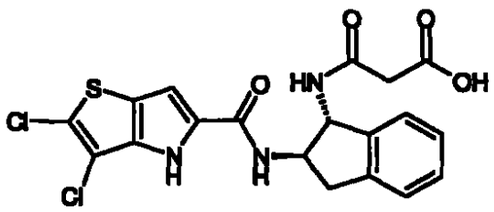


N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 8, 350 mg, 0.73 mmol) was added to a solution of *N*-*alpha*-*t*-Boc-*L*-aspartic acid *alpha*-*t*- butyl ester (232 mg, 0.80 mmol), 1-hydroxybenzotriazole monohydrate (123 mg, 0.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (154 mg, 0.80 mmol), 4-methylmorpholine (0.18 mL, 1.6 mmol) in *N*,*N*-dimethylformamide (20 mL). The mixture was stirred at ambient temperature for 16 hours. The volatiles were removed by evaporation and the residue was dissolved in ethyl acetate (20 mL) and water (10 mL), the layers were separated before washing with 2*M* HCl then saturated $NaHCO_3$. Evaporation afforded a white solid which was redissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL), the solution was allowed to stir at ambient temperature for 2 hours. The volatiles were removed by evaporation and the residue triturated with ether, collected by filtration, washed with ether (2 x 10 ml) and dried to give the title compound (210 mg, 48%) as a white solid.

^{1}H NMR 2.85 (m, 2H), 3.25 (m, 2H), 3.94 (t, 1H), 4.56 (m, 1H), 5.45 (t, 1H), 7.11 (s, 1H), 7.23 (m, 4H), 8.64 (d, 1H), 8.73 (d, 1H); MS m/z 481.

The following examples were prepared in a similar manner to Example 60 using *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 8) or *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)-2-carboxamide (Method 21) as the amine component and the appropriately protected carboxylic acid as starting material, prior to deprotection.

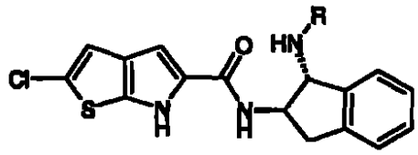
Example 61: *N*-{(1*R*,2*R*)-1-[(2-Carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

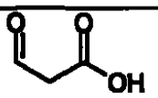
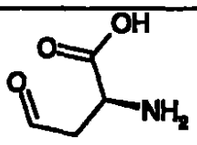


^{1}H NMR 2.84 (m, 1H), 3.25 (m, 3H), 4.56 (m, 1H), 5.47 (t, 1H), 7.11 (s, 1H), 7.20 (m, 4H), 8.59 (m, 1H), 12.36 (s, 1H); MS m/z 452.

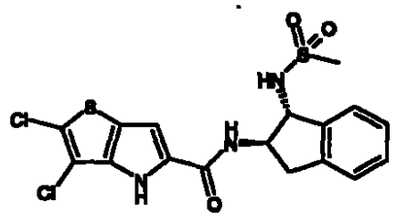
Example 62: *N*-[(1*R*,2*R*)-1-[(2-Carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 63: *N*-[(1*R*,2*R*)-1-[((3*S*)-3-Amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Ex.	R	^{1}H NMR	m/z
62		2.84 (m, 1H), 3.17 (m, 3H), 4.55 (m, 1H), 5.47 (t, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.20 (m, 4H), 8.53 (t, 2H), 11.82 (s, 1H), 12.42 (s, 1H)	419, 421
63		2.64 (m, 1H), 2.85 (m, 2H), 3.23 (m, 1H), 4.00 (t, 1H), 4.56 (m, 1H), 5.45 (t, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.23 (m, 4H), 8.53 (d, 1H), 8.71 (d, 1H)	447, 449

Example 64: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



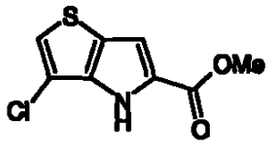
N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide trifluoroacetate salt (Method 8, 223 mg, 0.5 mmol) was dissolved in THF (4 mL) and the solution cooled to 0 °C. Et_3N (223 µL, 1.6 mmol) then methanesulfonyl chloride (43 µL, 0.55 mmol) were added and the reaction was stirred 0 °C for 5 mins. Saturated aqueous $NaHCO_3$ (5 mL) was added, the phases separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with H_2O

(20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to purification by reverse phase preparative HPLC to afford the title compound (30 mg, 15%) as a white solid.

^{1}H NMR 2.83 (dd, 1H), 2.98 (s, 3H), 3.22 (dd, 1H), 4.55 (m ,1H), 4.96 (t, 1H), 7.01 (s, 1H), 7.23 (m, 5H), 7.87 (d, 1H), 8.57 (d, 1H), 11.90 (s, 1H); MS m/z 410, 412.

Method 1

3-Chloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole



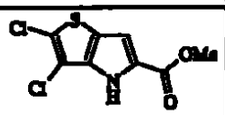
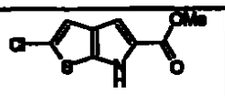
Methanolic sodium methoxide solution (28%) (5 ml, 25.9 mmol) was diluted with MeOH (5 ml) and was cooled to -25°C under nitrogen. A solution of 4-chloro-2-thiophenecarboxaldehyde (J Heterocyclic Chem, 1976, 13, 393; 1.1 g, 7.5 mmol) and methyl azidoacetate (3.0 g, 26.1 mmol) in MeOH (20 ml) was added 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.

Method 2 and 2a

The following compounds were made by the process of Method 1 using the appropriate starting materials

Method 2: 2,3-Dichloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole

Method 2a: : 2-Chloro-5-methoxycarbonyl-6*H*-thieno[2,3-*b*]pyrrole

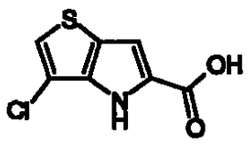
Method	Compound	NMR ($CDCl_3$)	M/z
2[1]		9.2 (1H, br), 7.0 (1H, s), 3.9 (3H, s)	248.2
2a[2]		9.4-9.2 (1H, br), 7.0 (1H, s), 6.9(1H, s), 3.9 (3H, s)	214

1 Aldehyde: DE 2814798

2 Aldehyde: Gronowitz *et al.* Tetrahedron Vol.32 1976 p.1403

Method 3

5-Carboxy-3-chloro-4*H*-thieno[3,2-*b*]pyrrole



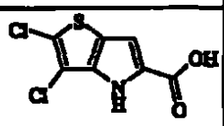
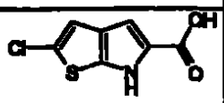
3-Chloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole (Method 1; 0.61 g, 2.83 mmol) was taken up in MeOH (10 ml) and was heated under reflux. Aqueous lithium hydroxide (2.0 M, 3.0 ml, 6.0 mmol) was added portionwise over 45 minutes. The mixture was heated under reflux for 30 minutes before being cooled 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.

Method 4 and 4a

The following compounds were made by the process of Method 3 using Methods 2 and 2a as starting materials.

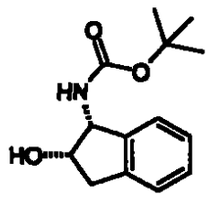
Method 4: 5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

Method 4a: 5-Carboxy-2-chloro-6*H*-thieno[2,3-*b*]pyrrole

Method	Compound	NMR	M/z	SM
4		7.0 (1H, s)	234.2	Method 2
4a		12.6-12.7 (1H, b), 12.0-12.1 (1H, b), 7.15 (1H, s), 6.9 (1H, s)	183	Method 2a

Method 5

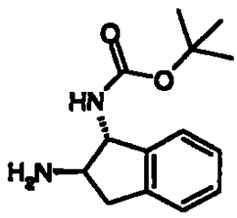
Cis-1-[(1,1-Dimethylethoxy)carbonylamino]-2 hydroxyindan



Cis-1-Amino-2-hydroxyindan (12.0g, 80.5mmol) was dissolved in DCM (500 ml) and triethylamine (22.4 ml, 161mmol). Di-*tert*-butyl dicarbonate (22.0g, 100mmol) in DCM (50 ml) was added and the mixture stirred at room temperature for 20 hours then evaporated. EtOAc (200 ml) 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:EtOAc as eluent to give the title compound (17.9 g, 90%) as a white solid.
^{1}H NMR 1.42 (s, 9H), 2.78 (dd, 1H), 3.00 (dd, 1H), 4.40 (m, 1H), 4.85 (m, 1H), 4.95 (m, 1H), 6.30 (d, 1H), 7.10 (m, 4H).

Method 6

Trans-2-Amino-1-[(1,1-dimethylethoxy)carbonylamino]indan



Cis-1-[(1,1-Dimethylethoxy)carbonylamino]-2-hydroxyindan (Method 5; 14.0g, 56.2mmol) was dissolved in DCM (200 ml) and triethylamine (11.8 ml, 84.3mmol). Methanesulfonyl chloride (7.1g, 61.9mmol) dissolved in DCM (20 ml) was added and the mixture stirred at room temperature for 3 hours. The mixture was evaporated and EtOAc (250 ml) added. After washing with water and drying over magnesium sulphate the organic solution was evaporated to yield *Cis*-1-[(1,1-dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan (9.7g, 98%) as a white solid.

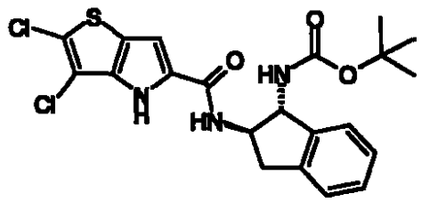
^{1}H NMR 1.45 (s, 9H), 3.15 (m, 2H), 3.18 (s, 3H), 5.20 (m, 1H), 5.35 (m, 1H), 7.15 (m, 4H), 7.45 (d, 1H).

Cis-1-[(1,1-dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan (18.1g, 55.3mmol) was dissolved in dry dimethyl acetamide (100 ml). Sodium azide (5.4g, 83.0mmol) was added and the mixture heated to 90°C for 6 hours. The reaction was cooled, diluted with ethyl acetate (150 ml), washed with water (6 x 200 ml) and dried over magnesium sulphate. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 24 hours. Filtration through celite followed by evaporation gave the title compound (2.6g, 98%) as a white solid.

^{1}H NMR: 1.45 (s, 9H), 2.50 (dd, 1H), 3.05 (dd, 1H), 3.30 (m, 3H), 4.55 (m, 1H), 7.1 (m, 5H).

Method 7

2,3-Dichloro-5-{*N*-{(1*R*,2*R*)-1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole



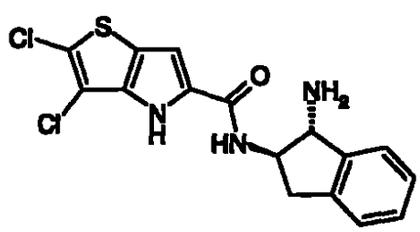
5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method 4; 2.36g, 10.0mmol), *trans*-2-amino-1-{*N*-[(1,1-dimethylethoxy)]carbonylamino}indan (Method 6; 2.5g, 10.0mmol), DIPEA (1.7 ml, 10.0mmol) and HOBT (1.35g, 10.0mmol) was stirred in DCM (75 ml) at room temperature for 2 minutes. EDCI (2.4g, 12.5mmol) was added and the mixture stirred at room temperature for 20 hours during which time the product precipitated. The reaction was

filtered, washed with DCM (2 x 25 ml) and dried to give the title compound (3.7 g, 80%) as a pale green powder.

^{1}H NMR 1.40 (s, 9H), 2.81 (dd, 1H), 3.20 (dd, 1H), 4.55 (m, 1H), 5.15 (m, 1H), 7.15 (m, 5H), 7.35 (d, 1H), 8.55 (d, 1H), 12.36 (broad s, 1H); m/z 463.7/465.7.

Method 8

N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

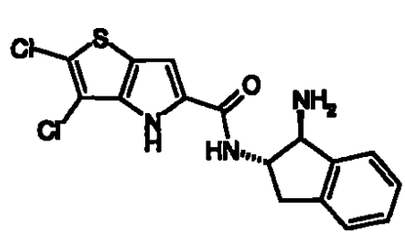


2,3-Dichloro-5-(*N*-{1-[(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole (Method 7; 3.7g, 7.9mmol) was dissolved in DCM (75 ml). Trifluoroacetic acid (10 ml) was added and the mixture stirred at room temperature for 24 hours. The reaction was filtered and the isolated solid washed with DCM to give the trifluoroacetic acid salt of the title compound (3.1g, 82%) as a pale green powder.

^{1}H NMR 3.05 (dd, 1H), 3.42 (d, 1H), 4.7 (m, 2H), 7.20(d, 1H), 7.35 (m, 3H), 7.55 (d, 1H), 8.60 (broad s, 3H), 8.80 (d, 1H), 12.5 (broad s, 1H).

Method 9

N-[(1*S*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

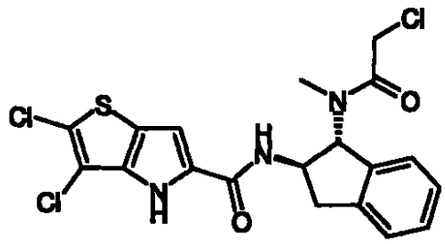


The title compound was prepared in an analogous fashion to Method 8.

^{1}H NMR 3.05 (dd, 1H), 3.42 (d, 1H), 4.7 (m, 2H), 7.20(d, 1H), 7.35 (m, 3H), 7.55 (d, 1H), 8.60 (broad s, 3H), 8.80 (d, 1H), 12.5 (broad s, 1H).

Method 10

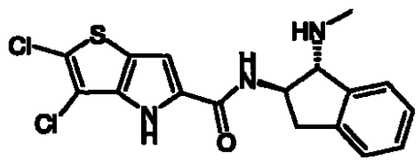
2,3-Dichloro-*N*-[(1*R*,2*R*)-1-[(chloroacetyl)(methyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



2,3-Dichloro-*N*-[(1*R*,2*R*)-1-(methylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Method 11; 300 mg, 0.79 mmol) and triethylamine (167 µL, 1.2 mmol) was dissolved in DCM (5 mL), chloroacetyl chloride (73 µL, 0.9 mmol) added and the reaction stirred at ambient temperature for 2 hours. The volatiles were removed by evaporation under reduced pressure and EtOAc (15 mL) added. The mixture was washed with water (10 mL), brine (10 ml), dried ($MgSO_4$) and the volatiles were removed by evaporation under reduced preasure to give the title compound (310 mg, 86%) as a pale brown foam. ^{1}H NMR 2.73 (d, 3H), 2.98 (m, 1H), 3.24 (m, 1H), 4.45 (m, 2H), 4.82 (m, 1H), 5.77 (dd, 1H), 7.05 (m, 2H), 7.28 (m, 3H), 8.65 (m, 1H); MS m/z 456.

Method 11

2,3-Dichloro-*N*-[(1*R*,2*R*)-1-(methylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

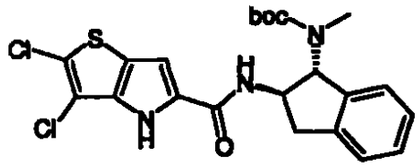


tert-Butyl ((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate (Method 12; 900 mg, 1.87 mmol) was dissolved in DCM (20 mL), TFA (2 mL) added and the reaction stirred at ambient temperature for 1 hour. The volatiles were removed by evaporation under reduced pressure and the residue purified by ion exchange chromatography (MeOH:Water 1:1 then MeOH:Water:NH_4OH 1:1:0.05) to afford, after evaporation, the title compound (300 mg, 32%) as an off white powder.

^{1}H NMR 2.75 (s, 3H), 3.01 (dd, 1H), 3.49 (dd, 1H), 4.75 (m, 1H), 4.86 (m, 1H), 7.11 (d, 1H), 7.35 (m, 3H), 7.58 (d, 1H), 8.74 (d, 1H), 9.04 (m, 1H), 12.37 (s, 1H); MS m/z 380.

Method 12

tert-Butyl ((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate

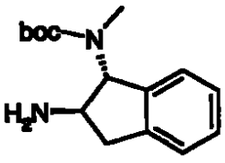


5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (Method 4, 472 mg, 2.0 mmol), *tert*-butyl [(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methylcarbamate (Method 13; 524 mg, 2.0 mmol), DIPEA (348 µL, 2.0 mmol), HOBT (270 mg, 2.0 mmol) and EDCI (480 mg, 2.5 mmol) were dissolved in DCM (10 mL) and stirred at ambient temperature for 20 hours. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (50 mL), washed with water (3 x 25 mL), brine (25 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (900 mg, 93%) as a pale brown foam.

^{1}H NMR 1.29 (m, 9H), 2.66 (s, 3H), 2.9-3.25 (m, 2H), 4.8 (m, 1H), 5.64 (m, 1H), 6.23-7.34 (m, 4H), 8.65 (m, 1H); MS m/z 480.

Method 13

tert-Butyl [(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methylcarbamate



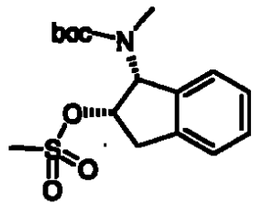
(1*R*,2*S*)-1-[(*tert*-Butoxycarbonyl)(methyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (Method 14; 3.0g, 8.8mmol) and sodium azide (2.3 g, 35.2 mmol) in dry DMA (30 mL) was heated to 90°C for 7 hours. The reaction was cooled and ethyl acetate (100 mL) added. The mixture was washed with water (6 x 25 mL), brine (50 mL) and dried ($MgSO_4$). 10% Palladium on carbon (400 mg) was added to the organic solution which was stirred under a hydrogen atmosphere for 4h, filtered through Celite and evaporated. The

residue was purified by column chromatography (EtOAc and then DCM:MeOH 9:1) to afford the title compound (1.2 g, 55%) as a pale brown oil.

^{1}H NMR 1.45 (m, 9H), 2.6 (s, 3H), 2.8 (m, 1H), 3.3 (m, 1H), 4.45 (m, 1H), 5.55 (dd, 1H), 7.26 (m, 4H); MS m/z 264.

Method 14

(1*R*,2*S*)-1-[(*tert*-Butoxycarbonyl)(methyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate

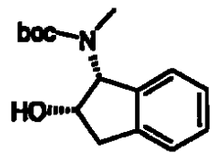


tert-Butyl [(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]methylcarbamate (Method 15; 3.0 g, 11.4 mmol) was dissolved in dry THF (40 mL) at 10°C. A solution of methane sulphonyl chloride (1.44 g, 12.55 mmol) in dry THF (10 mL) was added, the reaction allowed to warm to ambient temperature and stirred for 30 mins. The volatiles were removed by evaporation under reduced pressure and ethyl acetate (100 mL) added. The mixture was washed with water (2 x 50 mL), brine (50 mL) and the organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (EtOAc:Hexane) to afford the title compound (3.1g, 80%)as a colourless syrup.

^{1}H NMR 1.46 (s, 9H), 2.61 (s, 3H), 3.12 (m, 1H), 3.18 (s, 3H), 3.32 (m, 1H), 5.45 (m, 1H), 5.68 (m, 1H), 7.28 (m, 4H); MS m/z 342.

Method 15

***tert*-Butyl [(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]methylcarbamate**



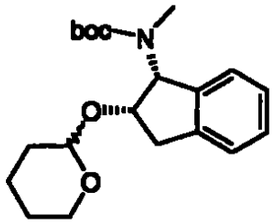
tert-Butyl methyl[(1*R*,2*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)-2,3-dihydro-1*H*-inden-1-yl]carbamate (Method 16; 4.0 g, 11.5 mmol) was dissolved in methanol (50 mL), 4-toluene sulphonic acid added and the reaction stirred at ambient temperature for 2 hours. Saturated

$NaHCO_3$ (50 mL), water (100 mL) was added and ethyl acetate (100 mL) was added and the mixture stirred for 30 mins. The organic phase was separated, washed with water (50 mL), brine (50 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (3.0 g, 99%) as an oil.

^{1}H NMR 1.45 (s, 9H), 2.6 (s, 3H), 2.75 (m, 1H), 3.05 (m, 1H), 4.5 (m, 1H), 5.05 (m, 1H), 5.34 (m, 1H), 7.03-7.3 (m, 4H).

Method 16

tert-Butyl methyl[(1*R*,2*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)-2,3-dihydro-1*H*-inden-1-yl]carbamate

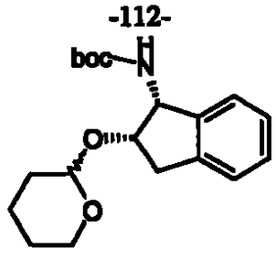


tert-Butyl [(1*R*,2*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)-2,3-dihydro-1*H*-inden-1-yl]carbamate (Method 17; 4.0 g, 12.0 mmol) was dissolved in dry DMA (25 mL) at 5°C. 60% Sodium hydride (575 mg, 14.4 mmol) was added, the reaction stirred at 5°C for 30 mins, allowed to warm to ambient temperature and stirred for a further 30 mins. Methyl iodide (896 µL, 14.4 mmol) was added and the reaction stirred at ambient temperature for 3 hours. The reaction was poured into water (100 mL) and extracted with ethyl acetate (2 x 50ml). The organic extracts were washed with water (6 x 25 mL), brine (50 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (4.1 g, 97%) as an oil.

^{1}H NMR 1.4-1.9 (m, 6H), 1.5 (s, 9H), 2.7 (dd, 3H), 2.85-3.3 (m, 2H), 3.5 (m, 1H), 3.7-4.0 (m, 1H), 4.6-4.9 (m, 2H), 5.5-5.85 (m, 1H), 7.2 (s, 4H).

Method 17

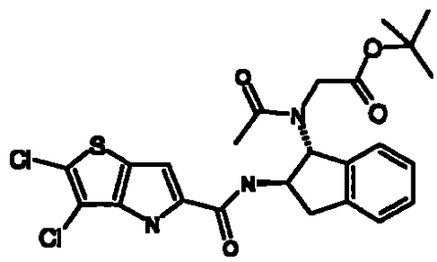
tert-Butyl [(1*R*,2*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)-2,3-dihydro-1*H*-inden-1-yl]carbamate



tert-Butyl [(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]carbamate (Method 15, 7.0 g, 28.1 mmol) and 3,4-dihydro-2H-pyran (4.7 g, 56.2 mmol) dissolved in DCM (50 mL). 4-Toluene sulphonic acid pyridinium salt (100 mg) was added and the reaction stirred for 4 hours at ambient temperature. The reaction was diluted with ethyl acetate (100 mL), washed with water (2 x 50 mL), brine (50 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to give the title compound (8.9 g, 95%) as an oil.
^{1}H NMR 1.25-1.85 (m, 6H), 1.45 (s, 9H), 2.85-3.1 (m, 2H), 3.4 (m, 1H), 3.8 (m, 1H), 4.35-5.1 (m, 3H), 6.8 (dd, 1H), 7.2(s, 1H).

Method 18

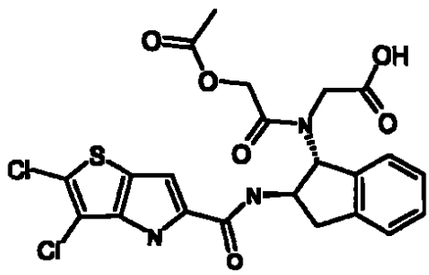
1,1-Dimethylethyl [acetyl((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate



Acetyl chloride (7 µL, 0.1 mmol) was added to a solution of *N*-(1*R*,2*R*)-1-[(*tert*-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 29, 50 mg, 0.1 mmol) in THF (5 mL). The reaction was stirred at ambient temperature for 1 h. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (5 mL), washed with water (2 x 5 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure and the residue purified by column chromatography (EtOAc:isohexane 1:1) to afford the title compound (168 mg, 76%) as a white solid.
^{1}H NMR 1.40 (s, 9H), 2.75 (dd, 1H), 3.42 (m, 2H), 3.60 (dd, 1H), 3.90 (s, 3H), 4.15 (d, 1H), 4.45 (m, 1H), 6.83 (d, 1H), 7.20 (m, 4H), 7.70 (d, 1H), 9.70 (s, 1H); MS m/z 522.

Method 19

[[(Acetyloxy)acetyl]((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetic acid

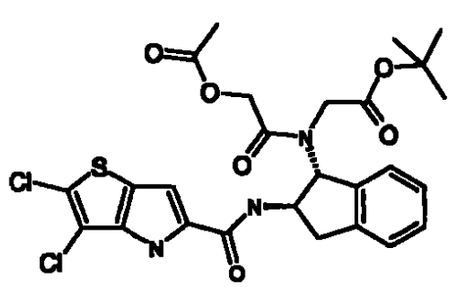


TFA (3 mL) was added to a solution of 1,1-dimethylethyl [[(acetyloxy)acetyl]((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (**Method 20**, 130 mg, 0.25 mmol) in DCM (10 mL) and the reaction was stirred at ambient temperature for 2 h. The volatiles were removed by evaporation under reduced pressure to afford the title compound (130 mg, 99%) as a white solid.

^{1}H NMR 2.20 (s, 3H), 2.78 (dd, 1H), 3.32 (dd, 1H), 3.97 (m, 2H), 4.35 (d, 1H), 4.68 (m, 2H), 4.90 (d, 1H), 6.42 (d, 1H), 6.83 (s, 1H), 7.25 (m, 4H), 11.14, (s, 1H); MS m/z 524.

Method 20

1,1-Dimethylethyl [[(acetyloxy)acetyl]((1*R*,2*R*)-2-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate



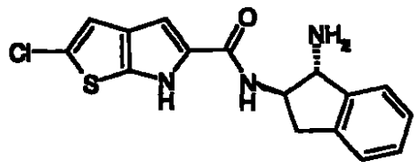
Acetoxyacetic acid (34 mg, 0.3 mmol) and DMTMM (81 mg, 0.3 mmol) were added to a solution of *N*-(1*R*,2*R*)-1-[(*tert*-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Example 29**, 140 mg, 0.3 mmol) in THF (10 mL). The reaction was stirred at ambient temperature for 7 h. The volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (10 mL),

washed with water (2 x 5 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by evaporation under reduced pressure to afford the title compound (145 mg, 83%) as a white solid.

^{1}H NMR 1.45 (s, 9H), 2.10 (s, 3H), 2.75 (dd, 1H), 3.50 (m, 3H), 3.90 (m, 2H), 4.15 (d, 1H), 4.50 (m, 1H), 6.83 (s, 1H), 7.20 (m, 4H), 7.70 (d, 1H), 9.70 (s, 1H); MS m/z 580.

Method 21

N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

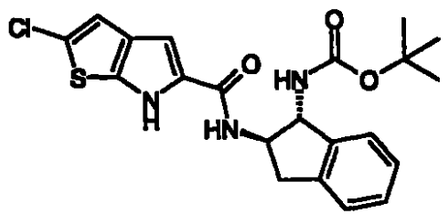


tert-Butyl ((1*R*,2*R*)-2-{[(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)carbamate (Method 22, 10.6 g, 24.5 mmol) was suspended in DCM (200 mL), TFA (20 mL) added and the reaction stirred at ambient temperature for 20 hours. The volatiles were removed by evaporation under reduced pressure and the residue triturated with DCM (50 mL) then filtered and dried to give the title compound (10.9 g, 100 %) as the trifluoroacetic acid salt.

^{1}H NMR 3.03 (dd, 1H), 3.38 (dd, 1H), 4.7 (m, 2H), 7.06 (d, 1H), 7.17 (s, 1H), 7.35 (m, 3H), 7.55 (m, 1H), 8.55 (s, 3H), 8.68 (d, 1H), 11.9 (s, 1H); MS m/z $(M\text{-}NH_3)^+$ 315, 317.

Method 22

tert-Butyl ((1*R*,2*R*)-2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)carbamate



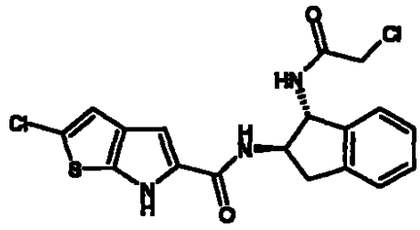
2-Chloro-5-carboxy-6*H*-thieno[3,2-*b*]pyrrole (Method 4a, 5.0 g, 25.0 mmol), *trans*-2-amino-1-[(1,1-dimethylethoxy)carbonylamino]indan (Method 6, 6.25 g, 25.0 mmol), DIPEA

(4.35 mL, 25.0 mmol) and HOBT (3.4 g, 25.0 mmol) were dissolved in DCM (200 mL) and stirred for 5 mins. EDCI (6.0 g, 31.0 mmol) was added, the reaction stirred for 24 hours and evaporated under reduced pressure. EtOAc (150 mL) was added and the mixture filtered, washed with water (2 x 200 mL), brine (200 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (10.6g, 98%) as a brown solid.

^{1}H NMR 1.38 (s, 9H), 2.81 (dd, 1H), 3.17 (dd, 1H), 4.56 (m, 1H), 5.14 (m, 1H), 7.01 (s, 1H), 7.16 (m, 5H), 7.32 (d, 1H), 8.47 (d, 1H), 11.82 (s, 1H).

Method 23

2-Chloro-*N*-[(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

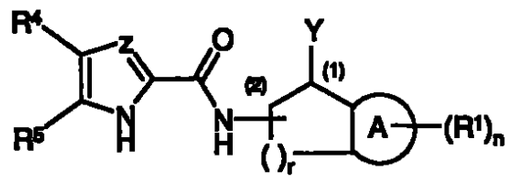


Et_3N (3 mL, 21.6 mmol) was added to a suspension of *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (Method 21, 3.11 g, 6.98 mmol) in anhydrous dichloromethane (55 mL) and stirred at ambient temperature for 5 miuntes. The suspension was cooled to –78 °C and chloroacetylchloride (611 µL, 7.68 mmol) was added and the reaction was warmed to 0 °C and stirred at this temperature for 3 hours. $NaHCO_3$ (50 mL) was added, the phases were separated and the aqueous phase was extracted with THF (2 x 50 mL). The combined organic fractions were washed with water (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was triturated (THF:isohexane, 1:5), collected by filtration, washed with hexane (20 mL) and dried to give the title compound (1.92 mg, 68%) as a brown solid.

^{1}H NMR 2.88 (dd, 1H), 3.24 (dd, 1H), 4.11 (dd, 2H), 4.61 (m, 1H), 5.46 (t, 1H), 6.99 (s, 1H), 7.20 (m ,5H), 8.55 (d, 2H), 8.73 (d, 1H), 11.84 (s, 1H); MS m/z 408, 410.

Claims

1. A compound of formula (1):



(1)

wherein:

Z is CH or nitrogen;

R^4 and R^5 together are either $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy and C_{1-4}alkanoyl;

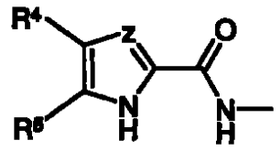
A is phenylene or heteroarylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, -S(O)$_b$$C_{1-4}$alkyl (wherein b is 0,1,or 2), C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

or, when n is 2, the two R^1 groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

r is 1 or 2; and when r is 1 the group

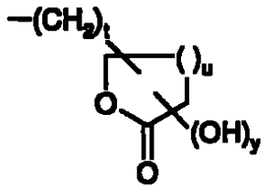


is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

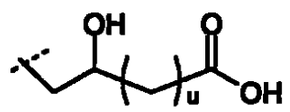
Y is $-NR^2R^3$ or $-OR^3$;

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, carbamoyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, heterocyclyl, aryl, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$, $-SO_bR^8$ (wherein b is 0, 1 or 2) and

groups of the formulae B and B':



(B)



(B')

wherein y is 0 or 1, t is 0, 1, 2 or 3 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen; or

wherein NR^2R^3 may form a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by –C(=O)-, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy and C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, (heterocyclyl)C_{1-4}alkyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, C_{1-4}alkyl or $-C(O)OC_{1-4}$alkyl), C_{1-4}alkanoyl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-N(OH)CHO$, $-C(=N-OH)NH_2$, $-C(=N-OH)NHC_{1-4}$alkyl, $-C(=N-OH)N(C_{1-4}alkyl)_2$, $-C(=N-OH)NHC_{3-6}$cycloalkyl, $-C(=N-OH)N(C_{3-6}cycloalkyl)_2$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NHSO_2(C_{1-4}alkyl)$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2$-, $-COCH_2OR^{11}$, $(R^9)(R^{10})N$- and

$-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, $-CH_2CH(CO_2R^9)OH$, $-CH_2C(O)NR^9R^{10}$, $-(CH_2)_wCH(NR^9R^{10})CO_2R^{9'}$ (wherein w is 1, 2 or 3), and $-(CH_2)_wCH(NR^9R^{10})CO(NR^{9'}R^{10'})$ (wherein w is 1, 2 or 3);

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, trihaloalkyl, aryl, heterocyclyl, heterocyclyl(C_{1-4}alkyl), and $-C(=O)O(C_{1-4})$alkyl; or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, C_{1-4}alkoxy and heterocyclyl; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl, and C_{1-4}alkoxy;

R^{11} is independently selected from hydrogen, C_{1-4}alkyl, and hydroxyC_{1-4}alkyl;

or a pharmaceutically acceptable salt or pro-drug thereof;

with the proviso that the compound of formula (1) is not:

i) 2,3-dichloro-5-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole;

ii) 5-[*N*-(1-aminoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iii) 5-[*N*-(1-acetamidoindan-2-yl)carbamoyl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole

iv) 2,3-dichloro-5-{*N*-[1-(methanesulphonamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole

v) 2,3-dichloro-5-{*N*-[1-(methylamino)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-b]pyrrole;

vi) 2,3-dichloro-5-{*N*-[1-(methylacetamido)indan-2-yl]carbamoyl}-4*H*-thieno[3,2-*b*]pyrrole;

vii) 2,3-dichloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole;

viii) 2-chloro-5-[*N*-(1-hydroxyindan-2-yl)carbamoyl-6*H*-thieno[2,3-*b*]pyrrole;

ix) 2,3-dichloro-5-[*N*-(6-fluoro-1-hydroxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole

x) 2,3-dichloro-5-[*N*-(1-methoxyindan-2-yl)carbamoyl-4*H*-thieno[3,2-*b*]pyrrole;

xi) 2,3-dichloro-5-[N-(1-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)carbamoyl]-4*H*-thieno[3,2-*b*]pyrrole.

2. A compound of the formula (1) as claimed in claim 1, wherein:

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, aryl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, dihalo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, aryl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), $-C(=O)O^tBu$, C_{2-4}alkenyl, cyano(C_{1-4})alkyl and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano); or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo,

hydroxy, carboxy, halo, nitro, cyano, carbonyl and C_{1-4}alkoxy; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^{13} is selected from halo, trihalomethyl and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

3. A compound of the formula (1) as claimed in claim 1 or claim 2, wherein:

R^2 and R^3 are independently selected from hydrogen, C_{1-4}alkyl [optionally substituted by 1 or 2 R^8 groups], $-COR^8$ and $-SO_bR^8$ (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, $-CO_2C_{1-4}$alkyl, phenyl and aryl(C_{1-4})alkyl], C_{2-4}alkenyl, C_{3-7}cycloalkyl (optionally substituted by $-C(O)OC_{1-4}$alkyl), 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, halo(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, cyano(C_{1-4})alkyl, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, pyridyl, tetrahydrofuryl, tetrahydropyranyl, 1-oxo-tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl$S(O)_b-$ (wherein b is 0, 1 or 2), C_{3-6}cycloalkyl$S(O)_b-$ (wherein b is 0, 1 or 2), aryl$S(O)_b-$ (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b-$ (wherein b is 0, 1 or 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ and $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} and $R^{10'}$ are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

4. A compound as claimed in any preceding claim wherein Y is NR^2R^3, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

5. A compound as claimed in any one of claims 1 to 3 wherein Y is OR^3, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

6. A compound as claimed in any preceding claim wherein R^4 and R^5 together are $-S-C(R^6)=C(R^7)-$, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

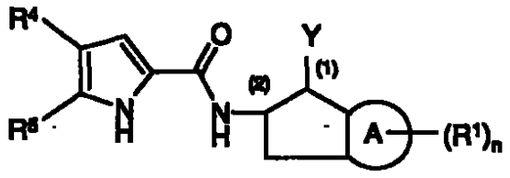
7. A compound as claimed in any one of claims 1 to 5 wherein R^4 and R^5 together are $-C(R^7)=C(R^6)-S-$; or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

8. A compound as claimed in any preceding claim wherein A is phenylene, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

9. A compound as claimed in any one of claims 1 to 7 wherein A is heteroarylene, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

10. A compound as claimed in any preceding claim wherein Z is CH, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

11. A compound of the formula (1) as claimed in any preceding claim, which is a compound of formula (1B):



(1B)

or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

12. A compound of the formula (1) as claimed in claim 1, which is any one of:
2,3-dichloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;
2,3-dichloro-*N*-((1*R*,2*R*)-1-{[(methyloxy)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-butoxycarbonylamino)-3-carbamoylpropanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(trifluoroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(furan-2-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(furan-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(3-thienylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(5-nitrofuran-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1S,2S)-1-[(pyridin-3-ylcarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-(acryloylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(3-hydroxyphenyl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-(acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*S*,2*S*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(dimethylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(4-methylpiperazin-1-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(ethylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-((1*S*,2*S*)-1-{[(prop-2-en-1-ylamino)carbonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*S*,2*S*)-1-({[(3,5-dinitrophenyl)amino]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-[(1*S*,2*S*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[((3*R*)-3-carboxy-3-hydroxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*S*, 2*S*)-1-[methyl(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[(tert-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-[(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-(1*R*,2*R*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(*1R*,2*R*)-1-[acetyl(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[*N*-(carboxymethyl)-*N*-(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-[(1*R*,2*R*)-1-({[(2*S*)-5-oxotetrahydrofuran-2-yl]carbonyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

2-chloro-*N*-[(1*R*,2*R*)-1-(formylamino)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole 5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(methoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

N-[(1*R*,2*R*)-1 (acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

N-{(1*R*,2*R*)-1-[(2-acetoxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

N-((1*S*,2*S*)-1-{[(2(*S*)-2-(*tert*-butoxycarbonylamino)-2-carbamoylacetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide·

N-{(1*S*,2*S*)-1-[(2-(*tert*-butoxycarbonylamino)acetylamino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide,

N-{(1*R*,2*R*)-1-[2-(tert-butoxycarbonyl)acetylamino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3,*b*]pyrrole-5-carboxamide,

2-chloro-*N*-((1*R*,2*R*)-1-{[3-hydroxy-2-(hydroxymethyl)propanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

N-{(1*R* 2*R*)-1-{((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden 2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-[(1*R*,2*R*)-1-({[(2 hydroxyethyl)(phenylmethyl)amino]acetyl} amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

2-chloro-*N*-{(1*R*,2*R*)-1-[(morpholin-4-ylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide,

2-chloro-*N*-((1*R* 2*R*)-1-({[(2-hydroxyethyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole 5-carboxamide

N-((1*R*,2*R*)-1-({[bis(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-({[ethyl(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2-chloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihydroxypropyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-((1*R*,2*R*)-1-({[bis(2-hydroxypropyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl)-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-[(1*R*,2*R*)-1-{(tert-butoxycarbonylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

2-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetylamino]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-{((3*S*)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2,3-dichloro-4*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

N-{(1*R*,2*R*)-1-[((3S)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-2-chloro-6*H*-thieno(3,2,*b*]pyrrole-5-carboxamide;

2,3-dichloro-*N*-{(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide;

or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

13. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12 in association with a pharmaceutically-acceptable diluent or carrier.

14. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12, for use in a method of treatment of a warm-blooded animal such as man by therapy.

15. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12, for use as a medicament.

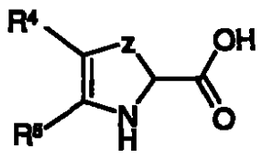
16. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

17. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12, 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.

18. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 12, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

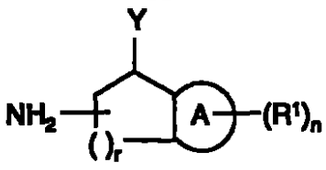
19. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

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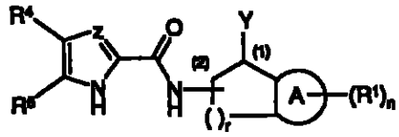
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(54) Título: DERIVADOS DE AMIDA HETEROCÍCLICA CON ACTIVIDAD INHIBIDORA DE GLUCÓGENO FOSFORILASA



(1)

(57) Extracto: Amidas heterocíclicas de fórmula (1) donde: Z es CH o nitrógeno; R^4 y R^5 juntos son bien sea –S-C(R^6)= C(R^7)- o C(R^7=C(R^6)-S- ; R^6 y R7 se seleccionan por ejemplo entre hidrógeno, halo, C_{1-4} alquilo y C_{1-4} alcanoilo; A es fenileno o heteroarileno; n es 0, 1 o 2; R^1 se selecciona por ejemplo entre halo, nitro, ciano, hidroxi, carboxi; r es 1 o 2; Y es -NR^2R^3 o –OR^3; R^2 y R^3 se seleccionan: por ejemplo entre hidrógeno, hidroxi, arilo, heterociclilo y C_{1-4}alquilo (opcionalmente sustituidos por 1 o 2 grupos R^8); R^4 se selecciona entre por ejemplo hidrógeno, halo, ciano, hidroxi C_{1-4}alquilo y C_{1-4}alcanoilo. R^8 se selecciona por ejemplo entre –COCOOR^9, -C(O)N(R^9)(R^{10}), -NHC(O)R^9; (R^9)(R^{10})N- y –COOR^9 ; R^9 y R^{10} se seleccionan por ejemplo entre hidrógeno, hidroxi, C_{1-4}alquilo (opcionalmente sustituidos por 1 o 2 grupos R^{13}); R^{13} se selecciona entre hidroxi, halo, trihalometilo y C_{1-4}alcoxi; o una sal o un profármaco farmacéuticamente aceptable de los mismos; que poseen una actividad inhibidora de glucógeno fosforilasa y por lo tanto es valioso para el tratamiento de patologías asociados con una mayor actividad glucógeno fosforilasa. Se describen los procesos de manufactura de los citados derivados de las aminas heterocíclicas y las composiciones farmacéuticas que los contienen.

WO 03/074531 A1

DERIVADOS DE AMIDA HETEROCÍCLICA CON ACTIVIDAD INHIBIDORA DE GLUCÓGENO FOSFORILASA

La presente invención se relaciona con derivados de amida heterocíclica, sales farmacéuticamente aceptables y ésteres hidrolisables *in vivo* de los mismos. Estas amidas heterocíclicas poseen una actividad inhibidora de glucógeno fosforilasa y por lo tanto son valiosas para el tratamiento de patologías asociadas con una mayor actividad de glucógeno fosforilasa de manera que son potencialmente útiles en los métodos para el tratamiento de un animal de sangre caliente como el hombre. La invención también se relaciona con procesos para la manufactura de los citados derivados de amida heterocíclica, con composiciones farmacéuticas que las contienen, y con su utilización en la manufactura de medicamentos para inhibir la actividad de glucógeno fosforilasa en un animal de sangre caliente como el hombre.

El hígado es el principal órgano en la regulación de la glucemia durante el estado posterior a la absorción. Adicionalmente, aunque juega un papel menor en la contribución a los niveles de glucosa post prandiales en sangre, la respuesta del hígado a unas fuentes exógenas de glucosa en plasma es clave para la preservación de la euglucemia. Se considera que una mayor producción de glucosa hepática (PGH) juega un papel importante para la preservación del elevado nivel de glucosa en plasma durante el ayuno (GPA) que se evidencia en los pacientes con diabetes tipo 2; particularmente aquellos con una GPA>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 orales actuales para la diabetes no logran llevar los niveles de GPA a los niveles normales de personas no diabéticas, y puesto que unos niveles mayores de GPA (y glycHbA1c) representan unos factores de riesgo tanto para enfermedades macro- (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) como micro-vasculares (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); la reducción y la normalización de los niveles elevados de la GPA siguen siendo una meta para el tratamiento de DM tipo 2.

Se ha estimado que después de un ayuno durante la noche, el 74% de la PGH se derivó de la glucogenólisis y el resto provino de precursores gluconeogénicos (Hellerstein y colaboradores (1997) Am J Physiol. 272: E163). La glucógeno fosforilasa es una enzima clave en la generación mediante glucogenólisis, de glucosa-1-fosfato, y por lo tanto hay glucosa en el hígado y también en otros tejidos tales como los tejidos musculares y neuronales.

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

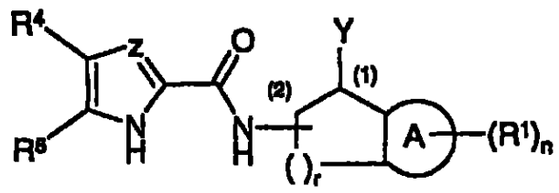
Se ha visto que la inhibición de la glucógeno fosforilasa hepática con inhibidores de cloroindol (CP91149 y CP320626) reduce tanto la glucogenólisis estimulada por glucagón y la producción de glucosa en hepatocitos (Hoover y colaboradores (1998) J Med Chem 41, 2934-8; Martin y colaboradores (1998) PNAS 95, 1776-81). Adicionalmente, se reduce la concentración de glucosa en plasma, en una forma relacionada con la dosis, ratones db/db y ob/ob después del tratamiento con estos compuestos.

Estudios en perros conscientes que han estado expuestos al glucagón en ausencia y en presencia de otro inhibidor de glucógeno fosforilasa, Bay K 3401, también muestran la potencial utilidad de dichos agentes donde existe un elevado nivel de circulación de glucagón, como en la diabetes Tipo 1 y en la Tipo 2. En presencia de Bay R 3401, la producción de glucosa hepática y la glucosa arterial en plasma después de una exposición al glucagón se redujo significativamente (Shiota y colaboradores, (1997), Am J Physiol, 273: E868).

Las amidas heterocíclicas de la presente invención poseen una

actividad inhibidora de glucógeno fosforilasa y por lo tanto se espera que sean útiles para el tratamiento de la diabetes Tipo 2, para la resistencia a la insulina, el síndrome X, la hiperinsulinemia, hiperglucagonemia, isquemia cardiaca y obesidad, particularmente la diabetes tipo 2.

De acuerdo con un aspecto de la presente invención, se dispone un compuesto de fórmula (1):



(1)

donde:

Z es CH o nitrógeno;

R^4 y R^5 juntos son bien sea -S-C(R^6)=C(R^7)- o -C(R^7)=C(R^6)-S-;

R^6 y R^7 se seleccionan independientemente entre hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, carboxi, carbamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi y C_{1-4}alcanoilo;

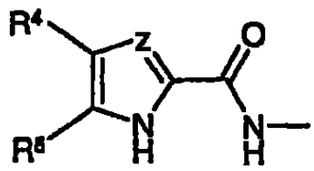
A es fenileno o heteroarileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, nitro, ciano, hidroxi, carboxi, carbamoilo, *N*-C_{1-4}alquilcarbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, sulfamoilo, *N*-C_{1-4}alquilsulfamoilo, *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, -S(O)$_b$ C_{1-4}alquilo (donde b es 0, 1, o 2), C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, hidroxi C_{1-4}alquilo, fluorometilo, difluorometilo, trifluorometilo y trifluorometoxi;

o, cuando n es 2, los dos grupos R^1, junto con los átomos de carbono de A a los cuales están adheridos, pueden formar un anillo de 4 a 7 miembros, opcionalmente conteniendo 1 o 2 heteroátomos seleccionados independientemente entre O, S y N, y opcionalmente sustituidos por uno o dos grupos metilo;

r es 1 o 2; y cuando r es 1 el grupo

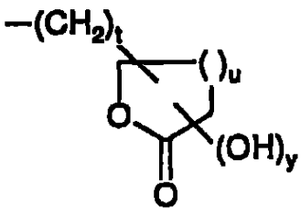


es un radical en el carbono (2) y cuando r es 2 (formando de esta manera un anillo de seis miembros) el mismo grupo es un radical en el carbono (2) o en el carbono (3);

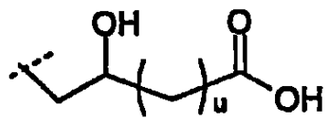
Y es $-NR^2R^3$ u OR^3;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcanoilo, carbamoilo, C_{3-7}cicloalquilo (sustituidos opcionalmente con 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, heterociclilo, arilo, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$, $-SO_bR^8$ (donde b es 0, 1 o 2) y

grupos de fórmula B y B':



(B)



(B')

donde y es 0 o 1, t es 0, 1, 2 o 3 y u es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno; o

donde NR^2R^3 puede formar un anillo de 4 a 7 miembros saturado, parcialmente saturado o insaturado, conteniendo opcionalmente 1, 2 o 3 heteroátomos adicionales, seleccionados independientemente entre N, O y S, donde cualquier $-CH_2-$ se puede reemplazar opcionalmente por -C(=O)-, y cualquier átomo N o S se puede oxidar opcionalmente para formar un *N*-óxido o un grupo SO o SO_2 respectivamente, y donde el anillo es sustituido opcionalmente por 1 o 2 radicales seleccionados independientemente entre halo, ciano, C_{1-4}alquilo, hidroxi, C_{1-4}alcoxi y C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo, C_{2-4}alquenilo, C_{1-4}alcoxi, ciano(C_{1-4})alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-}

$_4$alquilo, hidroxi, hidroxi (C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2 C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, C_{1-4} alcoxiC_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo hidroxiC_{1-4}alcoxi, acetales cíclicos de 5- y 6-miembros y mono- y di-metil derivados de los mismos, arilo, heterociclilo, (heterociclilo)C_{1-4}alquilo, C_{3-7}cicloalquilo (sustituidos opcionalmente con 1 o 2 grupos hidroxi, C_{1-4}alquilo o -C(O)OC_{1-4}alquilo), C_{1-4}alcanoilo, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -N(OH)CHO, -C(=N-OH)NH_2, -C(=N-OH)NHC_{1-4}alquilo, -C(=N-OH)N(C_{1-4}alquilo)$_2$, -C(=N-OH)NHC_{3-6}cicloalquilo, -C(=N-OH)N(C_{3-6}cicloalquilo)$_2$, -COCOOR^9, C(O)N(R^9)(R^{10}), -NHC(O)R^9, -C(O)NHSO_2(C_{1-4}alquilo), - NHSO_2R^9, (R^9)(R^{10})N- y –COOR^9, -CH_2OR^9, -CH_2COOR^9, -CH_2OCOR^9, -$CH_2CH(CO_2R^9)OH$, -$CH_2C(O)NR^9R^{10}$, -$(CH_2)_wCH(NR^9R^{10})CO_2R^{9'}$ (donde w es 1, 2 o 3), y -$(CH_2)_wCH(NR^9R^{10})CO(NR^{9'}R^{10'})$ (donde w es 1, 2 o 3);

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, trihaloalquilo, arilo, heterociclilo, heterociclilo(C_{1-4}alquilo), y -C(=O)O(C_{1-4})alquilo; o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo, C_{1-4}alcoxi y heterociclilo; o el anillo puede ser sustituido opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi,

R^{11} se selecciona independientemente entre hidrógeno, C_{1-4}alquilo, e

hidroxiC_{1-4}alquilo; o una sal o un profármaco farmacéuticamente aceptable de los mismos; con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

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

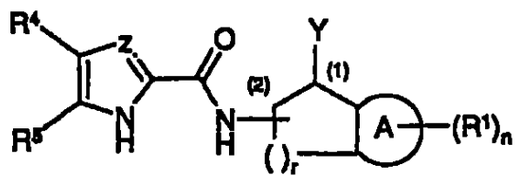
viii) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*] pirrol;

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

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

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

De acuerdo con otro aspecto de la presente invención, se dispone un compuesto de fórmula (1):



(1)

donde:

Z es CH o nitrógeno;

R^4 y R^5 juntos son bien sea S-C(R^6)=C(R^7)- o –C(R^7)=C(R^6)-S-;

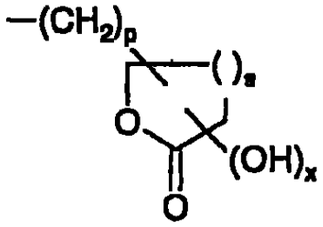
R^6 y R^7 se seleccionan independientemente entre hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, ureido, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *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}alquiloS(O)$_n$ 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} alquilsulfonilo-*N*-(C_{1-6} alquil)amino;

A es fenileno o heteroarileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, *N*-C_{1-4}alquilcarbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, sulfamoilo, *N*-C_{1-4}alquilsulfamoilo, *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, sulfino, sulfo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*- (C_{1-4}alquil)$_2$amino, hidroxiC_{1-4}alquilo, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, C_{1-4}alcoxi y

R^1 es de fórmula A' o A":

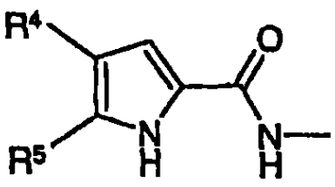


(A)



(A')

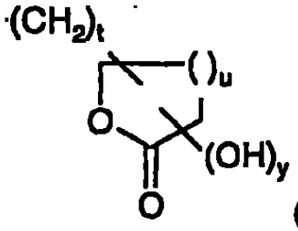
donde x es 0 o 1, p es 0, 1, 2 o 3 y s es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno; r es 1 o 2; y cuando r es 1 el grupo



es un radical en el carbono (2) y cuando r es 2 (formando con el mismo un anillo de seis miembros) el mismo grupo es un radical en el carbono (2) o en el carbono (3);

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo (sustituido por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{5-7}cicloalquilo (sustituidos opcionalmente con 1 o 2 grupos hidroxi siempre que cuando sean 2 grupos hidroxi no sean radicales en el mismo carbono), ciano(C_{1-4})alquilo, 4-butanolidilo, 5-pentanolidilo, tetrahidrotiopiranilo, grupo 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, fluorometilcarbonilo, difluorometilcarbonilo, trifluorometilcarbonilo, C_{1-4}alquilo [sustituido por 1 o 2 grupos R^8 (siempre que cuando haya 2 grupos R^8 no sean radicales en el mismo carbono)], $-COR^8$, $-SO_bR^8$ (donde b es 0, 1 o 2) y grupos de la fórmula B y B':



(B) $-CH_2CH(OH)(CH_2)_uCO_2H$ (B')

donde y es 0 o 1, t es 0, 1, 2 o 3 y u es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno);

{donde R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxilC_{1-4}alcoxi, 2,2-dimetil-1,3-dioxolan-4-ilo, heterociclilo (sustituidos opcionalmente en el carbono o nitrógeno por 1 o 2 grupos seleccionados entre hidrógeno, nitro, halo, ciano, hidroxi y C_{1-4}alquilo), (heterociclil) C_{1-4}alquilo (donde el heterociclilo es sustituido opcionalmente en el carbono o en el nitrógeno por 1 o 2 grupos seleccionados entre hidrógeno, nitro, halo, ciano, hidroxi y C_{1-4}alquilo), arilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), C_{1-4}alquilo, C_2-4alquenilo, ciclo(C_{3-8})alquilo, C_{1-4}alcoxi, ciano(C_{1-4}) alquilo, amino(C_{1-4})alquilo (sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre hidrógeno, C_{1-4}alquilo,

hidroxi, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, arilo y arilo(C_{1-4})alquilo), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0,-1 o 2), -N(OH)CHO, -$CH_2CH(CO_2R^9)N(R^9R^{10})$, -$CH_2OR^9$, $(R^9)(R^{10})$N-, -$COOR^9$ y -CH_2COOR^9, -$CH_2CON\ R^9R^{10}$, -$(CH_2)_uCH(NR^9R^{10})CO_2R^9$ (donde u es 1, 2 o 3);

[donde R^9 y R^{10} se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{5-7}cicloalquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{2-4}alquenilo, ciano(C_{1-4})alquilo, 4-butanolidilo, 5-pentanolidilo, tetrahidrotiopiranilo, grupo 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, 2,2-dimetil-1,3-dioxolan-4-ilo, arilo (sustituidos opcionalmente por 1 o 2 radicales seleccionados entre hidrógeno, nitro, halo, hidroxi y C_{1-4} alquil) y C_{1-4}alquilo sustituido por R^{13} ;

(donde R^{13} se selecciona entre hidroxi, C_{1-4}alcoxi, heterociclilo, C_{1-4}alcanoilo, C_{1-4}alquiloS(O)$_d$ (donde d es 0, 1 o 2)1, -N(OH)CHO, $(R^{11})(R^{12})$NCO-, $(R^{11})(R^{12})NSO_2$-, -$COCH_2OR^{11}$ y (R^{11}) (R^{12})-;

{donde R^{11} y R^{12} se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo, C_{1-4}alcoxi, hidroxiC_{1-4}alquilo, C_{1-4}alquiloS(O)$_e$ (donde e es 0, 1 o 2)}); y

R^9 y R^{10} pueden, junto con el nitrógeno al cual están adheridos, formar un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados entre oxo, hidroxi, carboxi, halo, nitro, nitroso, ciano, isociano, amino, *N*-C_{1-4}alquilamino, *N,N*-$(C_{1-4})_2$alquilamino, carbonilo, sulfo, C_{1-4}alcoxi, heterociclilo, C_{1-4}alcanoilo, C_{1-4}alquiloS(O)$_f$(C_{1-4})alquilo (donde f es 0, 1 o 2), -N(OH)CHO, $(R^{11})(R^{12})$NCO-. $(R^{11})(R^{12})NSO_2$-, -$COCH_2OR^{11}$, $(R^{11})(R^{12})$N-;

donde R^{11} y R^{12} son como se definen arriba]};

siempre que cuando R^1 es de fórmula A' o A'' entonces R^2 y R^3 no contienen un grupo de la fórmula B o B' y cuando R^2 o R^3 son de la fórmula B o B' entonces R^1 no contiene un grupo de la fórmula A' o A'' de manera

que un compuesto de fórmula (1) únicamente puede contener uno de A', A'', B y B';

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

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

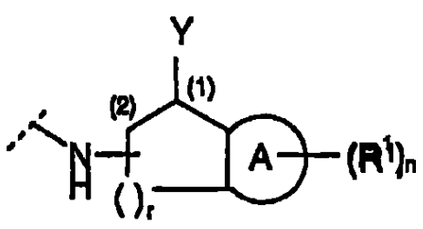
viii) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*]pirrol;

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

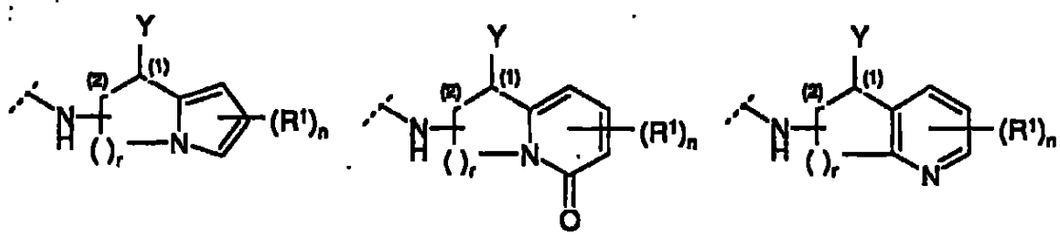
x) 2,3-dicloro-5-[*N*-(1-metoxiindan-2-il)carbamoilo-4*H*-tieno [3,2-*b*]pirrol

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

Se debe entender que cuando A es heteroarileno, los átomos en la cabecera del puente uniendo el anillo A al anillo de piperidinona pueden ser heteroátomos. Por lo tanto, por ejemplo, la definición de



cuando A es heteroarileno comprende las estructuras:



se debe entender que donde la sustitución opcional en los grupos alquilo o cicloalquilo en R^3, R^9 y R^{10} (como se define más arriba o en adelante) permite dos radicales hidroxi en el grupo alquilo o cicloalquilo, o un radical hidroxi y un segundo radical enlazado por un heteroátomo (por ejemplo alcoxi), entonces estos dos radicales no son radicales en el mismo átomo de carbono del grupo alquilo o cicloalquilo.

En otro aspecto, la invención se relaciona con los compuestos de la fórmula (1) como se definen arriba o con una sal farmacéuticamente aceptable.

En otro aspecto, la invención se relaciona con los compuestos de la fórmula (1) como se definen arriba o con un profármaco de los mismos. Ejemplos adecuados de profármacos de los compuestos de la fórmula (1) son ésteres hidrolisables in-vivo de los compuestos de la fórmula (1). Por lo tanto en otro aspecto, la invención se relaciona con los compuestos de la fórmula (1) como se definen arriba o con un éster hidrolisable in-vivo de los mismos.

Se debe entender que, en cuanto que ciertos compuestos de la fórmula (1) definidos arriba pueden existir en formas ópticamente activas o racémicas en virtud de uno o varios átomos asimétricos de carbono, la invención incluye en su definición cualquier forma ópticamente activa o racémica que posee una actividad inhibidora de glucógeno fosforilasa. La síntesis de las formas ópticamente activas se puede realizar mediante unas técnicas estándar de la química orgánica bien conocidas en el arte, por ejemplo por la síntesis de unos materiales de partida ópticamente activos o

por resolución de una forma racémica. De igual manera, la actividad previamente citada se puede evaluar empleando unas técnicas estándar de laboratorio descritas más adelante.

Dentro de la presente invención se debe entender que un compuesto de la fórmula (1) o una sal de este puede mostrar el fenómeno del tauterismo, y que los dibujos de las fórmulas dentro de esta especificación pueden representar únicamente una de las formas tautoméricas posibles. Se debe entender que la invención comprende cualquier forma tautomérica que tiene una actividad inhibidora de glucógeno fosforilasa, y no se debe limitar meramente a cualquier forma tautomérica empleada en los dibujos de las fórmulas. Los dibujos de las fórmulas en esta especificación pueden representar solamente una de las posibles formas tautoméricas, y se debe entender que la especificación comprende todas las posibles formas tautoméricas de los compuestos dibujados y no solo las formas que se han podido mostrar de manera gráfica en la presente.

También se debe entender que ciertos compuestos de la fórmula (1) y las sales de los mismos pueden existir en formas de solvatos o no solvatos, como por ejemplo en formas hidratadas. Se debe entender que la invención abarca todas estas formas de solvatos que tienen una actividad inhibidora de glucógeno fosforilasa.

También se debe entender que ciertos compuestos de la fórmula (1) pueden mostrar un polimorfismo y que la invención abarca todas estas formas que poseen una actividad inhibidora de glucógeno fosforilasa.

La presente invención se relaciona con los compuestos de la fórmula (1) como se definen más arriba, al igual que con las sales de los mismos. Las sales que se emplean en las composiciones farmacéuticas serán sales farmacéuticamente aceptables, pero otras sales podrán ser útiles en la producción de los compuestos de la fórmula (1) y sus sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables de la invención pueden incluir por ejemplo sales de adición de ácidos de los compuestos de la fórmula (1) como se definieron arriba que son lo suficientemente alcalinas para formar estas sales. Dichas sales de adición de

ácido incluyen por ejemplo sales con ácidos orgánicos o inorgánicos que aportan unos aniones farmacéuticamente aceptables como con los haluros de hidrógeno (especialmente el ácido clorhídrico o hidrobrómico, entre los cuales particularmente se prefiere el ácido clorhídrico) o con ácido sulfúrico o fosfórico, o con ácido trifluoroacético, cítrico o maleico. Las sales apropiadas incluyen clorhidratos, bromhidratos, fosfatos, sulfatos, sulfatos de hidrógeno, alquilsulfonatos, arilsulfonatos, acetatos, benzoatos, citratos, maleatos, fumaratos, succinatos, lactatos y tartratos. Adicionalmente, cuando los compuestos de la fórmula (1) son lo suficientemente acídicos, se pueden formar sales farmacéuticamente aceptables con una base orgánica o inorgánica que aporta un catión farmacéuticamente aceptable. Dichas sales con bases inorgánicas u orgánicas incluyen por ejemplo una sal de metal alcalino como una sal de sodio o de potasio, una sal de metal alcalinotérreo tal como la sal de calcio o de magnesio, una sal de amonio o por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Los compuestos de la invención se pueden administrar en forma de un profármaco que se descompone en el cuerpo de un humano o de un animal para obtener un compuesto de la invención. Se puede emplear un profármaco para alterar o mejorar el perfil físico y / o farmacocinético del compuesto inicial y se puede encontrar cuando el compuesto inicial contiene un grupo o radical adecuado que se puede derivar para formar un profármaco. Ejemplos de profármacos incluyen ésteres hidrolisables in-vivo de un compuesto de la invención o una sal farmacéuticamente aceptable de los mismos.

Se conocen varias formas de profármacos en el arte, por ejemplo consultar:

a) Design de Prodrugs, publicado por H. Bundgaard, (Elsevier, 1985) y Métodos in Enzymology, Vol. 42, p. 309-396, publicado por K. Widder *y colaboradores*. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, publicado por Krogsgaard-Larsen y H. Bundgaard, Capítulo 5 "Design and Application de

Prodrugs", por H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8,1-38 (1992);

d) H. Bundgaard *y colaboradores.*, Journal of Pharmaceutical Sciences, 77 285 (1988); y

e) N. Kakeya *y colaboradores.*, Chem Pharm Bull, 32, 692 (1984).

Un éster hidrolisable *in vivo* de un compuesto de fórmula (1) conteniendo un grupo carboxi o hidroxi es, por ejemplo un éster farmacéuticamente aceptable que se injerta en el cuerpo humano o animal para producir el ácido inicial o alcohol.

Ésteres farmacéuticamente aceptables de carboxi incluyen C_{1-6}alcoximetil ésteres por ejemplo metoximetilo, C_{1-6}alcanoiloximetil ésteres por ejemplo pivaloiloximetilo, ftalidilo ésteres, C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquilo ésteres por ejemplo 1-ciclohexilcarboniloxietilo; 1,3-dioxolen-2-onilometil ésteres por ejemplo 5-metil-1,3-dioxolen-2-onilometilo; y C_{1-6}alcoxicarboniloxietilo ésteres por ejemplo 1-metoxicarboniloxietilo y se pueden formar en cualquier grupo carboxi en los compuestos de esta invención.

Ésteres farmacéuticamente aceptables apropiados de hidroxi incluyen ésteres inorgánicos como fosfato ésteres (incluyendo ésteres fosforamídicos cíclicos) y α-aciloxialquilo éteres y compuestos relacionados los cuales, como resultado de la hidrólisis *in-vivo* se descomponen del éster para obtener el (los) grupo(s) inicial(es) hidroxi. Ejemplos de α-aciloxialquilo éteres incluyen acetoximetoxi y 2,2-dimetilpropioniloximetoxi. Una selección de grupos de formación de éster hidrolisable *in-vivo* para hidroxi incluye C_{1-10}alcanoilo, por ejemplo acetilo; benzoilo; fenilacetilo; benzoilo sustituido y fenilacetilo, C_{1-10}alcoxicarbonilo (para obtener ésteres alquilo carbonato), por ejemplo etoxicarbonilo; di-(C_{1-4})alquilcarbamoilo y *N*-(di-(C_{1-4})alquilaminoetilo-*N*-(C_{1-4})alquilcarbamoilo (para obtener carbamatos); di-(C_{1-4})alquilaminoacetilo y carboxiacetilo. Ejemplos de anillos de radicales en fenilacetilo y benzoilo incluyen aminometilo, (C_{1-4})alquilaminometilo y di(C_{1-4})alquil)aminometilo y morfolino o piperazino

enlazados de un anillo de átomos de nitrógeno por medio del grupo de enlace a la posición 3- o 4- del anillo de benzoilo. Otros ésteres hidrolisables in-vivo interesantes incluyen por ejemplo, $R^{A}C(O)O(C_{1-6})$alquilo-CO-, donde R^{A} es por ejemplo, benciloxi-(C_{1-4})alquilo o fenil). Unos radicales apropiados en un grupo fenilo en dichos ésteres incluyen por ejemplo, 4-(C_{1-4})piperazino-(C_{1-4})alquilo, piperazino-(C_{1-4})alquilo y morfolino-$(C_1$-$C_4)$alquilo.

En esta especificación, el término genérico "alquilo" incluye los grupos alquilo de cadenas rectas y de cadenas ramificadas. Sin embargo, las referencias a grupos alquilo individuales como "propilo" son específicas para la versión de cadena recta únicamente, y las referencias a grupos alquilo individuales de cadenas ramificadas como *t*-butilo son específicas para la versión de cadena ramificada únicamente. Por ejemplo, "C_{1-4}alquilo" incluye metilo, etilo, propilo, isopropilo y *t*-butilo y ejemplos de "C_{1-6} alquilo" incluyen los ejemplos de "C_{1-4}alquilo" y adicionalmente pentilo, 2,3-dimetilpropilo, 3-metilbutilo y hexilo. Una convención análoga rige para otros términos genéricos, por ejemplo "C_{2-4}alquenilo" incluye vinilo, alilo y 1-propenilo y ejemplos de "C_{2-6}alquenilo" incluyen los ejemplos de "C_{2-4} alquenilo" y adicionalmente 1-butenilo, 2-butenilo, 3-butenilo, 2-metilbut-2-enilo, 3-metilbut-1-enilo, 1-pentenilo, 3-pentenilo y 4-hexenilo. Ejemplos de "C_{2-4}alquinilo" incluyen etinilo, 1-propinilo y 2-propinilo y ejemplos de "C_{2-6}alquinilo" incluyen los ejemplos de "C_{2-4}alquinilo" y adicionalmente 3-butinilo, 2-pentinilo y 1-metilpent-2-inilo.

El término "hidroxiC_{1-4}alquilo" incluye hidroximetilo, hidroxietilo, hidroxipropilo, hidroxiisopropilo e hidroxibutilo. El término "hidroxietilo" incluye 1-hidroxietilo y 2-hidroxietilo. El término "hidroxipropilo" incluye 1-hidroxipropilo, 2-hidroxipropilo y 3-hidroxipropilo y una convención análoga rige para términos como hidroxibutilo. El término "dihidroxiC_{1-4}alquilo" incluye dihidroxietilo, dihidroxipropilo, dihidroxiisopropilo y dihidroxibutilo. El término "dihidroxipropilo" incluye 1,2-dihidroxipropilo y 1,3-dihidroxipropilo. Una convención análoga rige para términos como

dihidroxiisopropilo y dihidroxibutilo

El término "halo" hace referencia a fluoro, cloro, bromo y iodo El termino "dihaloC_{1-4} alquilo" incluye difluorometil y diclorometil El termino "trihaloC_{1-4}alquilo" incluye trifluorometilo

Ejemplos de "acetales cíclicos de 5- y 6-miembros y mono- y di-metil derivados de los mismos" son
1,3-dioxolan-4-ilo, 2-metil-1,3-dioxolan-4-ilo, 2,2-dimetil-1,3-dioxolan-4-ilo, 2,2-dimetil-1,3-dioxan-4-ilo, 2,2-dimetil-1,3-dioxan-5-ilo, 1,3-dioxan-2-ilo

Ejemplos de "C_{1-4}alcoxi" incluyen metoxi, etoxi, propoxi e isopropoxi Ejemplos de "C_{1-6}alcoxi" incluyen los ejemplos de "C_{1-4}alcoxi" y adicionalmente butiloxi, *t*-butiloxi, pentoxi y 1,2-(metil)$_2$propoxi Ejemplos de "C_{1-4}alcanoilo" incluyen formilo, acetilo y propionilo Ejemplos de "C_{1-6}alcanoilo" incluyen el ejemplo de "C_{1-4}alcanoilo" y adicionalmente butanoilo, pentanoilo, hexanoilo y 1,2-(metil)$_2$propionilo Ejemplos de "C_{1-4}alcanoiloxi" son formiloxi, acetoxi y propionoxi Ejemplos de "C_{1-6}alcanoiloxi" incluyen los ejemplos de "C_{1-4}alcanoiloxi" y adicionalmente butanoiloxi, pentanoiloxi, hexanoiloxi y 1,2-(metil)$_2$propioniloxi Ejemplos de "*N*-(C_{1-4}alquil)amino" incluyen metilamino y etilamino Ejemplos de "*N*-(C_{1-6}alquil)amino" incluyen los ejemplos de "*N*-(C_{1-4}alquil)amino" y adicionalmente pentilamino, hexilamino y 3-metilbutilamino Ejemplos de "*N,N*-(C_{1-4}alquil)$_2$amino" incluyen *N-N*-(metil)$_2$amino *N-N*-(etil)$_2$amino y *N*-etilo-*N*-metilamino Ejemplos de "*N,N*-(C_{1-6}alquil)$_2$amino" incluyen el ejemplo de "*N,N*-(C_{1-4}alquil)$_2$amino" y adicionalmente *N*-metil-*N*-pentilamino y *N,N*-(pentil)$_2$amino Ejemplos de "*N*-(C_{1-4}alquil)carbamoilo" son metilcarbamoilo y etilcarbamoilo Ejemplos de "*N*-(C_{1-4}alquil)carbamoilo" son los ejemplos de "*N*-(C_{1-4}alquil)carbamoilo" y adicionalmente pentilcarbamoilo, hexilcarbamoilo y 1,2-(metil)$_2$propilcarbamoilo Ejemplos de "*N,N*-(C_{1-4}alquil)$_2$carbamoilo" son *N,N*-(metil)$_2$carbamoilo, *N,N*-(etil)$_2$carbamoilo y *N*-metil-*N*-etilcarbamoilo Ejemplos de "*N,N*-C_{1-6}alquil)$_2$carbamoilo" son los ejemplos de "*N,N*-(C_{1-4}alquil)$_2$carbamoilo" y

adicionalmente *N*,*N*-(pentil)$_2$carbamoilo, *N*-metil-*N*-pentilcarbamoilo y *N*-etilo-*N*-hexilcarbamoilo. Ejemplos de "*N*-(C_{1-4}alquil)sulfamoilo" son *N*-(metil)sulfamoilo y *N*-(etil)sulfamoilo. Ejemplos de "*N*-(C_{1-6}alquil)sulfamoilo" son los ejemplos de "*N*-(C_{1-4}alquil)sulfamoilo" y adicionalmente *N*-pentilosulfamoilo, *N*-hexilosulfamoilo y 1,2-(metil)$_2$propilosulfamoilo. Ejemplos de "*N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo" son *N*,*N*-(metil)$_2$sulfamoilo, *N*,*N*(etil)$_2$sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo. Ejemplos de "*N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo" son los ejemplos de "*N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo" y adicionalmente *N*,*N*-(pentil)$_2$sulfamoilo, *N*-metil-*N*-pentilsulfamoilo y *N*-etilo-*N*-hexilsulfamoilo.

Ejemplos de "ciano(C_{1-4})alquilo" son cianometilo, cianoetilo y cianopropilo. Ejemplos de "C_{5-7}cicloalquilo" son ciclopentilo, ciclohexilo y cicloheptilo. Ejemplos de "C_{3-8}cicloalquilo" y "C_{3-7}cicloalquilo" incluyen "C_{5-7}cicloalquilo", ciclopropilo, ciclobutilo y ciclooctilo. Ejemplos de "C_{3-6}cicloalquilo" incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

El término "aminoC_{1-4}alquilo" incluye aminometilo, aminoetilo, aminopropilo, aminoisopropilo y aminobutilo. El término "aminoetilo" incluye 1-aminoetilo y 2-aminoetilo. El término "aminopropilo" incluye 1-aminopropilo, 2-aminopropilo y 3-aminopropilo y una convención análoga rige para términos como aminoetilo y aminobutilo.

Ejemplos de "C_{1-4}alcoxiC_{1-4}alcoxi" son metoximetoxi, etoximetoxi, etoxietoxi y metoxietoxi. Ejemplos de "hidroxiC_{1-4}alcoxi" son hidroxietoxi e hidroxipropoxi. Ejemplos de "hidroxipropoxi" son 1-hidroxipropoxi, 2-hidroxipropoxi y 3-hidroxipropoxi.

Ejemplos de "C_{1-4}alquiloS(O)$_b$ (donde b es 0, 1 o 2)", "C_{1-4}alquiloS(O)$_c$ (donde c es 0 a 2)", "C_{1-4}alquiloS(O)$_d$ (donde d es 0 a 2)", "C_{1-4}alquiloS(O)$_e$ (donde e es de 0 a 2)", y "C_{1-4}alquiloS(O)$_f$ (donde f es de 0 a 2)" independientemente incluyen metiltio, etiltio, propiltio, metanosulfinilo, etanosulfinilo, propanosulfinilo, mesilo, etanosulfonilo, propanosulfonilo e isopropanosulfonilo.

Ejemplos de "C_{3-6}cicloalquiloS(O)$_b$ (donde b es 0, 1 o 2)" incluyen ciclopropiltio, ciclopropilsulfinilo, ciclopropilsulfonilo, ciclobutiltio,

ciclobutilsulfinilo, ciclobutilsulfonilo, ciclopentiltio, ciclopentilsulfinilo y ciclopentilsulfonilo.

Ejemplos de "ariloS(O)$_b$ (donde b es 0, 1 o 2)" incluyen feniltio, fenilsulfinilo y fenilsulfonilo. Ejemplos de "benciloS(O)$_b$ (donde b es 0, 1 o 2)" incluyen bencilotio, bencilosulfinilo y bencilosulfonilo. Ejemplos de "heterociclilo S(O)$_b$ (donde b es 0, 1 o 2)" incluyen piridiltio, piridilsulfinilo, piridilsulfonilo, imidazoliltio, imidazolilsulfinilo, imidazolilsulfonilo, pirimidiniltio, pirimidinilsufinilo, pirimidinilsulfonilo, piperidiltio, piperidilsulfinilo y piperidilsulfonilo.

Ejemplos de "C_{1-6}alcoxicarbonilo" incluyen metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo. Ejemplos de "C_{1-6}alcoxicarbonilamino" incluyen metoxicarbonilamino, etoxicarbonilamino, *n*- y *t*-butoxicarbonilamino. Ejemplos de "C_{1-6}alquilsulfonilo-*N*-(C_{1-6}alquil)amino" incluyen metilsulfonilo-*N*-metilamino, etilsulfonilo-*N*-metilamino y propilsulfonilo-*N*-etilamino. Ejemplos de "C_{1-6}alquilsulfonilamino" incluyen metilsulfonilamino, etilsulfonilamino y propilsulfonilamino. Ejemplos de "C_{1-6}alcanoilamino" incluyen formamido, acetamido y propionilamino.

Donde se seleccionan radicales opcionales entre grupos "0, 1, 2 o 3", se debe entender que esta definición incluye todos los radicales que se están seleccionando entre uno de los grupos especificados o los radicales que se están seleccionando de dos o más de los grupos especificados. Una convención análoga rige para los radicales seleccionados entre los grupos "0, 1 o 2" y los grupos "1 o 2".

"Heterociclilo" es un anillo monocíclico saturado, parcialmente saturado o insaturado, opcionalmente sustituido conteniendo entre 5 y 7 átomos, de los cuales 1, 2, 3 o 4 átomos de los anillos se seleccionan entre nitrógeno, sulfuro u oxígeno, que pueden, salvo si se especifica en contrario, estar enlazados al carbono o al nitrógeno, donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)- y un anillo de átomos de sulfuro se puede oxidar opcionalmente para formar el S-óxido(s). Ejemplos y valores apropiados del término "heterociclilo" son morfolino, morfolinilo,

piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, dioxolanilo, tiadiazolilo, piperazinilo, isotiazolidinilo, triazolilo, tetrazolilo, pirrolidinilo, 2-oxazolidinonilo, 5-isoxazolonilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, 3-oxopirazolin-5-ilo, tetrahidropiranilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo y oxadiazolilo.

En forma apropiada, un "heterociclilo" es morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo y 1,2,4-oxadiazolilo

Es conveniente que el "heterociclilo" sea oxazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, tetrazolilo, tizoilo, tiadiazolilo, piridilo, imidazolilo, furilo, tienilo, morfolina, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo y piperazinilo.

Unos radicales opcionales apropiados para el "heterociclilo" como un anillo saturado o parcialmente saturado son 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi y C_{1-4}alquiloS$(O)_b$ (donde b es 0, 1 o 2). Otros radicales apropiados para el "heterociclilo como un anillo saturado o parcialmente saturado son 1, 2 o 3 radicales seleccionados independientemente entre fluoro, cloro, ciano, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo.

Unos radicales opcionales apropiados para el "heterociclilo" como un anillo insaturado son 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, nitro, amino, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}alquiloS$(O)_b$ (donde b es 0, 1 o 2), *N*-(C_{1-4}alquil)amino y *N*,*N*-(C_{1-4}alquil)$_2$amino. Otros radicales opcionales apropiados para el "heterociclilo" como un anillo insaturado son 1, 2 o 3 radicales

seleccionados independientemente entre fluoro, cloro, ciano, nitro, amino, metilamino, dimetilamino, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo.

Ejemplos de "(heterociclilo)C_{1-4}alquilo" son morfolinometilo, morfolinoetilo, morfolinoilometilo, morfolinoiloetilo, piperidinometilo, piperidinoetilo, piperidilometilo, piperidiloetilo, imidazolilometilo, imidazoliloetilo, oxazolilometilo, oxazoliloetilo, 1,3,4-oxadiazolilometilo, 1,2,4-oxadiazolilometilo, 1,2,4-oxadiazoliloetilo, piridilometilo, piridiloetilo, furilometilo, furiloetilo, (tienil)metilo, (tienil)etilo, pirazinilometilo, piraziniloetilo, piperazinilometil y piperaziniloetilo.

Ejemplos de "arilo" son fenilo y naftilo opcionalmente sustituidos.

Ejemplos de "arilo(C_{1-4})alquilo" son bencilo, fenetilo, naftilometilo y naftiloetilo.

Radicales opcionalmente apropiados para los grupos "arilo" son 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, nitro, amino, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}alquiloS(O)$_b$ (donde b es 0, 1 o 2), *N*-(C_{1-4}alquil)amino y *N*,*N*-(C_{1-4}alquil)$_2$amino. Otros radicales opcionales apropiados para los grupos "arilo" son 1, 2 o 3 radicales seleccionados independientemente entre fluoro, cloro, ciano, nitro, amino, metilamino, dimetilamino, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo

"Heteroarileno" es un diradical de un grupo heteroarilo. Un grupo heteroarilo es un anillo arilo monocíclico conteniendo de 5 a 7 átomos entre los cuales 1, 2, 3 o 4 átomos del anillo se seleccionan entre nitrógeno, sulfuro u oxígeno. Ejemplos de heteroarileno son oxazoliloeno, oxadiazoliloeno, piridiloeno, pirimidiniloeno, imidazoliloeno, triazoliloeno, tetrazoliloeno, piraziniloeno, piridaziniloeno, pirroliloeno, tienilocno y furilocno.

Radicales opcionalmente apropiados para los grupos heteroarilo, salvo si se definen en contrario, son 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, nitro, amino, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}alquiloS(O)$_b$ (donde b es 0, 1 o 2), *N*-(C_{1-4}alquil)amino y *N*,*N*-

$(C_{1-4}alquil)_2amino$. Otros radicales opcionales apropiados para los grupos "heteroarilo" son 1, 2 o 3 radicales seleccionados independientemente entre fluoro, cloro, ciano, nitro, amino, metilamino, dimetilamino, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo.

Los valores preferidos de A, Y, R^1, R^4, R^5, r y n son los siguientes. Estos valores se pueden emplear cuando sea apropiado con cualquiera de las definiciones, reivindicaciones, aspectos o incorporaciones definidos más arriba o a continuación.

En una incorporación de la invención, se disponen unos los compuestos de la fórmula (1), en una incorporación alterna se disponen unas sales farmacéuticamente aceptables de los compuestos de la fórmula (1), en otra incorporación alterna se disponen ésteres hidrolisables *in-vivo* de los compuestos de la fórmula (1) y en otra incorporación alterna se disponen sales farmacéuticamente aceptables ésteres hidrolisables *in-vivo* de los compuestos de la fórmula (1).

Ejemplos particulares de ésteres hidrolisables *in-vivo* de los compuestos fórmula (1) son aquellos ésteres de los compuestos de la fórmula (1) donde Y comprende un grupo conteniendo un grupo carboxi. Ésteres apropiados son aquellos descritos arriba para los grupos carboxi.

En un aspecto de la presente invención, se dispone un compuesto de fórmula (1) como se representa arriba donde Z es CH.

En otro aspecto de la invención, Z es nitrógeno.

En un aspecto de la presente invención, se dispone un compuesto de fórmula (1) como se representa arriba donde R^4 y R^5 son ambos $-S-C(R^6)=C(R^7)$.

En otro aspecto de la invención, R^4 y R^5 son ambos $-C(R^7)=(R^6)-S-$.

En aún otro aspecto de la invención, R^6 y R^7 se seleccionan independientemente entre hidrógeno, halo o C_{1-6}alquilo.

Preferiblemente R^6 y R^7 se seleccionan independientemente entre hidrógeno, cloro, bromo o metilo.

Particularmente R^6 y R^7 se seleccionan independientemente entre

hidrógeno o cloro.

Más particularmente uno de R^6 y R^7 es cloro.

En una incorporación, uno de R^6 y R^7 es cloro y el otro es hidrógeno.

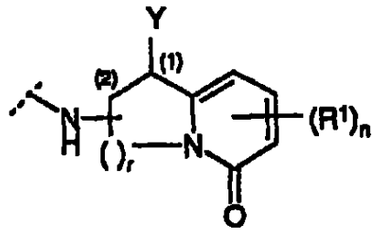
En otra incorporación, tanto R^6 como R^7 son cloro.

En un aspecto de la invención, A es fenileno.

En otro aspecto de la invención, A es heteroarileno.

Preferiblemente A se selecciona entre fenileno, piridiloeno, pirimidiniloeno, pirroliloeno, imidazoliloeno, triazoliloeno, tetrazoliloeno, oxazoliloeno, oxadiazoliloeno, tieniloeno y furiloeno.

En una incorporación, cuando A es heteroarileno, existe un nitrógeno en una posición de cabecera del puente. En otra incorporación, cuando A es heteroarileno, los heteroátomos no se encuentran en las posiciones de cabecera del puente. Se apreciará que la posición de cabecera del puente preferible (más estable) es como se muestra abajo:



En un aspecto de la invención, n es 0 o 1.

En un aspecto, preferiblemente n es 1.

En otro aspecto, preferiblemente n es 0.

Cuando n es 2, y los dos grupos R^1, junto con los átomos de carbono de A a los cuales están adheridos, forman un anillo de 4 a 7 miembros, conteniendo opcionalmente 1 o 2 heteroátomos seleccionados independientemente entre O, S y N, es conveniente que este anillo sea de 5- o 6- miembros conteniendo dos átomos O, (es decir un acetal cíclico). Cuando los dos grupos R^1 juntos forman el citado acetal cíclico, preferiblemente no se sustituyen. Más preferiblemente los dos grupos R^1 juntos son el grupo $-O-CH_2-O-$.

En otro aspecto de la presente invención, R^1 se selecciona entre halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo y C_{1-4}alcoxi.

En aún otro aspecto, R^1 se selecciona entre halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, $-S(O)_bC_{1-4}$alquilo (donde b es 0, 1 o 2), C_{1-4}alquilo y C_{1-4}alcoxi.

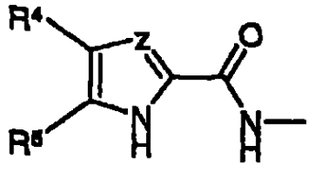
En aún otro aspecto, R^1 se selecciona entre halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, $-S(O)_bMe$ (donde b es 0, 1 o 2), metil y metoxi.

En aún otro aspecto, R^1 es C_{1-4}alquilo.

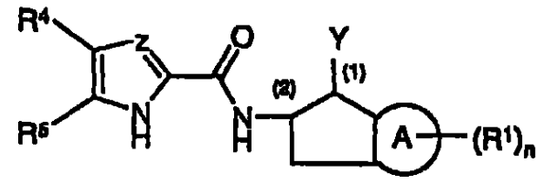
Preferiblemente R^1 se selecciona entre halo y C_{1-4}alcoxi.

En otra incorporación, preferiblemente R^1 se selecciona entre fluoro, cloro, metilo, etilo, metoxi y $-O-CH_2-O-$.

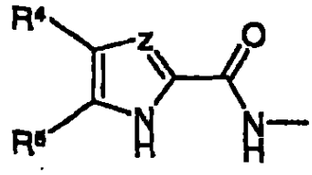
En un aspecto de la invención, r es 1 y cuando r es 1 el grupo



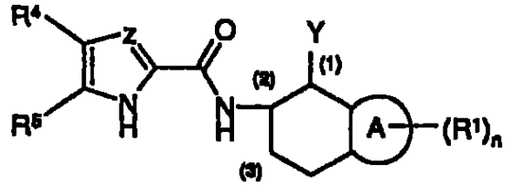
es un radical en el carbono (2) de manera que un ejemplo de cuando r es 1 es:



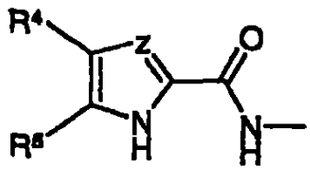
En otro aspecto de la invención, r es 2 y cuando r es 2 el grupo



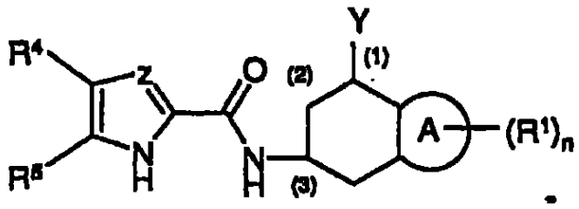
es un radical en el carbono (2) de manera que un ejemplo de cuando r es 2 es:



En otro aspecto de la invención, r es 2 y cuando r es 2 el grupo



es un radical en el carbono (3) de manera que un ejemplo de cuando r es 2 es:



En un aspecto de la invención, Y es $-NR^2R^3$.

En otro aspecto de la invención, Y es $-OR^3$.

Valores apropiados para R^2 y R^3 como un heterociclilo son morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo.

Unos valores más apropiados para R^2 y R^3 como un heterociclilo son piridilo, pirimidinilo e imidazolilo.

Otros valores apropiados para R^2 y R^3 como un heterociclilo son tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo.

En un aspecto de la invención, R^2 y R^3 se seleccionan independientemente entre grupos de las fórmulas B y B' como se describió más arriba.

En un aspecto de la invención, R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido

opcionalmente con 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales monocíclicos de 5- y 6-miembros y mono- y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), benciclo$S(O)_b$- (donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c(C_{1-4})$alquilo (donde c es 0, 1 o 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), $-C(=O)O^tBu$, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-

miembros, donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi.

Aún en otro aspecto de la invención, R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), -COR^8 y -SO_bR^8 (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o

2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -$CH_2COOR^{9'}$ -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, $R^{10'}$ y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi.

En otro aspecto de la invención, R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], -COR^8 y -SO_bR^8 (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro),

morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2 -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano).

En un aspecto, uno de R^9 y R^{10} es hidrógeno y el otro se selecciona entre heterociclilo y heterociclilo(C_{1-4}alquil). Es conveniente que R^9 o R^{10} como heterociclilo y heterociclilo(C_{1-4}alquil) se seleccionen entre oxazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, tetrazolilo, tiazoilo, tiadiazolilo, piridilo, imidazolilo, furilo, tienilo, morfolina, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, piperazinilo, morfolinometilo, morfolinoetilo, morfolinilometilo, morfoliniloetilo, piperidinometilo, piperidinoetilo, piperidilometilo, piperidiloetilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, imidazolilometilo, imidazoliloetilo, oxazolilometilo, oxazoliloetilo, 1,3,4-oxadiazolilometilo, 1,2,4-oxadiazolilometilo, 1,2,4-oxadiazoliloetilo, piridilometilo, piridiloetilo, furilometilo, furiloetilo, (tienil)metilo, (tienil)etilo, pirazinilometilo, piraziniloetilo, piperazinilometil y piperaziniloetilo;

Donde el anillo heterocíclico es sustituido opcionalmente en cualquier

átomo disponible y 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi y C_{1-4}alquiloS(O)$_b$ (donde b es 0, 1 o 2) y adicionalmente cuando el anillo heterociclilo es un anillo heteroarilo, otros radicales opcionalmente apropiados se seleccionan entre nitro, amino, *N*-(C_{1-4}alquil)amino y *N*,*N*-(C_{1-4}alquil)$_2$amino, y / o donde cualquier anillo heterocíclico se oxida opcionalmente de manera que un grupo -CH_2- sea reemplazado por un -C(O)- y / o un átomo de sulfuro de un anillo se oxida para formar el S-óxido(s).

En otro aspecto de la invención, R^2 se selecciona entre hidrógeno, acetilo y C_{1-4}alquilo.

En aún otro aspecto de la invención, Y es NR^2R^3 y NR^2R^3 forma un anillo de 4 a 7 miembros saturado, parcialmente saturado o insaturado, conteniendo opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados independientemente entre N, O y S, donde cualquier -CH_2- se puede reemplazar opcionalmente por -C(=O)-, y cualquier átomo N o S se puede oxidar opcionalmente para formar un N-óxido o un grupo SO o SO_2 respectivamente, y donde el anillo es sustituido opcionalmente por 1 o 2 radicales seleccionados independientemente entre halo, ciano, C_{1-4}alquilo, hidroxi, C_{1-4}alcoxi y C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2).

Valores apropiados para NR^2R^3 como un anillo de 4 a 7 miembros, son morfolino, 2,5-dioxomorfolino, piperidinilo, pirrolidinilo, pirazolilo, pirrolilo, imidazolilo, piperazinilo y tiomorfolinilo.

En aún otro aspecto de la invención, R^3 se selecciona entre hidrógeno, 1,3-dihidroxiisopropilo, 1,2-dihidroxipropilo, cianometilo, trifluorometilcarbonilo, carboxiacetilo, carboximetilo, formilo, acetilo, carbamoilacetilo, carbamoilometilo, metoxiacetilo, metoxipropanoilo, acetoxiacetilo, metanosulfonilo, clorometilsulfonilo, trifluorometilsulfonilo, morfolinometilcarbonilo, furilcarbonilo, tienilcarbonilo, nitrofurilcarbonilo, *N*,*N*-dimetilcarbamoilo, 4-metilpiperazinocarbonilo, *N*-etilcarbamoilo, *N*-allilcarbamoilo, *N*-dinitrofenilcarbamoilo, piridinilcarbonilo, tetrahidrofuran-2-on-5-ilcarbonilo, hidroxifenilcarbonilo, acriloilo, 2-(tert-butoxicarbonil) metilcarbonilo, aminoacetilo, 1-amino-1-carboxipropanoilo,

cloroacetilo, hidroxiacetilo, carbamoilacetilo, carbamoilometilo, metoxiacetilo, metoxipropanoilo, acetoxiacetilo, hidroxipiperidinoaminoacetilo, hidroxipirrolidinilaminoacetilo, *N*-metil-*N*-hidroxietilaminoacetilo, *N*-bencilo-*N*-hidroxietilaminoacetilo, *N*-(2,3-dihidroxipropil)-*N*-metilaminoacetilo, *N*,*N*-bis(hidroxietil)aminoacetilo, *N*,*N*-bis(hidroxipropil)aminoacetilo, (1-amino-1-carbonilamino)etilcarbonilo, 1-hidroxi-1-carboxietilcarbonilo, tert-butoxicarbonilmetilo, 1,3-dihidroxiisoprop-2-ilcarbonilo, 1-(tert-Butoxicarbonilamino)-1-(carbamoil) propanoilo, *N*-etilo-*N*-(2-hidroxietil)aminoacetilo, tienilometilo, tetrazolilometilo, [2-(etoxicarbonil)ciclopropil]metilo, *N*-(tert-butoxicarbonil)aminoacetilo y *N*-(aminocarbonil)-*N*-(tert-butoxicarbonil) aminoacetilo.

En aún otro aspecto de la invención, R^3 se selecciona entre trifluorometilcarbonilo, carboxiacetilo, formilo, acetilo, metanosulfonilo, morfolinometilcarbonilo, furilcarbonilo, tienilcarbonilo, nitrofurilcarbonilo, *N*,*N*-dimetilcarbamoilo, 4-metilpiperazinocarbonilo, *N*-etilcarbamoilo, *N*-allilcarbamoilo, *N*-dinitrofenilcarbamoilo, piridinilcarbonilo, tetrahidrofuran-2-on-5-ilcarbonilo, hidroxifenilcarbonilo, acrilooilo, 2-(tert-butoxicarbonil)metilcarbonilo, aminoacetilo, 1-amino-1-carboxipropanoilo, cloroacetilo, hidroxiacetilo, Carbamoilacetilo, carbamoilometilo, metoxiacetilo, metoxipropanoilo, acetoxiacetilo, *N*-metil-*N*-hidroxietilaminoacetilo, *N*-bencilo-*N*-hidroxietilaminoacetilo, *N*-(2,3-dihidroxipropil)-*N*-metilaminoacetilo, *N*,*N*-bis(hidroxietil)aminoacetilo, *N*,*N*-bis(hidroxipropil)aminoacetilo, (1-amino-1-carbonilamino)etilcarbonilo, 1-hidroxi-1-carboxietilcarbonilo, tert-butoxicarbonilmetilo, 1,3-dihidroxiisoprop-2-ilcarbonilo, 1-(tert-Butoxicarbonilamino)-1-(carbamoil) propanoilo y *N*-etilo-*N*-(2-hidroxietil)aminoacetilo.

Una clase preferida del compuesto es la de la fórmula (1) donde;

Z es CH;

R^4 y R^5 son ambos S-C(R^6)=C(R^7)-;

R^6 es halo o hidrógeno;

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R^7 es halo o hidrógeno;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi,

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), benciclo$S(O)_b$-(donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c(C_{1-4})$alquilo (donde c es 0, 1 o 2), -

$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), $-C(=O)O^tBu$, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por $-O-CH_2-O-$ para formar un acetal cíclico donde uno o ambos hidrógenos del grupo $-O-CH_2-O-$ se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea

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

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

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

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

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

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

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

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

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

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

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es CH;

R^4 y R^5 son ambos $-C(R^7)=C(R^6)-S-$;

R^6 es cloro;

R^7 es hidrógeno;

A es fenileno;

n es 0 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-}

$_4$alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), benciloS$(O)_b$-(donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (I) no sea:

i) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*] pirrol;

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es CH;

R^4 y R^5 son ambos -S-C(R^6)=C(R^7)-;

R^6 es cloro;

R^7 es hidrógeno o cloro;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo,

tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclioS(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-. -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es CH;

R^4 y R^5 son ambos S-C(R^6)=C(R^7)

R^6 es hidrógeno o halo;

R^7 es hidrógeno o halo;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

R es 1 o 2;

Y es $-OR^3$;

R^3 se selecciona entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

donde R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o

2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi,

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

Otra clase aún más preferida del compuesto es la de la fórmula (1) donde;

Z es CH;

R^4 y R^5 son ambos –$C(R^7)$=$C(R^6)$-S-;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, -SO_2Me y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), bencilo$S(O)_b$- (donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c(C_{1-4})$alquilo (donde c es 0, 1 o 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), $-C(=O)O^tBu$, C_{2-}

$_4$alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es CH;

R^4 y R^5 son ambos -C(R^7)=C(R^6)-S-;

R^6 es hidrógeno o halo;

R^7 es hidrógeno o halo;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

R es 1 o 2;

Y es $-OR^3$;

R^3 se selecciona entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4}alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})altilo, trihalo(C_{1-4})alquilo, hidroxiC_{1-4}alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono

por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclioS(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), $-C(=O)O^tBu$, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

siempre que el compuesto de fórmula (1) no sea:

2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*]pirrol.

Aún otra clase preferida del compuesto es la de la fórmula (1) donde;

Z es CH,

R^4 y R^5 son ambos $-C(R^7)=C(R^6)-S-$;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0

r es 1;

Y es $-NR^2R^3$;

R^2 es hidrógeno o C_{1-4}alquilo;

R^3 se selecciona entre C_{1-4}alquilo [sustituido opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$, y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Aún otra clase preferida del compuesto es la de la fórmula (1) donde;

Z es CH;

R^4 y R^5 son ambos -S-C(R^6)=C(R^7)-;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0;

r es 1;

Y es -NR^2R^3;

R^2 es hidrógeno o C_{1-4}alquilo;

R^3 se selecciona entre C_{1-4}alquilo [sustituido opcionalmente por 1 o 2 grupos R^8], -COR^8 y -SO_bR^8 (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2 -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$,- CH_2OR^9, (R^9)(R^{10})N-, -$COOR^9$, -CH_2COOR^9, -C(O)N(R^9)(R^{10}), -

$CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

siempre que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

Una clase preferida del compuesto es la de la fórmula (1) donde;

Z es nitrógeno;

R^4 y R^5 son ambos $-S-C(R^6)=C(R^7)-$;

R^6 es halo o hidrógeno;

R^7 es halo o hidrógeno;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi,

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), bencilo$S(O)_b$- (donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c(C_{1-4})$alquilo (donde c es 0, 1 o 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$,$-COOR^9$,$-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), $-C(=O)O^tBu$, C_{2-}

$_4$alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi, o el anillo se puede sustituir opcionalmente en los dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

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

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

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

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

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es nitrógeno;

R^4 y R^5 son ambos $-C(R^7)=C(R^6)-S-$;

R^6 es cloro;

R^7 es hidrógeno;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-}$

$_4$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$-(donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

ii) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*] pirrol;

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es nitrógeno;

R^4 y R^5 son ambos -S-C(R^6)=C(R^7)-;

R^6 es cloro;

R^7 es hidrógeno o cloro;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1

o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclioS(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es nitrógeno;

R^4 y R^3 son ambos -S-$C(R^6)$=$C(R^7)$-;

R^6 es hidrógeno o halo;

R^7 es hidrógeno o halo;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, -SO_2Me y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es -OR^3;

R^3 se selecciona entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], -COR^8 y -SO_bR^8 (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo,

dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Aún otra clase preferida del compuesto es la de la fórmula (1) donde;

Z es nitrógeno;

R^4 y R^5 son ambos -$C(R^7)$=$C(R^6)$-S-;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o

2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4}alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es nitrógeno;

R^4 y R^5 son ambos -$C(R^7)=C(R^6)$-S-;

R^6 es hidrógeno o halo;

R^7 es hidrógeno o halo;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, -SO_2Me y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es -OR^3;

R^3 se selecciona entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], -COR^8 y –SO_bR^8 (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-}

$_4$alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, ($R^9$)($R^{10}$)N-, -$COOR^9$, -$CH_2COOR^9$, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Aún otra clase preferida del compuesto es la de la fórmula (1) donde;

Z es nitrógeno;

R^4 y R^5 son ambos -$C(R^7)$=$C(R^6)$-S-;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0;

r es 1;

Y es $-NR^2R^3$;

R^2 es hidrógeno o C_{1-4}alquilo;

R^3 se selecciona entre C_{1-4}alquilo [sustituido opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4}alquilo, $-CO_2C_{1-4}$alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y dimetil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-}

$_4$alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);
o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Aún otra clase preferida del compuesto es la de la fórmula (1) donde;

Z es nitrógeno;

R^4 y R^5 son ambos –S-C(R^6)=C(R^7)-;

R^6 es halo;

R^7 es hidrógeno;

A es fenileno;

n es 0

r es 1;

Y es -NR^2R^3;

R^2 es hidrógeno o C_{1-4}alquilo;

R^3 se selecciona entre C_{1-4}alquilo [sustituido opcionalmente por 1 o 2 grupos R^8], -COR^8 y -SO_bR^8 (donde b es 0, 1 o 2);

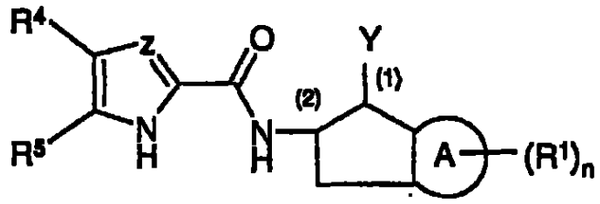
R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4}alquilo, -CO_2C_{1-4}alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por -C(O)OC_{1-4}alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo

(sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

En aún otro aspecto preferido de la invención se dispone un compuesto de la fórmula (1A):



(1A)

donde Z es CH;

R^4 y R^5 son ambos $-S-C(R^6)=C(R^7)-$ o $-C(R^7)=C(R^6)-S-$;

R^6 es hidrógeno o halo;

R^7 es hidrógeno o halo;

A es fenileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi,

Y es $-NR^2R^3$ o OR^3;

R^2 es hidrógeno o C_{1-4}alquilo;

R^3 se selecciona entre C_{1-4}alquilo [sustituido opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Aún otra clase preferida del compuesto es la de la fórmula (I) donde;

Z es CH;

R^4 y R^5 son ambos –S-C(R^6)=C(R^7)- o -C(R^7)=C(R^6)-S-;

R^6 es halo o hidrógeno;

R^7 es halo o hidrógeno;

A es heteroarileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, ciano, nitro, hidroxi, metilo, fluorometilo, difluorometilo, trifluorometilo, metoxi, -SMe, -SOMe, $-SO_2Me$ y, (cuando n es 2) metilenodioxi;

r es 1 o 2;

Y es $-NR^2R^3$ o $–OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-}

$_6$cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$ (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$C(O)N(R^9)(R^{10})$, -$CH_2CH(CO_2R^9)OH$, -$CH_2CONR^9R^{10}$, -$CH_2CH(NR^9R^{10})CO_2R^{9'}$ y -CH_2OCOR^9;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), -C(=O)O^{t}Bu, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH_2-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH_2-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi;

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Una clase preferida del compuesto es la de la fórmula (1) donde;

Z es CH;

R^4 y R^5 son ambos -S-$C(R^6)$=$C(R^7)$-;

R^6 es halo o hidrógeno;

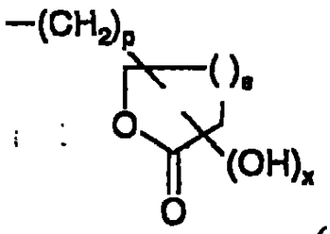
R^7 es halo o hidrógeno;

A es fenileno;

n es 1 o 2;

R^1 se selecciona independientemente entre hidrógeno, halo, ciano, nitro, hidroxi, fluorometilo, difluorometilo, trifluorometilo, C_{1-4}alcoxi y R^1 es de la

fórmula A' o A":



(A) $-CH_2CH(OH)(CH_2)_uCO_2H$ (A')

donde x es 0 o 1, p es 0, 1, 2 o 3 y s es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno;

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{5-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), ciano(C_{1-4})alquilo, fluorometilcarbonilo, difluorometilcarbonilo, trifluorometilcarbonilo, C_{1-4}alquilo [sustituido por 1 o 2 grupos R^8 (siempre que cuando haya 2 grupos R^8 no sean radicales en el mismo carbono)], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

{donde R^8 se selecciona independientemente entre hidrógeno, hidroxi, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, tetrahidrofurilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, morfolino, piridilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo, C_{2-4}alquenilo, ciclo(C_{3-8})alquilo, C_{1-4}alcoxi, ciano(C_{1-4})alquilo, amino(C_{1-4})alquilo (sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre hidrógeno, C_{1-4}alquilo,

hidroxi, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, arilo y arilo(C_{1-4})alquilo), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -$CH_2CH(CO_2R^9)N(R^9R^{10})$, -$CH_2OR^9$, $(R^9)(R^{10})N$-, -$COOR^9$, -CH_2COOR^9, -$CH_2CONR^9R^{10}$ y -$CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

[donde R^9 y R^{10} se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano) y C_{1-4}alquilo sustituido por R^{13};

(donde R^{13} se selecciona entre C_{1-4}alcoxi, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, tetrahidrofurilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, C_{1-4}alquiloS(O)$_d$(C_{1-4})alquilo (donde d es 0, 1 o 2)); y

R^9 y R^{10} pueden junto con el nitrógeno al cual están adheridos, formar un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados entre oxo, hidroxi, carboxi, halo, nitro, nitroso, ciano, isociano, amino, *N*-C_{1-4}alquilamino, *N*,*N*-(C_{1-4})$_2$alquilamino, carbonilo, sulfo, C_{1-4}alcoxi, heterociclilo, C_{1-4}alcanoilo, y C_{1-4}alquiloS(O)$_f$(C_{1-4})alquilo (donde f es 0, 1 o 2)]};

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

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

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

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

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

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

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

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

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

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

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

Otra clase preferida del compuesto es la de la fórmula (1) donde:

Z es CH;

R^4 y R^5 son ambos -C(R^7)=C(R^6)-S-;

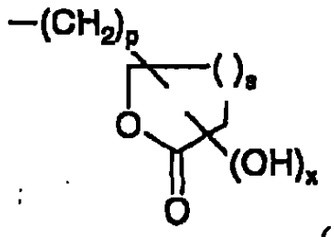
R^6 es cloro;

R^7 es hidrógeno;

A es fenileno;

n es 1 o 2;

R^1 se selecciona independientemente entre hidrógeno, halo, nitro, hidroxi, C_{1-4}alquilo, C_{1-4}alcoxi y R^1 es de la fórmula A' o A":



(A) $-CH_2CH(OH)(CH_2)_uCO_2H$ (A')

donde x es 0 o 1, p es 0, 1, 2 o 3 y s es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno;

r es 1 o 2;

Y es $-NR^2R^3$ o $-OR^3$;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{5-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), ciano(C_{1-4})alquilo, fluorometilcarbonilo, difluorometilcarbonilo, trifluorometilcarbonilo, C_{1-4}alquilo [sustituido por 1 o 2 grupos R^8 (siempre que cuando haya 2 grupos R^8 no sean radicales en el mismo carbono)], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 ó 2);

{donde R^8 se selecciona independientemente entre hidrógeno, hidroxi, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, tetrahidrofurilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, C_{1-4}alquilo, C_{2-4}alquenilo, ciclo(C_{3-8})alquilo, C_{1-4}alcoxi, ciano(C_{1-4})alquilo, amino(C_{1-4})alquilo (sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre hidrógeno, C_{1-4}alquilo, hidroxi, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, arilo y arilo(C_{1-4})alquilo), C_{1-4}alquiloS(O)$_c$(C_{1-}

$_4$)alquilo (donde c es 0, 1 o 2), $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$ y $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, $-CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

[donde R^9 y R^{10} se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{5-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi siempre que cuando haya 2 grupos hidroxi no sean radicales en el mismo carbono), C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano) y C_{1-4}alquilo sustituido por R^{13};

(donde R^{13} se selecciona entre C_{1-4}alcoxi, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, tetrahidrofurilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, C_{1-4}alquiloS(O)$_d$(C_{1-4})alquilo (donde d es 0, 1 o 2)); y

R^9 y R^{10} pueden junto con el nitrógeno al cual están adheridos, formar un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados entre oxo, hidroxi, carboxi, halo, nitro, nitroso, ciano, isociano, amino, *N*-C_{1-4}alquilamino, *N*,*N*-(C_{1-4})$_2$alquilamino, carbonilo, sulfo, C_{1-4}alcoxi, heterociclilo, C_{1-4}alcanoilo, y C_{1-4}alquiloS(O)$_f$(C_{1-4})alquilo (donde f es 0, 1 o 2)]};

o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos;

con la salvedad de que el compuesto de fórmula (1) no sea:

i) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-

b]pirrol;

En otro aspecto de la invención, los compuestos preferidos de la invención son cualquiera de:

2,3-dicloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*R*,2*R*)-1-{[(metiloxi)acetil]amino}-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-Butoxicarbonilamino-3-carbamoilpropanoil] amino}-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il] acetil}amino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]-pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[(2-acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[(2-carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{ (1*R*,2*R*)-1-[(trifluoroacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(furan-2-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(furan-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(3-tienilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(5-nitrofuran-2-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(piridin-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*S*,2*S*)-1-(acriloilamino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-

tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(3-hidroxifenil)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-[(1*S*,2*S*)-1-(acetilamino)-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-[(1*S*,2*S*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(dimetilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(4-metilpiperazina-1-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(etilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(prop-2-en-1-ilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-[(1*S*,2*S*)-1-({[(3,5-dinitrofenil)amino]carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-[(1*S*,2*S*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoilpropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-(1*R*,2*R*)-1-[((3*R*)-3-carboxi-3-hidroxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*S*,2*S*)-1-[metil(morfolin-4-ilacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-(1*R*,2*R*)-1-[(tert-butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-

2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-(carboximetilamino)-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-(1*R*,2*R*)-1-[*N*-acetilo-*N*-(carboximetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[acetil(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[*N*-(carboximetil)-*N*-(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2-cloro-*N*-[(1*R*,2*R*)-1-({[(2*S*)-5-oxotetrahidrofuran-2-il]carbonil}amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno [2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-[(metoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-(Acetilamino)-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno [2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-[(2-acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*S*,2*S*)-1-{[(2(*S*)-2-(*tert*-Butoxicarbonilamino)-2-Carbamoilacetil]amino}-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*S*,2*S*)-1-[(2-(*tert*-Butoxicarbonilamino)Acetilamino}-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-[2-Carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[2-(tert-butoxicarbonil)Acetilamino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-{[3-hidroxi-2-(hidroximetil)propanoil]amino}-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

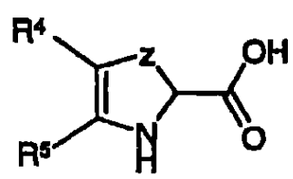
N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoilpropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-(1*R*,2*R*)-1-[(aminoacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2-cloro-*N*-[(1*R*,2*R*)-1-({[(2-hidroxietil)(fenilmetil)amino]acetil}amino) -2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2-cloro-*N*-{(1*R*,2*R*)-1-[(morfolin-4-ilacetil)amino-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2-cloro-*N*-((1*R*,2*R*)-1-({[(2-hidroxietil)(metil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-((1*R*,2*R*)-1-({[bis(2-hidroxietil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2-cloro-*N*-((1*R*,2*R*)-1-({[etil(2-hidroxietil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2-cloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihidroxipropil)(metil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-((1*R*,2*R*)-1-({[bis(2-hidroxipropil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-[(1*R*,2*R*)-1-[(tert-butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-(carboximetilamino)-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2-cloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetilamino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[((3*S*)-3-amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

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N-{(1*R*,2*R*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[((3*S*)-3-amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

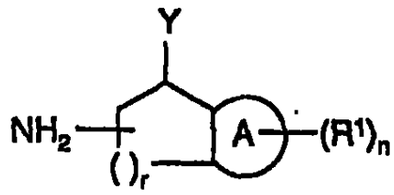
En otro aspecto de la invención, otros compuestos aún más preferidos de la invención son uno cualquiera de:
2-cloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetilamino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos.

Otro aspecto de la presente invención dispone un proceso para preparar un compuesto de la fórmula (1) o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* del mismo, proceso en el cual (donde A, Y, R^1, R^4, R^5, r y n son, salvo si se especifica en contrario, como se definen en la fórmula (1)) que consiste en:
a) hacer reaccionar un ácido de la fórmula (2):



(2)

o un derivado activo del mismo, con una amina de fórmula (3):



(3)

y posteriormente, si es necesario:

i) convertir un compuesto de la fórmula (1) en otro compuesto de la fórmula (1);

ii) retirando cualesquiera grupos de protección;

iii) formando una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo*.

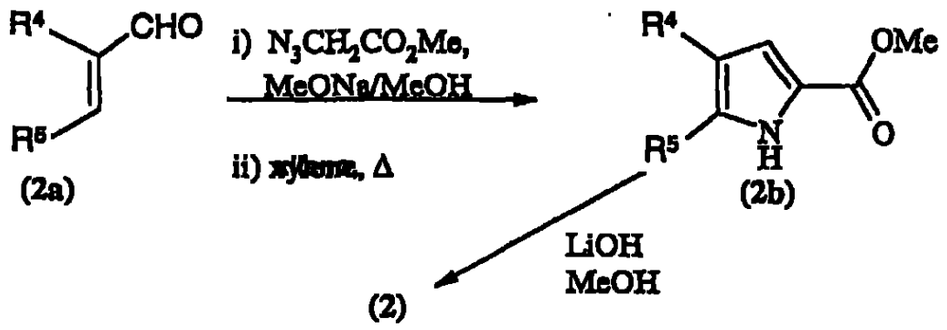
Las condiciones específicas para la reacción descrita arriba son las siguientes:

Proceso a) Se pueden agrupar ácidos de la fórmula (2) y aminas de la fórmula (3) en presencia de un reactivo de asociación apropiado. Se pueden emplear unos reactivos de peptidas estándar de asociación conocidos en el arte, o por ejemplo carbonilodiimidazole, clorhidrato de 1-etilo-3-(3-dimetilaminopropil)carbodi-imida (EDCI) y diciclohexilo-carbodiimida (DCCI), opcionalmente en presencia de un catalizador como 1-hidroxibenzotriazole, dimetilaminopiridina o 4-pirrolidinopiridina, opcionalmente en presencia de una base por ejemplo trietilamina, di-isopropiletiloamina, piridina, o 2,6-di-*alquilo*-piridinas tales como 2,6-lutidina o 2,6-di-*tert*-butilpiridina. Unos solventes apropiados incluyen dimetilacetamida, diclorometano, benceno, tetrahidrofurano y dimetilformamida. La reacción de asociación se puede efectuar en forma conveniente a una temperatura en el rango entre -40 a 40°C.

Unos derivados activados de ácidos apropiados incluyen haluros de ácidos, por ejemplo cloruros de ácido y ésteres activos, por ejemplo pentafluorofenilo ésteres. La reacción de estos tres tipos de compuestos con aminas es muy conocida en el arte, por ejemplo se pueden hacer reaccionar en presencia de una base, tal como las que se describieron arriba, y en un solvente apropiado, como los que se describieron arriba. La reacción se

puede efectuar en forma conveniente a una temperatura en el rango entre -40 a 40°C.

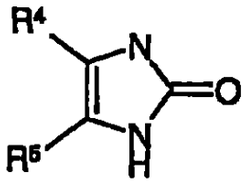
Se pueden preparar compuestos de la fórmula (2) donde Z es CH de acuerdo con el Esquema 1:



Esquema 1

Los compuestos de la fórmula (2a) están disponibles en el comercio o son compuestos conocidos, o se preparan mediante procesos conocidos en el arte.

Se puede preparar un compuesto de la fórmula (2) donde X es nitrógeno, a partir de un compuesto de la fórmula (4):

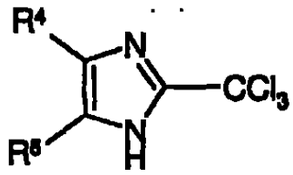


(4)

convirtiendo en primer lugar el grupo oxo a cloro o bromo por medio de un agente halogenante como $POCl_3$ o $POBr_3$, en un solvente orgánico inerte como el diclorometano en un rango de temperatura de temperatura ambiente hasta reflujo (por ejemplo consultar *Nucleic Acid Chem.* 1991, 4, 24-6), posteriormente desplazando el grupo de cloro o bromo con cianuro usando una sal de cianuro como cianuro de potasio, en un solvente orgánico inerte tal como tolueno, benceno o xiloeno, opcionalmente en presencia de un catalizador tal como un 18-crown-6 (por ejemplo consultar *J. Heterocycl. Chem* 2000, 37(1), 119-126) y finalmente hidrolizando el grupo ciano a un grupo carboxi, con por ejemplo, un ácido acuoso como un cloruro de hidrógeno acuoso (por ejemplo consultar *Chem. Pharm. Bull.* 1986, 34(9),

3635-43).

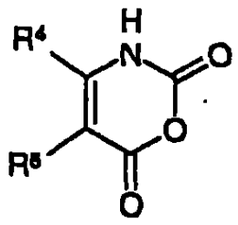
Alternativamente se puede formar un compuesto de la fórmula (2) donde X es nitrógeno, al hacer reaccionar el compuesto de la fórmula (4) con $(Cl_3CCO)_2O$ y Cl_3CCO_2H en presencia de cloruro de magnesio empleando Cl_3CCO_2H como solvente, para formar un compuesto de la fórmula (5):



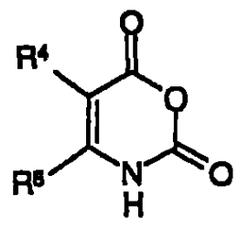
(5)

y luego hidrolizando el compuesto de la fórmula (5), utilizando por ejemplo, dióxido de sodio acuoso, a un rango de temperatura de temperatura ambiente a reflujo (por ejemplo consultar *J Heterocycl. Chem.* 1980, 17(2), 381-2).

El compuesto de la fórmula (4) se puede preparar a partir de un compuesto de las fórmulas (6) y (7) utilizando condiciones conocidas para el reordenamiento Curtius (*Tetrahedron* 1999, 55, 6167):

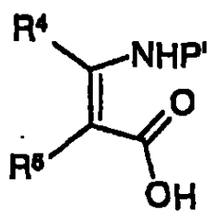


(6)

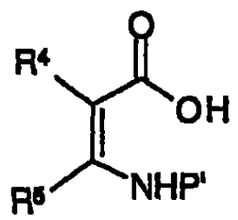


(7)

Los compuestos de las fórmulas (8) y (9):



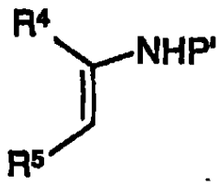
(8)



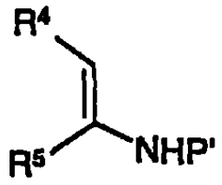
(9)

se transforman en compuestos de las fórmulas (6) y (7) respectivamente. Esta transformación ocurre en forma espontánea, o puede ser inducida por un ácido o por una base.

Se pueden preparar compuestos de las fórmulas (8) y (9) introduciendo un grupo carboxi en un compuesto de la fórmula (10) u (11):



(10)



(11)

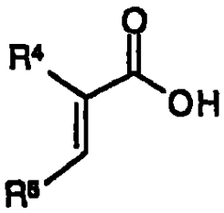
donde P' es un grupo de protección amino como el butoxicarbonilo.

Se introduce un grupo carboxi en el compuesto de la fórmula (10) u (11) haciendo reaccionar un reactivo alquilo de litio tal como n-butilo litio, en un solvente orgánico inerte tal como THF, a baja temperatura, por ejemplo en el rango entre -10°C y -78°C y luego se forma el compuesto de la fórmula (8) o (9) según lo apropiado, bien sea al

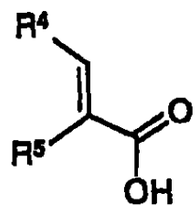
a) hacer reaccionar el compuesto resultante con el dióxido de carbono; o al

b) hacerlo reaccionar con DMF en el rango de temperatura entre -10°C y la temperatura ambiente para formar el respectivo aldehído y oxidando el aldehído a un carboxi con unos reactivos estándar para obtener el compuesto de la fórmula (8) o (9).

Se pueden preparar compuestos de la fórmula (10) y (11) a partir de un compuesto de las fórmulas (12) y (13)



(12)



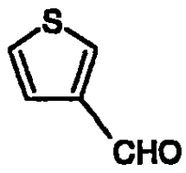
(12)

utilizando condiciones conocidas para la reacción Curtius.

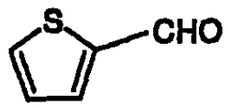
Se pueden preparar compuestos de las fórmulas (12) y (13) oxidando el respectivo aldehído empleando unos reactivos de oxidación estándar como el manganato de potasio o el periodato de sodio.

Se puede preparar el precursor del aldehído de un compuesto de la

fórmula (12) o (13) empleando técnicas estándar conocidas en el arte. Por ejemplo, se pueden preparar muchos compuestos de la fórmula (12) o (13) introduciendo el R^6 y el R^7 adecuado en un compuesto de la fórmula (14) o (15) según lo apropiado:



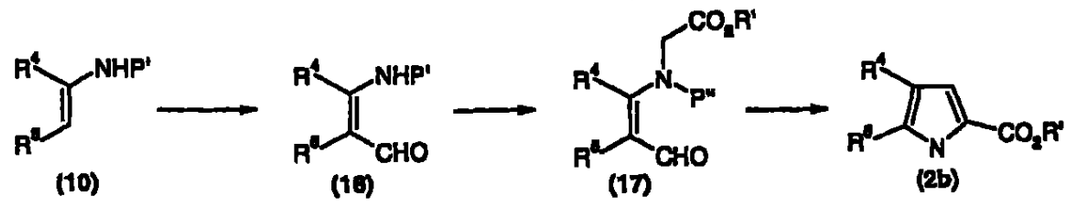
(14)



(15)

Por ejemplo, cuando R^6 y R^7 son ambos cloro, se puede clorar un compuesto de la fórmula (14) o (15) con un agente de clorado como el cloro en presencia de cloruro de aluminio o cloruro de hierro (III), en un solvente orgánico inerte clorado como el diclorometano o 1,2-dicloroetano, seguido por el tratamiento con una base acuosa tal como el hidróxido de sodio acuoso. El compuesto mono clorado se puede formar de la misma manera.

También se pueden preparar los compuestos de la fórmula (2b) como se ilustra en el Esquema 2:

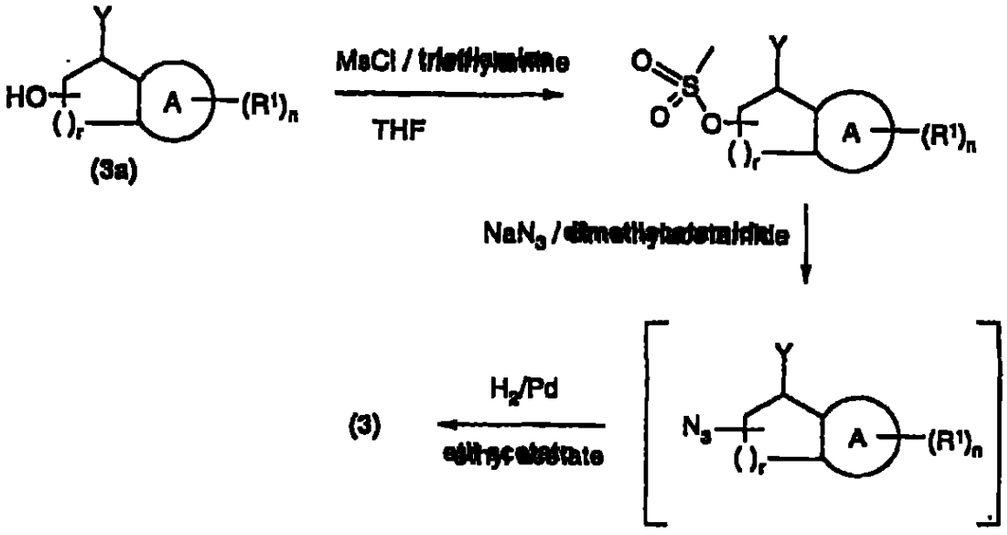


Esquema 2

La conversión de los compuestos de la fórmula (10) a los compuestos de la fórmula (16) se puede efectuar por medio de unas reacciones de orto litiación dirigidas (J. Org. Chem, 2001, volumen 66, 3662-3670), por ejemplo con n-butilo litio y $(CHO)N(alquil)_2$. El grupo de protección P' en los compuestos de la fórmula (10) deben ser unos grupos de dirección apropiados para esta reacción y pueden ser por ejemplo CO_2tBu. La reacción de los compuestos de la fórmula (16) con LCH_2CO_2R donde L es un grupo de residuos y el reemplazo del grupo de protección P' con un P" alterno (por ejemplo -COalquilo) de acuerdo con procesos convencionales, produce un compuesto de la fórmula (17). Estos se pueden convertir en un ciclo empleando una base, por ejemplo carbonato de potasio o metóxido de

sodio.

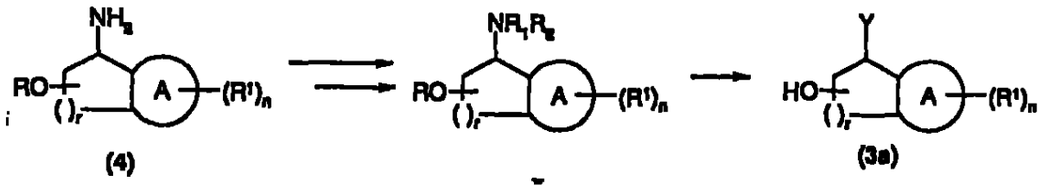
Los compuestos de la fórmula (3) donde Y es OR^3 están disponibles en el comercio o son compuestos conocidos o que se preparan mediante unos procesos conocidos en el arte. Cuando Y es NR^2R^3, las aminas de fórmula (3) se pueden preparar de acuerdo con el Esquema 3:



Esquema 3

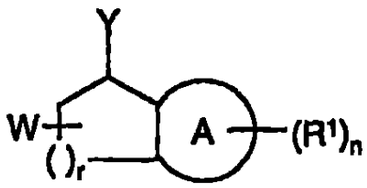
Los compuestos de la fórmula (3a) están disponibles en el comercio o son compuestos conocidos o que se preparan mediante unos procesos conocidos en el arte. Por ejemplo, partiendo de las aminas primarias de la fórmula (4), en las cuales R es H o un grupo de protección apropiado, uno o ambos de R^1 y / o R^2 se pueden introducir mediante acilación, (por ejemplo haciéndolo reaccionar con ácido acetoxiacético e hidrocloruro 1-(3-dimetilaminopropil)-3-etilo-carbodiimida -EDAC), alquiloación, alquiloación reductiva, sulfonación o procesos relacionados seguidos por una O-desprotección cuando sea lo indicado. Alternativamente, uno o ambos de R^1 y / o R^2 se pueden obtener por medio de la modificación de la funcionalidad en los grupos previamente introducidos así, por reducción, oxidación, hidrólisis (por ejemplo la conversión de un grupo acetoxi a un grupo hidroxi), el desplazamiento nucleofílico, la amidación o un proceso relacionado o una combinación de estos procesos seguida por una O-desprotección cuando sea lo apropiado. Se apreciará que dichas modificaciones pueden incluir modificaciones que convierten un compuesto

de la fórmula (1) a otro compuesto de la fórmula (1).



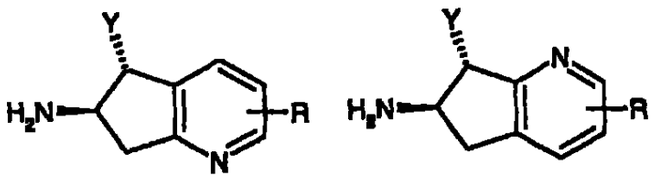
(4) (3a)

Alternativamente se pueden obtener aminas de la fórmula (3) aplicando los procesos descritos para la preparación de los compuestos de la fórmula (3a) a los compuestos de la fórmula (20) en la cual W es NH_2 o un átomo de nitrógeno con uno o dos grupos de protección apropiados.



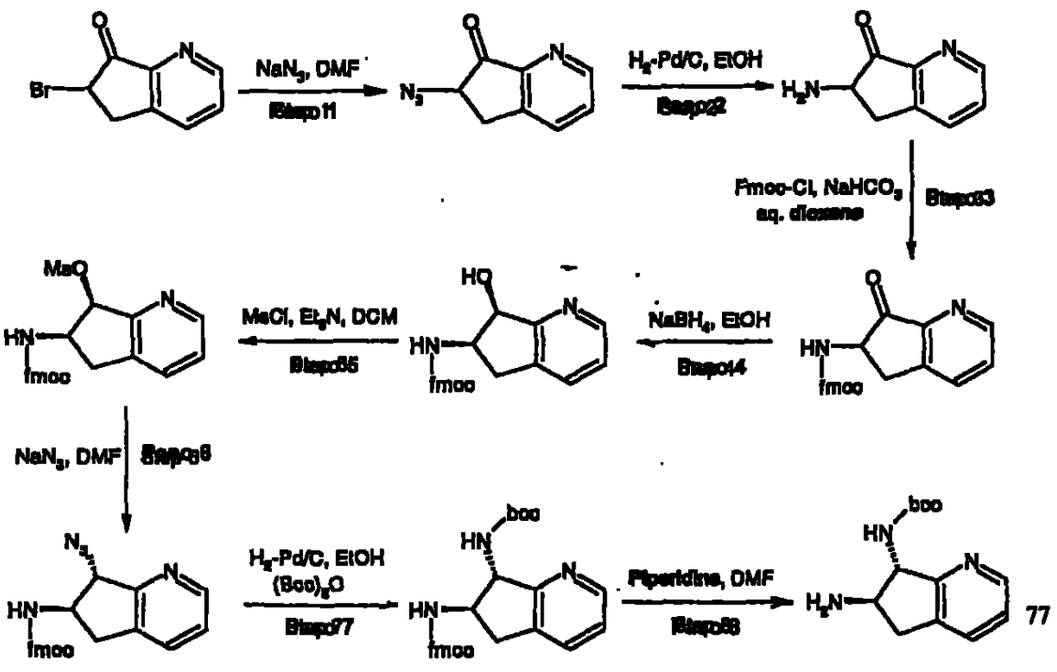
(20)

Se pueden preparar los compuestos de la fórmula (3) donde r=1 y donde A es heteroarileno a partir de heterociclos fusionados de un cicloalquilo apropiadamente funcionalizados. Por ejemplo, cuando A es piridina,



(3b) (3c)

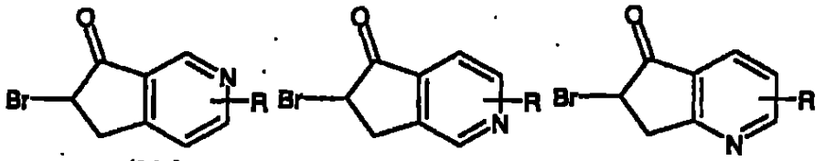
los compuestos de las fórmulas (3b) y (3c) se pueden preparar a partir del respectivo regioisómero de pirindinona de acuerdo con el Esquema 4:-



Esquema 4

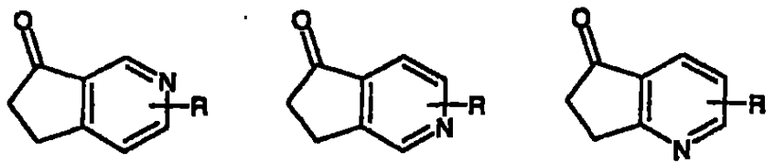
El Paso 1 se efectúa sobre un compuesto conocido en la literatura (*Jpn Kokai Tokkyo Koho*, 1995, 14. JP 07070136). Los pasos 2, 3, 4, 5, 6, 7 y 8 se siguen mediante unas técnicas estándar conocidas en el arte.

Se apreciará que los isómeros de bromopirindinona (21a, 21b y 21c) podrían



(21a) (21b) (21c)

convertirse a la respectiva versión heterocíclica (3) por los medios descritos en el Esquema 4. Se pueden preparar las bromopirindinonas a partir de la respectiva pirindinona por técnicas estándar conocidas en el arte. Las pirindinonas (22a, 22b, 22c) se conocen en la literatura o se preparan mediante procesos conocidos en el arte.



(22a) (22b) (22c)

Los procesos descritos arriba y que se muestran en el Esquema 4 también se pueden aplicar a otros heterociclos de seis miembros conteniendo más de un nitrógeno.

Se apreciará que en forma similar, los compuestos de la fórmula (3), donde A es heteroarileno conteniendo un nitrógeno de cabecera de puente se pueden preparar a partir de los heterociclos fusionados de un cicloalquilo apropiadamente funcionalizados.

Se apreciará que los procesos descritos arriba para la formación y modificación de Y como NR^1R^2 se pueden aplicar en forma similar bien sea para obtener el compuesto de la fórmula (3) antes de la asociación al ácido de la fórmula (2) o al producto de la citada asociación.

Se apreciará que algunos de los diferentes anillos de radicales en los compuestos de la presente invención, por ejemplo R^1 se pueden introducir

por medio de unas reacciones estándar de sustitución aromática o se pueden generar por modificaciones de los grupos funcionales convencionales antes o inmediatamente después de los procesos citados arriba, y como tal se incluyen en el proceso aspecto de la invención. Estas reacciones pueden convertir un compuesto de la fórmula (1) en otro compuesto de la fórmula (1). Estas reacciones y modificaciones incluyen por ejemplo, la introducción de un radical por medio de una reacción de sustitución aromática, de una reducción de radicales, la alquiloación de radicales y la oxidación de radicales. Los reactivos y las condiciones de la reacción para estos procesos son muy conocidos en el arte de la química. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro empleando ácido nítrico concentrado, la introducción de un grupo acilo, empleando por ejemplo un haluro acilo y ácido Lewis (como el tricloruro de aluminio) bajo condiciones Friedel Crafts; la introducción de un grupo alquilo usando un haluro alquilo y ácido Lewis (como el tricloruro de aluminio) bajo condiciones Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro a un grupo amino por ejemplo la hidrogenación catalítica con un catalizador de níquel o el tratamiento con hierro en presencia de ácido clorhídrico con calentamiento; oxidación de alquilotio a alquilosulfinilo o alquilsulfonilo.

Igualmente se apreciará que en algunas de las reacciones citadas en la presente, puede ser necesario / deseable proteger cualquier grupo sensible en los compuestos. Las instancias donde la protección es necesaria o deseable y para aquellos con destreza en el arte que conocen unos métodos de protección apropiados, se pueden emplear grupos de protección convencionales de conformidad con prácticas estándar (para ilustración, consultar T.W. Green, Protective Groups in Organic Synthesis, John Wiley y Sons, 1991). Por lo tanto, si los reactantes incluyen grupos como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones aquí citadas.

Un grupo de protección apropiado para un grupo amino o alquilamino

es por ejemplo un grupo acilo, por ejemplo un grupo alcanoilo como acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilometoxicarbonilo por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección de los grupos de protección citados arriba necesariamente varían según el grupo de protección elegido. Así por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo se puede retirar por ejemplo, por hidrólisis con una base apropiada tal como un hidróxido metal alcalino, por ejemplo hidróxido de litio o de sodio. Alternativamente se puede retirar un grupo acilo tal como un grupo *t*-butoxicarbonilo, por ejemplo por el tratamiento con un ácido apropiado como el ácido clorhídrico, sulfúrico o fosfórico o un ácido trifluoroacético y un grupo arilometoxicarbonilo como un grupo benciloxicarbonilo se puede retirar, por ejemplo, por hidrogenación sobre un catalizador como paladio en carbono o por el tratamiento con un ácido Lewis por ejemplo boron tris(trifluoroacetato). Un grupo de protección alterno para un grupo amino primario es por ejemplo un grupo ftaloilo que se puede retirar para ser tratado con una alquiloamina, por ejemplo dimetilaminopropilamina o con hidrazina.

Un grupo de protección 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 arilometilo, por ejemplo bencilo. Las condiciones de desprotección para los anteriores grupos de protección necesariamente varían según el grupo de protección elegido. Así por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo se puede retirar por ejemplo, por hidrólisis con una base apropiada tal como un hidróxido metal alcalino, por ejemplo hidróxido de litio o de sodio. Alternativamente se puede retirar un grupo arilometilo como un grupo bencilo por ejemplo, por hidrogenación sobre un catalizador como paladio en carbono.

Un grupo de protección apropiado para un grupo carboxi es por ejemplo, un grupo de esterificación por ejemplo un grupo metilo o etilo que

se puede retirar por ejemplo por hidrólisis con una base como el hidróxido de sodio, o por ejemplo un grupo *t*-butilo que se puede retirar por ejemplo, por el tratamiento con un ácido, por ejemplo un ácido orgánico como el ácido trifluoroacético, o por ejemplo un grupo bencilo que se puede retirar por ejemplo por hidrogenación sobre un catalizador como paladio en carbono.

Los grupos de protección se pueden retirar en cualquier momento en la síntesis cuando sea conveniente, empleando unas técnicas convencionales bien conocidas en el arte de la química.

Ciertos intermedios en la preparación de un compuesto de la fórmula (1) son novedosos y componen otro aspecto de la invención.

Como ya se manifestó anteriormente, los compuestos definidos en la presente invención poseen una actividad inhibidora de glucógeno fosforilasa. Esta propiedad se puede evaluar por ejemplo usando el procedimiento descrito a continuación.

Análisis

La actividad de los compuestos se determina al medir el efecto de inhibición de los compuestos en la dirección de la síntesis de glucógeno, la conversión de glucosa-1-fosfato a glucógeno con la liberación de fosfato inorgánico, como se describe en EP 0 846 464 A2. Las reacciones se desarrollaron en formatos de microplacas de 96 pozos en un volumen de 100µl. El cambio en la densidad óptica debido a la formación de fosfato inorgánico se midió a 620nM en un Lector MF de Labsystems iEMS por el método general (Nordlie R.C y Arion W.J, Methods of Enzymology, 1966, 619-625). La reacción es en 50mM de HEPES (N-(2-Hidroxietil)piperazina-N'-(2-ácido etanosulfónico); 4-(2-Hidroxietil)piperazina-1- ácido etanosulfónico), 2.5mM de $MgCl_2$, 2.25mM de etilenglicol-bis(b-aminoetilo éter) *N,N,N',N'*-ácido tetraacético, 100mM de KCl, 2mM de D-(+)-glucosa pH 7.2, conteniendo 0.5mM de ditiotreitol, la solución amortiguadora del análisis, con 0.1mg de glucógeno tipo III, 0.15ug de glucógeno fosforilasa *a* (GF*a*) de músculo de conejo y 0.5mM de glucosa-1-fosfato. El GF*a* se incuba previamente en la solución

amortiguadora del análisis con el glucógeno tipo III a 2.5 mg ml^{-1} durante 30 minutos. Se agregan 40µl de la solución de la enzima a 25µl de la solución amortiguadora del análisis y se inicia la reacción con la adición de 25µl 2mM de glucosa-1-fosfato. Los compuestos que se van a ensayar se preparan en 10µl al 10% de DMSO en una solución amortiguadora del análisis, con una concentración final al 1% de DMSO en el análisis. La actividad no inhibida del GF*a* se mide en presencia de 10µl al 10% de DMSO en la solución amortiguadora del análisis y la inhibición máxima medida en presencia de 30µM de CP320626 (Hoover y colaboradores (1998) J Med Chem 41, 2934-8; Martin y colaboradores (1998) PNAS 95, 1776-81). La reacción se detiene después de 30 min. con la adición de 50µl de una solución acídica de amonio molibdato, 12ug ml^{-1} al 3.48% de H_2SO_4 con 1% de sulfato de sodio laurilo y 10ug ml^{-1} de ácido ascórbico. La absorbencia se mide después de 30 minutos a temperatura ambiente a 620nm.

El análisis se efectúa a una concentración de inhibidor de 10µM o 100µM. Los compuestos que muestran una inhibición significativa en una o en ambas concentraciones se pueden evaluar posteriormente empleando un rango de concentraciones de prueba de inhibidor para determinar un IC_{50}, una concentración esperada para inhibir la reacción de la enzima por 50%.

La actividad se calcula como sigue:-

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

OD620 = densidad óptica a 620nM.

Los valores típicos de IC_{50} para los compuestos de la invención cuando se ensayaron en el análisis anterior están en el rango de 100µM a 1nM.

La actividad de los compuestos se determina alternativamente midiendo el efecto de inhibición de los compuestos en la degradación de glucógeno, la producción de glucosa-1-fosfato de glucógeno se monitorea por medio del análisis asociado a multienzimas, 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 desarrollaron en un formato de microplacas de 384 pozos a un volumen de 50µl. El cambio de la fluorescencia debido a la conversión del co-factor NAD a NADH se mide a 340nM de excitación, 465nm de emisión en un Lector de Microplacas Multifuncional Tecan Ultra. La reacción es a 50mM de HEPES, 3.5mM de KH_2PO_4, 2.5mM de $MgCl_2$, 2.5mM de etilenglicol-bis(b-aminoetilo éter) *N,N,N',N'*- ácido tetraacético, 100mM de de KCl, 8mM D-(+)-glucosa pH 7.2, conteniendo 0.5mM de ditiotreitol, la solución amortiguadora del análisis. El glucógeno fosforilasa humano recombinante del hígado se pre-incuba a (hrl GP*a*) 20nM en una solución amortiguadora del análisis con 6.25mM de NAD, 1.25mg de glucógeno tipo III a 1.25 mg ml^{-1} el reactivo de la solución amortiguadora durante 30 minutos. Se preparan las enzimas de asociación, fosfoglucomutasa y glucosa-6-fosfato dehidrogenasa (Sigma) en el reactivo de la solución amortiguadora, una concentración final de 0.25 unidades por pozo. Se agregan 20µl de la solución hrl GFa a 10µl de la solución del compuesto y se comienza la reacción con la adición de 20ul de la solución de la enzima de asociación. Se preparan los compuestos que se van a ensayar en 10µl al 5% de DMSO en la solución amortiguadora del análisis, con una concentración final al 1% de DMSO en el análisis. La actividad no inhibida del GF*a* se mide en presencia de 10µl al 5% de DMSO en la solución amortiguadora del análisis y la inhibición máxima medida en presencia de 5mgs ml^{-1} de N-etilmaleimida. Después de 6 horas a 30°C se midieron las Unidades Relativas de Fluorescencia (URFs) a 340nM de excitación, 465nm de emisión.

El análisis se efectúa a una concentración de inhibidor de 10µM o 100µM. Los compuestos que muestran una inhibición significativa en uno o en ambas concentraciones se pueden evaluar posteriormente usando un rango de ensayos de concentraciones de inhibidor para determinar un IC_{50}, una concentración esperada para inhibir la reacción de la enzima al 50%.

La actividad se calcula como sigue:-

% inhibición = (1 - (URFs del compuesto – URFs totalmente inhibido/ (tasa

URF no inhibido – URFs totalmente inhibido)) * 100.

Los valores típicos IC_{50} de los compuestos de la invención cuando se ensayan en el análisis anterior están en el rango entre 100 μM a 1nM. Por ejemplo, se encontró que el ejemplo 10 tenía un IC_{50} de 4.5μm.

La actividad inhibidora de los compuestos se probó adicionalmente en hepatocitos primarios de rata. Se aislaron hepatocitos de rata por medio de la técnica de perfusión con colagenasa, método general de Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Se cultivaron células en placas de cultivo Nunclon de seis pozos en DMEM (Medio Modificado Tagle de Dulbeco) con un alto nivel de glucosa conteniendo 10% de suero fetal bovino, AANE (amino ácidos no esenciales), Glutamina, penicilina / estreptomicina ((100 unidades / 100ug) /ml) entre 4 y 6 horas. Luego los hepatocitos se cultivaron en la solución de DMEM sin suero fetal bovino y con 10nM de insulina y 10nM de dexametasona. Se iniciaron los experimentos de 18-20 horas después del cultivo lavando los pozos y agregando solución amortiguadora de bicarbonato Krebs-Henseleit conteniendo 2.5mM de $CaCl_2$ y 1% de gelatina. Se agregó el compuesto de ensayo y 5 minutos más tarde los pozos estuvieron expuestos a 25nM de glucagón. Se retiró la solución Krebs-Henseleit después de 60 min. de incubación a 37°C, 95% de O_2 / 5% de CO_2 y se midió la concentración de glucosa de la solución Krebs-Henseleit.

De acuerdo con otro aspecto de la invención, se dispone una composición farmacéutica que comprende un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define arriba, en asocio con un diluyente o excipiente farmacéuticamente aceptable.

Las composiciones de la invención pueden ser en una forma apropiada para el uso oral (por ejemplo como tabletas, pastillas para chupar, cápsulas duras o blandas, suspensiones acuosas o aceitosas, emulsiones, polvos o gránulos dispersables, jarabes o elíxires), para uso tópico (por ejemplo como cremas, pomadas, geles o soluciones o suspensiones acuosas o aceitosas), para su administración por inhalación (por ejemplo como un

polvo finamente dividido o un aerosol líquido), para su administración por insuflación (por ejemplo como un polvo finamente dividido) o para una administración parenteral (por ejemplo como una solución acuosa o aceitosa estéril para dosis intravenosas, subcutáneas o intramusculares o como un supositorio de dosis rectal).

Las composiciones de la invención se pueden obtener por medio de unos procedimientos convencionales usando unos excipientes farmacéuticos convencionales bien conocidos en el arte. Así las composiciones que se utilizarán en forma oral pueden contener por ejemplo uno o varios agentes colorantes, edulcorantes, saborizantes y / o conservantes.

Unos excipientes apropiados farmacéuticamente aceptables para una formulación en tableta incluyen por ejemplo, diluyentes inertes como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, y agentes desintegrantes como almidón de maíz o ácido algénico; agentes aglutinantes como el almidón; agentes lubricantes como el estearato de magnesio, ácido esteárico o talco, agentes conservantes como etilo o propilo p-hidroxibenzoato y anti-oxidantes como el ácido ascórbico. Las formulaciones de las tabletas pueden ser recubiertas o sin recubrir bien sea para modificar la desintegración y posterior absorción del ingrediente activo en el tracto gastrointestinal o para mejorar su estabilidad y / o apariencia, en cualquier caso, empleando agentes convencionales para la cubierta y unos procedimientos bien conocidos en el arte.

Las composiciones para el uso oral pueden ser en forma de cápsulas duras de gelatina donde el ingrediente activo se mezcla con un diluyente inerte sólido por ejemplo carbonato de calcio, fosfato de calcio o caolín; o como cápsulas blandas de gelatina donde el ingrediente activo se mezcla con agua o con un aceite como aceite de maní, parafina líquida o aceite de oliva.

Por lo general las suspensiones acuosas contienen el ingrediente activo en forma de polvo muy fino para formar, junto con uno o varios agentes de suspensión, como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilo-pirrolidona, goma tragacanto y goma acacia; agentes de dispersión y de hidratación como

lecitina o agentes de condensación como un óxido de alquiloeno con ácidos grasos (por ejemplo polioxetileno estearato), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadenas largas por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol como polioxietileno sorbitol monooleato, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadenas largas por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol como polioxietileno sorbitol monooleato, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo polietileno sorbitan monooleato. Las suspensiones acuosas también pueden contener uno o varios conservantes (como etilo o propilo p-hidroxibenzoato, anti-oxidantes (como el ácido ascórbico), agentes colorantes, saborizantes y / o edulcorantes (como sacarosa, sacarina o aspartame).

Las suspensiones aceitosas se pueden formular por medio de la suspensión del ingrediente activo en un aceite vegetal (como aceite de cacahuete aceite de oliva, aceite de ajonjolí o aceite de coco) o en un aceite mineral (como parafina líquida). Las suspensiones aceitosas también pueden contener un agente espesante como cera de abejas, parafina dura o alcohol cetilo. Se pueden agregar los agentes edulcorantes como los que se enumeran arriba y los agentes saborizantes para obtener una preparación oral de sabor más agradable. Estas composiciones se pueden conservar por medio de la adición de un antioxidante como el ácido ascórbico.

Polvos y gránulos dispersables apropiados para la preparación de una suspensión acuosa mediante la adición de agua por lo general contienen el ingrediente activo junto con un agente dispersante o hidratante, un agente de suspensión y uno o varios conservantes. Unos agentes de dispersión o de hidratación apropiados y unos agentes de suspensión están ejemplificados en los que ya se citaron arriba. También pueden estar presentes unos excipientes adicionales como agentes edulcorantes, saborizantes y

colorantes.

Las composiciones farmacéuticas de la invención también pueden ser en forma de emulsiones de aceite en agua. La fase aceitosa puede ser un agente vegetal, como aceite de oliva o de cacahuete o de un aceite mineral como por ejemplo parafina líquida o una mezcla de cualquiera de estos. Unos agentes emulsificantes apropiados pueden ser por ejemplo, gomas naturales como la goma de acacia o la goma de tragacanto, o fosfátidos naturales como aceite de soya, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo sorbitan monooleato) y productos de condensación de los citados ésteres parciales con óxido de etileno como polioxietileno sorbitan monooleato. Las emulsiones también pueden contener agentes edulcorantes, saborizantes y conservantes.

Los jarabes y elíxires se pueden formular con agentes edulcorantes como glicerol, propilenglicol, sorbitol, aspartame o sacarosa y también pueden contener un agente emoliente, conservante, saborizante y / o colorante.

Las composiciones farmacéuticas también pueden ser en la forma de una suspensión inyectable estéril acuosa o aceitosa, que se puede formular de acuerdo con unos procedimientos conocidos empleando uno o varios de los agentes de dispersión o de hidratación y unos agentes de suspensión que se mencionaron más arriba. Una preparación estéril inyectable también puede ser una solución o suspensión estéril inyectable en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo una solución en 1,3 -butanediol.

Las composiciones para la administración por inhalación pueden ser en la forma de un aerosol convencional presurizado configurado de forma que dispense el ingrediente activo bien sea en forma de aerosol conteniendo un sólido finamente dividido o unas goticas. Se pueden emplear unos propulsores convencionales como hidrocarburos volátiles fluorados y el dispositivo aerosol está configurado convenientemente para dispensar una cantidad medida del ingrediente activo.

Para mayor información sobre la formulación, se remite el lector al

Capítulo 25.2 del Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman de Editorial Board), Pergamon Press 1990.

La cantidad del ingrediente activo que se combina con uno o varios excipientes para obtener una forma de una sola dosis necesariamente varía según el anfitrión tratado y la ruta de administración en particular. Por ejemplo, una formulación para una administración oral a humanos por lo general va a contener por ejemplo, de 0.5 mg a 2 g del agente activo del compuesto con una cantidad apropiada y conveniente de excipientes que puede variar de entre alrededor de 5 a alrededor de 98 por ciento por peso de la composición total. Por lo general, las unidades de formas de dosis van a contener alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo. Para mayor información sobre la Rutas de Administración y los Regímenes de Dosis, se remite el lector al Capítulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman de Editorial Board), Pergamon Press 1990.

El compuesto de fórmula (1) normalmente se administrará a un animal de sangre caliente a una unidad de dosis en el rango de 5-5000 mg por metro cuadrado del área del cuerpo del animal, es decir aproximadamente 0.1-100 mg/kg, y por lo general esto dispone una dosis terapéuticamente efectiva. Una forma de unidad de dosis como una tableta o una cápsula por lo general va a contener 1-250 mg de ingrediente activo. Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg. Sin embargo, necesariamente la dosis diaria va a variar dependiendo del anfitrión tratado, de la ruta particular de administración y de la gravedad de la enfermedad que se está tratando. Por lo tanto, el médico que está tratando cualquier paciente en particular determinará la dosis óptima.

La actividad inhibidora de glucógeno fosforilasa aquí descrita se puede aplicar como una terapia individual o puede comprender, además del tema de la presente invención, una o varias sustancias y / o tratamientos. Dicho tratamiento conjunto se puede administrar mediante la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. El tratamiento simultáneo puede ser en una sola tableta o en

tabletas separadas. Por ejemplo, en el tratamiento de la diabetes sacarina la quimioterapia puede incluir las siguientes categorías de tratamiento principales:

1) Insulina y análogos de insulina;
2) Secretores de insulina incluyendo sulfoniloúreas (por ejemplo glibenclamida, glipicida) y reguladores prandiales de glucosa (por ejemplo repaglinida, nateglinida);
3) Agentes de sensibilidad a la insulina incluyendo agonistas PPARg (por ejemplo pioglitazona y rosiglitazona);
4) Agentes que suprimen la producción de glucosa hepática (por ejemplo metformina).
5) Agentes diseñados para reducir la absorción de glucosa del intestino (por ejemplo acarbosa);
6) Agentes diseñados para tratar las complicaciones de la hiperglucemia prolongada;
7) Agentes contra la obesidad (por ejemplo sibutramina y orlistat);
8) Agentes anti-dislipidemia como inhibidores de reductasa, HMG-CoA (estatinas, por ejemplo pravastatina); agonistas PPARα (fibratos, por ejemplo gemfibrozil); secuestrantes de ácido biliar (colestiramina); inhibidores de absorción de colesterol (estanoles vegetales, inhibidores sintéticos); inhibidores de absorción del ácido biliar (IBATi) y ácido nicotínico y análogos (niacina y formulaciones de liberación lenta);
9) Agentes antihipertensivos como los β bloqueadores (por ejemplo atenolol, inderal); inhibidores de ACE (por ejemplo lisinopril); antagonistas de calcio (por ejemplo nifedipino); antagonistas del receptor angiotensina (por ejemplo candesartan), antagonistas α y agentes diuréticos (por ejemplo furosemida, benztiazida);
10) Moduladores de hemostasis como, antitrombóticos, activadores de fibrinólisis y antiagregantes plaquetarios; antagonistas de trombina; inhibidores del factor Xa; inhibidores del factor VIIa); antiagregantes plaqueatarios (por ejemplo aspirina, clopidogrel);

anticoagulantes (heparina y análogos de bajo peso molecular, hirudina) y warfarina; y

11) Agentes antiinflamatorios como fármacos antiinflamatorios o esteroides (por ejemplo aspirina) y agentes antiinflamatorios esteroides (por ejemplo cortisona).

De acuerdo con otro aspecto de la presente invención, se dispone un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define más arriba, para el uso en un método de tratamiento de un animal de sangre caliente como el hombre, como terapia.

De acuerdo con un aspecto adicional de la invención, se dispone un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define más arriba, para su uso como un medicamento.

De acuerdo con un aspecto adicional de la invención, se dispone un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define más arriba, para el uso como un medicamento en el tratamiento de la 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 dispone el uso de un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define más arriba, en la manufactura de un medicamento para el uso en el tratamiento de la 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 dispone el uso de un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo* de los mismos, como se define más arriba, en la manufactura de un medicamento para el uso en el tratamiento de la diabetes

tipo 2 en un animal de sangre caliente como el hombre.

De acuerdo con otra característica de este aspecto de la invención, se dispone un método para producir un glucógeno fosforilasa de efecto inhibidor en un animal de sangre caliente, como el hombre, que necesite el citado tratamiento que comprende administrar al citado animal, una cantidad efectiva de un compuesto de fórmula (1).

De acuerdo con esta otra característica de este aspecto de la invención, se dispone un método para tratar la diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca u obesidad en un animal de sangre caliente, como el hombre, que necesite el citado tratamiento que comprende administrar al citado animal, una cantidad efectiva de un compuesto de fórmula (1).

De acuerdo con otra característica de este aspecto de la invención, se dispone un método para tratar la diabetes tipo 2 en un animal de sangre caliente, como el hombre, que necesite el citado tratamiento que comprende administrar al citado animal, una cantidad efectiva de un compuesto de fórmula (1).

Como se explicó arriba, el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de una enfermedad en particular relacionada con la proliferación de células necesariamente deberá variar dependiendo del anfitrión tratado, de la ruta de administración y de la gravedad de la enfermedad que se está tratando. Se considera una unidad de dosis en el rango por ejemplo de 1-100 mg/kg, preferiblemente 1-50 mg/kg.

Además de su uso en la medicina terapéutica, los compuestos de la fórmula (1) y sus sales farmacéuticamente aceptables son también útiles como herramientas farmacológicas para el desarrollo y la estandarización de sistemas de ensayo *in vivo* para la evaluación de los efectos de los inhibidores de los ciclos de actividad de las células en animales de laboratorio como gatos, perros, conejos, micos, ratas y ratones como parte de la investigación de nuevos agentes terapéuticos.

En las otras composiciones farmacéuticas, los procesos, métodos, usos y características para la manufactura de medicamentos descritos arriba,

las incorporaciones alternas y preferidas de los compuestos de la invención aquí descritos también aplican.

Ejemplos

Ahora la invención se ilustrará por los siguientes ejemplos no limitantes, en los cuales, salvo si se indica en contrario:

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

(ii) las soluciones orgánicas se secaron sobre sulfato anhidro de magnesio; la evaporación del solvente se efectuó empleando un evaporador rotatorio bajo presión reducida (600-4000 Pascals; 4.5-30 mmHg) con una temperatura de baño de hasta 60°C;

(iii) cromatografía significa una cromatografía instantánea en gel de sílice; la cromatografía en capa delgada (CCD) se efectuó en placas de gel de sílice; donde se hace referencia a una columna Bond Elut, esto significa una columna conteniendo 10 g o 20 g o 50 g de sílice de tamaño de partícula de 40 micrones, el sílice se contiene en 60 ml de una jeringa desechable y soportada en un disco poroso obtenido en Varian, Harbor City, California, USA bajo el nombre de "Mega Bond Elut SI;" Mega Bond Elut" es una marca registrada; donde se hace referencia a un cartucho Biotage, esto significa un cartucho conteniendo sílice KP-SIL™ , 60μ de tamaño de partícula 32-63mM, suministrado por Biotage, una división de Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) en general se hizo un seguimiento al curso de las reacciones seguido por una CCD, y los tiempos de reacción únicamente se dan para efectos de ilustración,

(v) los rendimientos se dan únicamente para ilustración y no son necesariamente los que se pueden obtener por medio de un proceso diligente; las preparaciones se repitieron si se requería más material;

(vi) donde se dan, los datos NMR están en la forma de valores delta para los grandes protones de diagnóstico dados en partes por millón (ppm) relativos

a tetrametilsilano (TMS) como un estándar interno, determinados a 300 MHz usando perdeuterio dimetil sulfoxida (DMSO-δ_6) como solvente salvo si se indica en contrario, otros solventes (donde se indica en el texto) incluyen cloroformo deuterado $CDC1_3$;

(vii) los símbolos químicos tienen sus significados acostumbrados; se emplean unidades y símbolos SI;

(viii) las presiones reducidas se dan como presiones absolutas en Pascals (Pa); las presiones elevadas se dan como presiones de calibrado en bar;

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

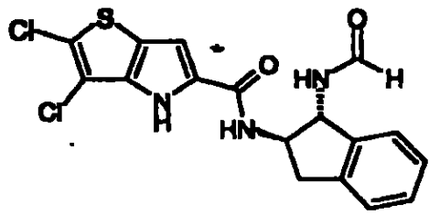
(x) se efectuaron unos espectros de masa (EM) con una energía de electrón de 70 voltios en el modo de ionización química (IQ) usando un ensayo de exposición directa, donde la ionización indicada se efectuó mediante el impacto de electrón (IE), un rápido bombardeo de átomos (RBA) o electrobarrido (EB); los valores de m/z están dados; por lo general únicamente se reportan los iones que indican la masa inicial y salvo si se indica en contrario, el valor citado es $(M-H)^-$;

(xi) Se utilizan las siguientes abreviaturas:

SM	material de inicio;
EtOAc	etilo acetato;
MeOH	metanol;
EtOH	etanol;
DCM	diclorometano;
HOBT	1-hidroxibenzotriazol;
DIPEA	di-isopropiletilamina;
EDCI	1-etilo-3- (3-dimetilaminopropil) hidrocloruro de carbodiimida;
Et_2O	dietilo éter,
THF	tetrahidrofurano;
DMF	*N, N* -dimetilformamida;
HATU	O-(7-Azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluroniohexafluorofosfato

EDAC	1-(3- dimetilaminopropil) -3-etilo- hidrocloruro de carbodiimida
TFA	Ácido trifluoroacético
DMTMM	4-(4,6-Dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio cloruro
DMA	N,N-dimetilacetamida

Ejemplo 1: 2,3-Dicloro-N-[(1R,2R)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida

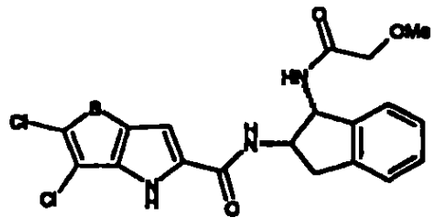


Se disolvió *N*-[(1*R*2 *R*)-1- Amino-2,3-dihidro-1*H*-inden -2-il]- 2,3-dicloro -4*H*-tieno[3,2-*b*]pirrol- 5-carboxamida sal de ácido trifluoroacético (**Método 8**, 240 mg, 0.5 mmol), ácido fórmico (50 µL, 1.4 mmol), DIPEA (174 µL, 1.0 mmol) y HOBT (67 mg, 0.5 mmol) en DCM (5 ml), se revolvió durante 5 minutos, se agregó EDCI (120 mg, 0.625 mmol) y la reacción se revolvió durante 1 hora. Se agregó ácido fórmico (50 µL, 1.4 mmol) y EDCI (240 mg, 1.25 mmol), la reacción se revolvió durante 2 horas y los volátiles se retiraron por evaporación bajo presión reducida. El residuo Se disolvió en EtOAc (20 mL), se lavó con agua (2 x 10 mL), solución salina (10 mL), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida. El residuo se purificó por medio de una cromatografía en columna (2:1 EtOAc:Hexano) para obtener el compuesto del título (175mg, 89%) como una espuma blanca.

^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 4.6 (m, 1H), 5.53 (m, 1H), 7.12 (m, 2H), 7.25 (m, 1H). 8.2 (s, 1H), 8.55 (d, 1H), 8.63 (d, 1H), 12.36 (s, 1H); MS m/z 394.

Ejemplo 2 2,3-Dicloro-*N*-((1*R*,2*R*)-1-{[((metiloxi)acetil]amino}-2,3-

dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se agregó DIPEA (180 µL, 1.05 mmol), HOBT (68 mg, 0.5 mmol), ácido metoxiacético (0.5 mmol, 38 µL) y EDAC (120 mg, 0.63 mmol) a una suspensión de *N*-[(1*R*, 2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro - 4*H*-tieno [3,2-*b*]pirrol-5 carboxamida (**Método 8**, 240 mg, 0.5 mmol) en anhidro de DCM (7 mL). La reacción se revolvió a temperatura ambiente durante aproximadamente 16 horas. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (10 mL), se lavó con agua (2 x 10 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por cromatografía instantánea en columna en SiO_2 (1:1 EtOAc.isohexano); el solvente se retiró por evaporación bajo presión reducida y se secó para obtener el compuesto del título (44 mg, 20%) como un sólido blanco.

^{1}H NMR 2.88 (dd, 1H), 3.26 (dd, 1H), 3.87 (dd, 2H), 4.73 (m 1H), 5.51 (t, 1H), 7.17 (m, 5H), 8.26 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H); MS m/z 439.

Se prepararon los siguientes ejemplos para el proceso similar al **Ejemplo 2** utilizando *N*- [(1*R*.2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3 dicloro -4*H*-tieno [3,2-*b*] pirrol-5- carboxamida (**Método 8**) y el ácido carboxílico apropiado disponible en el comercio:

Ejemplo 3: *N*-((1S.2S)-1-{[(3(*R*)-3-(*tert*-Butoxicarbonilamino)-3-Carbamoilpropanoil]amino}-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol – 5 –carboxamida

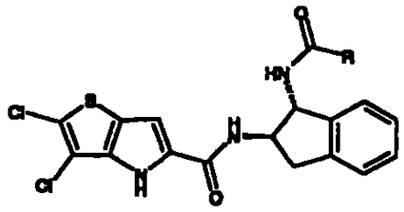
Ejemplo 4: 2,3-Dicloro-*N*-[(1R,2R)-1-({[(4*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il]acetil}amino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*] pirrol-5-carboxamida

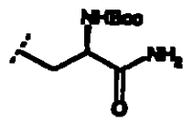
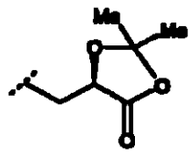
Ejemplo 5: 2,3-Dicloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 6: *N*-{(1*R*,2*R*)-1-[(2-Acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 7: *N*-{(1*R*,2*R*)-1-[(2-Carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-ilo-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol-5-carboxamida

Ejemplo 55: 2,3-Dicloro-*N*-{(1*R*,2*R*)-1-[(trifluoroacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Ex	R	NMR	M/Z
3		(DMSO-d_6) 1.37 (s, 9H), 2.89 (dd, 1H), 3.23 (dd, 1H), 4.25 (m, 1H), 4.55 (m, 1H), 5.46 (t, 1H), 6.68 (d, 1H), 6.97 (s, 1H), 7.17 (m, 6H), 8.31 (d, 1H),	578
4			523
5	CH_2CH_2OMe	(DMSO-d_6) 2.33 (m, 2H), 2.84 (dd, 1H), 3.28 (s, 3H) 3.24(m,1H), 3.56 (m, 2H), 4.57 (m, 1H), 5.47 (t, 1H), 7.17 (m, 5H), 8.35 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H)	452
6	CH_2OAc	-	466
7	$CH_2C(O)NH_2$	(DMSO-de) 2.86 (dd, 1H), 3.07 (m, 2H), 3.25 (m, 1H), 4.57 (m, 1H), 5.47 (m, 1H), 6.98 (s, 1H), 7.11 (s, 1H), 7.22 (m, 4H), 7.37 (s, 1H), 8.51 (d, 1H), 8.62 (d, 1H), 12.35 (s, 1H);	451
55	CF_3	-	462

Los siguientes ejemplos se efectuaron para el proceso del **Ejemplo 2** utilizando *N*-[(1S,2S)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida (**Método 9**) y el ácido carboxílico apropiado disponible en el mercado.

Ejemplo 8; 2,3-Dicloro-*N*-{(1S,2S)-1-[(furan-2-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il} -4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 9: 2,3-Dicloro-*N*-{(1S,2S)-1-[(furan-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-ilo }-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 10: 2,3-Dicloro-*N*-{(1S,2S)-1-[(3-tienilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

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Ejemplo 11: 2,3-Dicloro-*N*-(1S,2S)-1-{[(5-nitrofuran-2-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

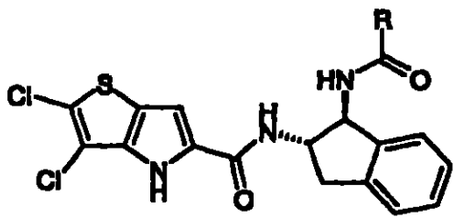
Ejemplo 12: 2,3-Dicloro-*N*-(1S,2S)-1-[(piridin-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

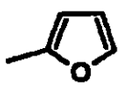
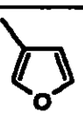
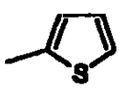
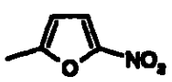
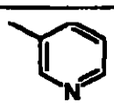
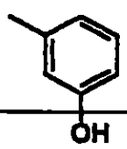
Ejemplo 13: *N*-[(1S,2S)-1-(Acriloilamino)-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 14: 2,3-Dicloro-*N*-(1S,2S)-1-{[(3-hidroxifenil)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

Ejemplo 15: *N*-[(1S,2S)-1-(Acetilamino)-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

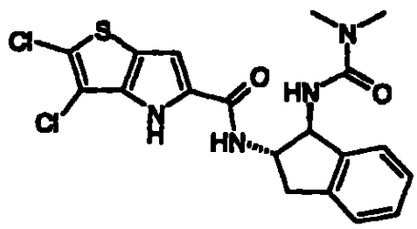
Ejemplo 16: *N*-[(1S,2S)-1-[(2-Carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Ex	R	NMR	M/Z
8		-	458 $(M-H)^-$
9		-	458 $(M-H)^-$
10		-	476 $(M-H)^-$
11		-	503 $(M-H)^-$
12		-	471
13		-	417 $(M-H)^-$
14		-	484

15	CH_3	1.87 (s, 3H), 2.83 (m, 1H), 3.23 (m, 1H), 4.55 (m,- 1H), 5.45 (m,1H), 7.1 (s, 1H), 7.13 (m, 1H), 7.22 (m, 3H), 8.34 (d, 1H), 8.59 (d, 1H), 12.36 (s, 1H)	-
16	CH_2CO_2H	-	452

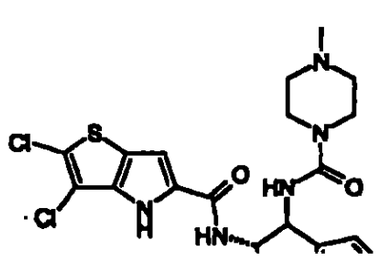
Ejemplo 17: 2,3-Dicloro-*N*-((1S2S)-1-{[(dimetilamino)carbonil] amino}2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



A una solución de *N*-[(1S,2S)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3dicloro-4*H*-tieno[3,2-*b*]pirrol-5-Carboxamida (**Método 9**, 240 mg, 0.5 mmol) y Et_3N (101 mg, 1.0 mmol) en DCM (4 mL) se agregó una solución de cloruro de dimetilcarbamoilo (54 mg, 0.5 mmol) en DCM (1 mL). La reacción se revolvió a temperatura ambiente durante 2 horas, se lavó con $NaHCO_3$ saturado (1 mL), agua (1 mL), solución salina (1 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (50 mg, 23%) como una espuma.

^{1}H NMR 2.81 (s, 6H), 2.83 (m, 1H), 3.25 (m, 1H), 4.61 (m, 1H), 5.33 (m, 1H), 7.16 (m, 5H), 8.6 (d, 1H), 12.37 (s, 1H); MS m/z 437.

Ejemplo 18: 2,3-Dicloro-*N*-((1S,2S)-1-{[(4-metilpiperazin-1-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*] pirrol- 5-carboxamida



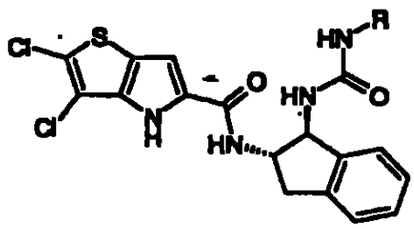
A una solución de *N*-[(1S,2S)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Método 9**, 240 mg, 0.5 mmol) y Et_3N (101 mg, 1.0 mmol) en DCM (4 mL) se agregó una solución de 4-metil-1-piperazina cloruro de carbonilo (100 mg, 0.5 mmol) en DCM (1 mL). La reacción se revolvió a temperatura ambiente durante 2 horas, se lavó con $NaHCO_3$ saturado (1 mL), agua (1 mL), solución salina (1 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (110 mg, 45%) como una espuma.
MS m/z$(M-H)^-$491.

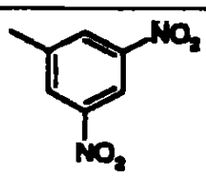
Los siguientes ejemplos se efectuaron según el método a continuación, empleando *N*-[(1S,2S)-1-amino- 2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol-5-carboxamida sal de ácido trifluoroacético (**Método 9**) y el ixocianato apropiado disponible en el comercio: Se disolvió *N*-[(1S,2S)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol-5- carboxamida sal de ácido trifluoroacético (0.5 mmol) y Et_3N (1.0 mmol) en THF seco (5 mL), se agregó el respectivo isocianato (1.0 mmol) y la reacción se revolvió a temperatura ambiente durante 20 horas. Se agregó EtOAc (15 mL) y la mezcla se lavó con agua (2x5 mL), solución salina (5 mL), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título como una espuma.

Ejemplo 19: 2,3-Dicloro-*N*-((1S,2S)-1-{[(etilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-ilo-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

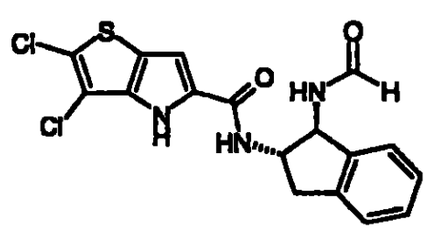
Ejemplo 20: 2,3-Dicloro-*N*-((1S,2S)-1-{[(prop-2-en-1-ilamino) carbonil] amino)-2,3-dihidro-1*H*-inden-2-il)-4H-tieno[3,2-*b*] Pirrol-5-carboxamida

Ejemplo 21: 2,3-Dicloro-*N*-((1S,2S)-1-({[(3,5-dinitrofenil]amino] carbonil}amino)-2,3-dihidro-1*H*-inden-2-ilo-4H-tieno[3,2-*b*]Pirrol-5-carboxamida



EX	R	M/z
19	CH_2CH_3	437/439
20		449/451
21		364/366(-$C_7H_3N_3O_5$)

Ejemplo 22: 2,3-Dicloro-*N*-[(1S,2S)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

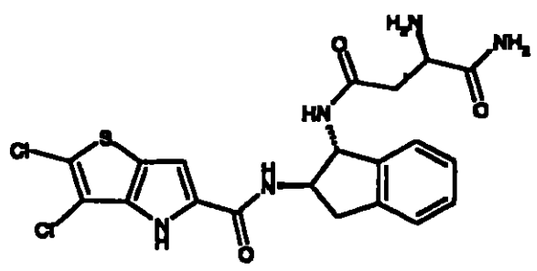


Se disolvió *N*-[(1S,2S)-1-Amino-2,3-dihidro-1*H*-indeņ-2-il]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida sal de ácido trifluoroacético (**Método 9**, 240 mg, 0.5mmol), ácido fórmico (50 µL, 1.4 mmol), DIPEA (174 µL, 1.0 mmol) y HOBT (67 mg, 0.5 mmol) en DCM (5 ml), se revolvió durante 5 minutos, se agregó EDCI (120 mg, 0.625 mmol) y la reacción se revolvió durante 1hora. Se agregó ácido fórmico (50 µL, 1.4 mmol) y EDCI (240 mg, 1.25 mmol), la reacción se revolvió durante 2 horas y los volátiles se retiraron por evaporación bajo presión reducida. El residuo se disolvió en EtOAc (20 mL), se lavó con agua (2 x 10 mL), solución salina

(10 mL), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida. El residuo se purificó por medio de una cromatografía en columna (2:1 EtOAc: Hexano) para obtener el compuesto del título (180mg, 97%) como una espuma blanca.

^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 4.6 (m, 1H), 5.53 (m, 1H), 7.12 (m, 2H), 7.25 (m, 1H), 8.2 (s, 1H), 8.55 (d, 1H), 8.63 (d, 1H), 12.36 (s, 1H); MS m/z 394.

Ejemplo 23: *N*-{(1*R*,2*R*)-1-[((3*R*)-3-Amino-3-carbamoilpropanoil) amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

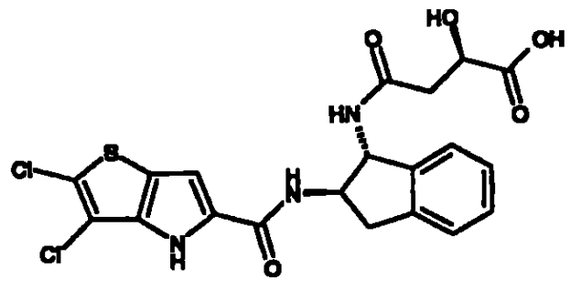


Se disolvió *N*-((1S,2S)-1-{[(3(*R*)-3-(*tert*-Butoxicarbonilamino)-3-carbamoilpropanoil]amino}-2,3-dihidro-1*H*-inden-2-y)-2,3dicloro-4*H*-tieno[3,2-*b*]pirrol-5carboxamida (**Ejemplo 3**; 290 mg, 0.5 mmol) en TFA (3 mL) y la reacción se revolvió a temperatura ambiente durante 1 hora. Los volátiles se evaporaron bajo presión reducida y el material bruto se destiló mediante destilación azeotrópica con cloroformo (3x5 mL) para obtener una goma. La goma se trituró con éter (5 mL), el sólido se recolectó mediante filtración, se lavó con éter (2x5 mL) y se secó para obtener la sal de trifluoroacetato del compuesto del título (270 mg, 91%) como un sólido amarillo.

^{1}H NMR 1.24 (m, 1H), 2.72 (m, 1H), 2.90 (dd, 1H), 3.26 (dd, 1H), 4.04 (m, 1H), 4.61 (m, 1H), 5.50 (t, 1H). 7.12 (s, 1H), 7.24 (m, 4H), 7.55 (s, 1H), 7.74 (s, 1H), 8.06 (br, 3H), 8.66 (d, 1H), 8.72 (d, 1H), 12.36 (s, 1H); MS m/z 502 $(M+Na)^+$.

Ejemplo 24: *N*-(1*R*,2*R*)-1-[((3R)-3-Carboxi-3-hidroxipropanoil)amino]-

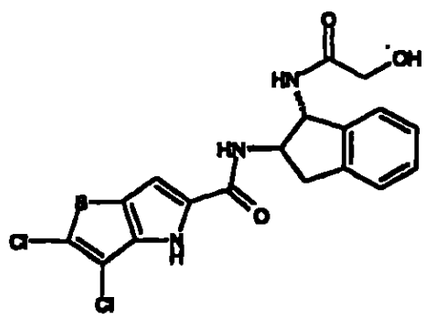
2,3-dihidro-1*H*-inden-2-il}-2,3- dicloro-4*H*-tieno[3,2-*b*]pirrol-5carboxamida



Se disolvió 2,3-Dicloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)- 2,2-dimetil – 5-oxo-1,3-dioxolan-4-il]acetil}amino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5carboxamida (**Ejemplo 4**; 200 mg, 0.4 mmol) en THF (2 mL) y agua (2 mL) y se agregó NaOH (100 mg) y la suspensión se revolvió a temperatura ambiente durante 48 horas. Se agregó 2*N* HCl hasta alcanzar un pH 1 y se extrajo la fase acuosa con EtOAc (3x5 mL). Las fases orgánicas combinadas se lavaron con agua (10 mL), solución salina (10 mL) y se secaron con ($MgSO_4$). El solvente se evaporó bajo presión reducida y el residuo se trituró con Et_2O, se filtró y se secó para obtener el compuesto del título (133 mg, 69%) como un sólido marrón.

^{1}H NMR 2.45 (obs m, 2H), 2.87 (dd, 1H), 3.26 (obs dd, 1H), 4.39 (m, 1H), 4.57 (m,1H) 5.52 (t, 1H), 7.18 (m, 5H), 8.43 (d, 1H), 6.63 (d, 1H), 12.39 (s, 1H); MS m/z 483.

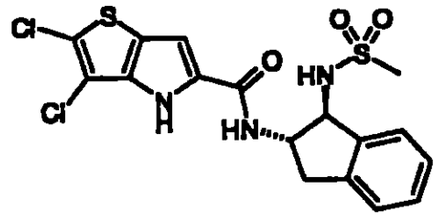
Ejemplo 25: 2,3-Dicloro-*N*-{(1R,2R)-1-(hidroxiacetil)amino]-2,3-1*H*-inden-2-il}-4H-tieno[3,2-*b*]pirrol-5-carboxamida



Se disolvió *N*-{(1*R*,2*R*)-1-[(2-Acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il} -2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Ejemplo 6**; 632 mg, 1.36 mmol) en THF (10 mL), MeOH (10 mL) y luego se agregó.

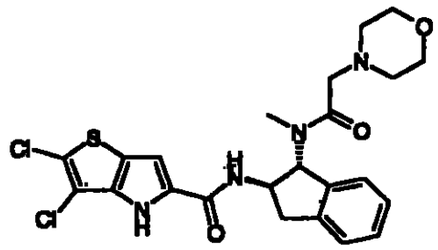
K_2CO_3 (100 mg) y la suspensión se revolvió a temperatura ambiente durante 16 horas. Se agregó agua (50 mL) y la fase acuosa se extrajo con EtOAc (3 x 30 mL). Las fases orgánicas combinadas se lavaron con agua (2 x 50 mL), solución salina (50 mL) y se secaron con ($MgSO_4$). El solvente se retiró por evaporación bajo presión reducida, el producto bruto se trituró (EtOAc;isohexano, 1:10), se filtró, se lavó con isohexano (5 mL) y se secó para obtener el compuesto del título (428 mg, 74%) como un sólido blanco.
^{1}H NMR 2.86 (dd, 1H), 3.25 (obs dd, 1H), 3.89 (m, 2H), 4.72 (m, 1H), 539 (t, 1H). 5.51 (t, 1H), 7.17 (m, 5H), 8.13 (d, 1H), 8.59 (d, 1H), 12.35 (s, 1H); MS m/z 424.

Ejemplo 26: 2,3-Dicloro-*N*-{(1S,2S)-1[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se disolvió 5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (**Método 4**, 236 mg, 1.0 mmol), *N*-[(1S,2S)-2-amino-2,3-dihidro-1*H*-inden-1-il] metanosulfonamida (226 mg, 1.0 mmol), DIPEA (174 µL, 1.0 mmol) y HOBT (135 mg, 1.0 mmol) en DCM (10 mL) y se revolvió durante aproximadamente 5 minutos. Se agregó EDCI (240 mg, 1.25 mmol) y la reacción se revolvió durante 20 horas. Los volátiles se retiraron por evaporación, se agregó EtO Ac (25mL), la mezcla se lavó con agua (2 x 10 mL) y solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (430mg, 97%) como una espuma.
^{1}H NMR 2.83 (m, 1H), 2.99 (s, 3H), 3.23 (m, 1H), 4.57 (m, 1H), 4.95 (m, 1H), 7.13 (s, 1H), 7.21-7.34 (m, 4H), 7.87 (d, 1H), 8.66 (d, 1H), 12.41 (s, 1H); MS m/z $(M-H)^-$ 442.

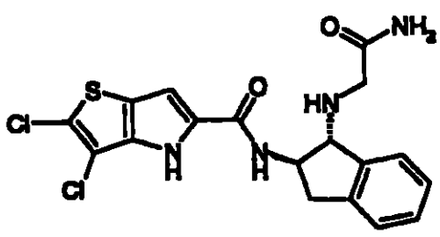
Ejemplo 27: 2,3-Dicloro-*N*-{(1S,2S)-1-[metil(morfolin-4-ilacetil) amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se disolvió 2,3-Dicloro-*N*-{(1R,2R)-1-[(cloroacetil)(metil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5- carboxamida (**Método 10**, 100 mg, 0.22 mol) y morfolina (100 mg, 12.6 mmol) en DCM, se revolvió a temperatura ambiente durante 20 horas y los volátiles se retiraron por evaporación bajo presión reducida. Se agregó EtOAc (10 mL) y la mezcla se lavó con agua (2x5 mL), solución salina (5 mL), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (60 mg, 54%) como un polvo de color amarillo claro.

^{1}H NMR 2.36 (m, 4H), 2.74 (d, 3H), 2.9-3.55 (m, 7H), 4.8 (m, 1H), 5.96 (dd, 1H), 7.0 (m, 1H), 7.09 (d, 1H), 7.26 (m, 3H), 8.62 (dd, 1H); MS m/z 507.

Ejemplo 28: *N*-{(1*R*,2*R*)-1-[(2-Amino-2-oxoetil)amino]-2,3-dihidro)-1*H*-inden-2-il)- 2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

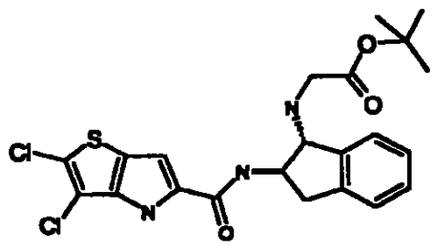


Se preparó en forma similar a la del **Ejemplo 29** usando *N*-{(1*R*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-ilo-2-carboxamida (**Método 8**) y bromoacetamida.

^{1}H NMR 2.69 (s, 1H), 2.8 (dd, 1H). 3.16 (m, 2H), 3.24 (m, 1H), 4.21 (m, 1H), 4.44 (m, 1H) 7.03 (s,1H), 7.12 (s, 1H), 7.23 (m, 3H), 7.28 (s, 1H), 7.37

(s, 1H), 8.49 (d, 1H). 12.36 (s, 1H); MS m/z(M-H)⁻422.

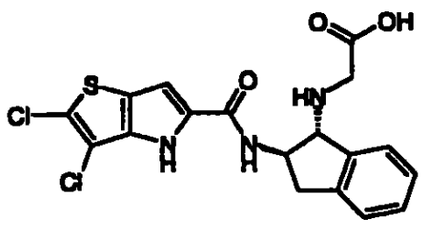
Ejemplo 29 *N*-(1*R*,2*R*)-1-[(tert-Butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se agregó DIPEA (520 µL, 3.0 mmol) y *t*-butilo bromoacetato (150 µL, 1.0 mmol) a una solución de *N*-{(1*R*,2*R*)- 1-amino-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-ilo-2-carboxamida (**Método 8**, 479 mg, 1.0 mmol) en CH_3CN (15 mL). La suspensión resultante se revolvió a 60°C durante aproximadamente 2 horas. Después de su enfriamiento, los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (20 mL), se lavó con agua (2 x 20 mL), solución salina (20 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por cromatografía en columna (EtOAc:isohexano 1:1) para obtener el compuesto del título (100 mg, 21%) como un sólido blanco.

^{1}H NMR 1.49 (s, 9H), 1.87 (brs, 1H), 2.75 (dd, 1H), 3.62 (d, 2H), 3.65 (dd, 1H), 4.15 (d, 1H), 4.40 (m, 1H), 6.82 (s, 1H), 7.10 (d, 1H), 7.25 (s, 2H), 7.40 (d, 1H), 9.80 (s, 1H); MS m/z 480.

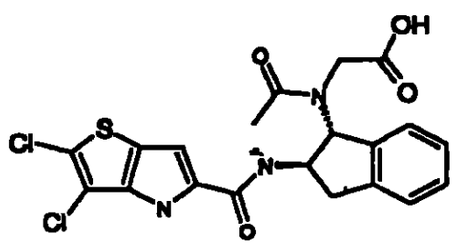
Ejemplo 30: *N*-[(1*R*,2*R*)-1-(Carboximetilamino)-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se disolvió *N*-(1*R*,2*R*)-1-[(*tert*-Butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Ejemplo 29**; 100 mg, 0.21 mmol) en DCM (10 mL). Se agregó TFA (1 mL) y la reacción se revolvió a temperatura ambiente durante 6 horas. Evaporación bajo presión reducida, co-evaporación con $CHCl_3$ (2 x 10 mL) y el secado produjo el compuesto del título (8.5mg, 36%) como un polvo blanco.

^{1}H NMR 2.71 (dd, 1H), 3.16 (dd, 1H), 3.29 (m, 2H), 4.25 (m, 1H), 4.39 (m, 1H), 6.97 (m, 2H), 7.08 (m, 3H), 7.24 (m, 2H), 7.48 (d, 1H), 8.63 (d, 1H), 11.62 (s, 1H); MS m/z $(M-H)^-$ 422.

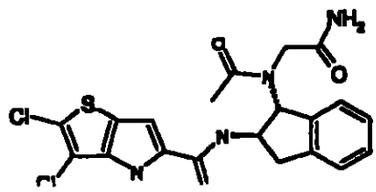
Ejemplo 31; *N*-(1*R*,2*R*)-1-[*N*-Acetilo-*N*-(carboximetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se agregó TFA (1 mL) a una solución de 1,1-dimetiletilo [acetil((1*R*,2*R*)-2-{[(2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil] amino}-2,3-dihidro-1*H*-inden-1-il)amino]acetato (**Método 18**, 40 mg, 0.08 mmol) en DCM (5 mL) y la reacción se revolvió a temperatura ambiente durante 1 hora. Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (35 mg, 94%) como un sólido blanco.

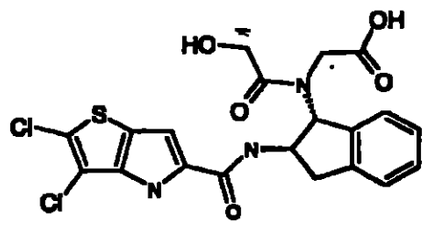
^{1}H NMR 2.49 (s, 3H), 2.97 (dd, 1H), 3.20 (dd, 1H), 3.90 (m, 2H), 4.70 (m, 1H), 5.50 (d, 1H), 7.25 (m, 5H), 8.60 (d, 1H), 12.43, (s, 1H); MS m/z 466, 349.

Ejemplo 32: *N*-{(1*R*, 2*R*)-1-[Acetil(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se agregó cloruro de acetilo (17 µL, 0.24 mmol) a una solución de *N*-{(1*R*,2*R*)-1-[(2- amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Ejemplo 28**, 100 mg, 0.24 mmol) en THF (10 mL). La reacción se revolvió a temperatura ambiente durante 1 hora. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (50 mL), se lavó con agua (2 x 10 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por cromatografía en columna (EtOAc:isohexano 1:2) para obtener el compuesto del título (50 mg, 45%) como un sólido blanco.
^{1}H NMR 2.49 (s, 3H), 2.98 (dd, 1H), 3.20 (dd, 1H), 3.29 (brs, 2H), 4.0 (m, 2H), 4.65 (m, 1H), 5.70 (d, 1H), 7.25 (m, 5H), 8.30 (d, 1H), 12.10, (s, 1H); MS m/z 487.

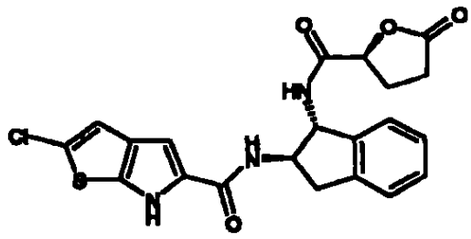
Ejemplo 33: *N*-{(1*R*,2*R*)-1-[*N*-(Carboximetil)-*N*-(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida



Se agregó carbonato de potasio (20 mg) y MeOH (1 mL) a una solución de [[(acetiloxi)acetil]((1*R*,2*R*)-2-{[(2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil]amino}-2,3-dihidro- 1*H*-inden-1-il)amino] ácido acético (**Método 19**, 120 mg, 0.23 mmol) en THF (5 mL) y la reacción se revolvió a temperatura ambiente durante 24 horas. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en agua y se

acidificó para obtener un pH 2.0 y luego se extrajo en EtOAc (3 x 10 mL). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (110 mg, 100%) como un sólido blanco.
^{1}H NMR 3.07 (dd, 1H), 3.18 (dd, 1H), 3.92 (d, 1H), 4.35 (d, 1H), 4.82 (m, 3H), 5.96 (d, 1H), 7.25 (m, 5H), 8.67 (d, 1H), 12.40 (s, 1H); MS m/z 482.

Ejemplo 34: 2-Cloro-*N*-[(1*R*,2*R*)-1-({[(2S)-5-oxotetrahidrofuran-2-il]carbonil}amino)2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*] pirrol-5-carboxamida



Se agregó DIPEA (180 µL, 1.05 mmol), HOBT (68 mg, 0.5 mmol), (2S)-5-oxotetrahidrofuran-2-ácido carboxílico (CAS Reg. No: [21461-84-7], 0.5 mmol, 65 mg) y EDAC (120 mg, 0.63 mmol) a una suspensión de *N*-[(1*R*,2*R*)-1- amino-2,3- dihidro- 1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*] pirrol-5-carboxamida (**Método 21**, 223 mg, 0.5 mmol) en anhidro DCM (7 mL). La reacción se revolvió a temperatura ambiente durante aproximadamente 16 horas. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (5 mL), se lavó con agua (2x5 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se trituró (EtOAc:hexano, 1:10), se recolectó por filtración, se lavó con hexano (2x5 mL) y se secó para obtener el compuesto del título (112 mg, 56%) como un sólido marrón.
^{1}H NMR 2.15 (m, 1H), 2.43 (m, 3H), 2.91 (dd, 1H), 3.25 (dd, 1H), 4.70 (m, 1H), 4.92 (m, 1H), 5.46 (t, 1H), 7.03 (s, 1H), 7.13 (m, 1H), 7.18 (s.. 1H), 7.25 (m, 3H), 8.55 (d, 1H), 8.75 (s, 1H), 11.85 (s, 1H); MS m/z 444,446

Los siguientes ejemplos se prepararon mediante un proceso similar al

Ejemplo 34 empleando *N*-[(1*R*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*]pirrol5-carboxamida (**Método 21**) y el ácido carboxílico apropiado disponible en el mercado:

Ejemplo 35; 2-Cloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 36: 2-Cloro-*N*-{(1*R*,2*R*)-1-[(metoxiacetil) amino]-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 37; *N*-[(1*R*,2*R*)-1-(Acetilamino)-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 38: 2-Cloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 39: *N*-{(1*R*,2*R*)-1-[(2-Acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 40: *N*-((1S,2S)-1-{[(2(S)-2-(*tert*- Butoxicarbonilamino)-2-Carbamoilacetil]amino}-2,3dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

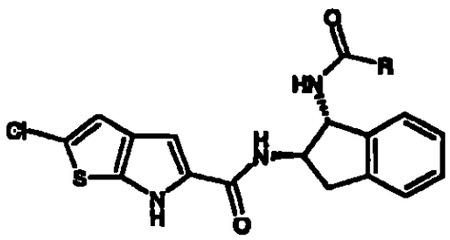
Ejemplo 41; *N*-{(1S,2S)-1-[(*tert*-Butoxicarbonilamino)Acetilamino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*- tieno[2,3-*b*]pirrol-5-carboxamida

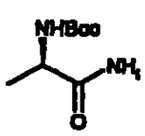
Ejemplo 42: *N*-{(1R,2R)-1-[2-Carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3,*b*]pirrol-5-carboxamida

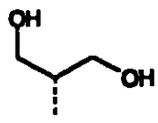
Ejemplo 56: *N*-[(1*R*,2*R*)-1-[2-(*tert*-Butoxicarbonil)Acetilamino]-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 57: 2-Cloro-*N*-[(1*R*,2*R*)-1-{[3-hidroxi-2-(hidroximetil) propanoil] amino}-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

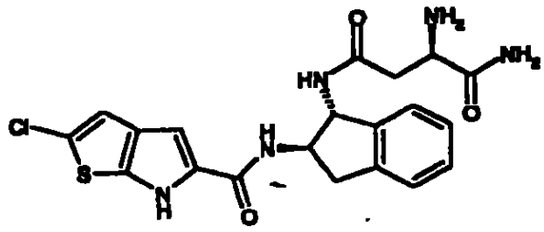
123
129



Ex	R	NMR	M/z
35	H	(DMSO-d_6) 2.88 (dd, 1H), 3.21 (dd, 1H), 4.58 (m, 1H), 5.51 (t, 1H), 7.00 (s, 1H), 7.18 (m ,5H), 8.19 (s, 1H), 8.53 (d ,2H), 11.82 (s,1H)	358,360
36	CH_2OMe	(DMSO-d_6) 2.88 (dd, 1H), 3.21 (dd, 1H), 3.30 (s, 3H), 3.86 (m, 2H), 4.71 (m ,1H), 5.51 (t, 1H), 6.99 (s, 1H), 7.15 (m, 5H), 8.23 (d, 1H), 8.50 (d, 1H), 11.82 (brs, 1H)	404,406
37	Me	(DMSO-d_6) 1.88 (s, 3H), 2.84 (dd, IH), 3.22 (dd, 1H), 4.53 (m, 1H), 5.44 (t, 1H), 6.99 (d, 1H), 7.17 (m, 5H), 8.32 (d, 1H), 8.51 (d, 1H), 11.82 (s, 1H);	374,376
38	CH_2CH_2OMe	(DMSO-d_6) 2.38 (m, 2H), 2.84 (dd, IH), 3.20 (m, 4H), 3.55 (m, 2H), 4.55 (m, 1H), 5.47 (t, 1H), 6.99 (d, 1H), 7.15 (m, 5H), 8.33 (d, 1H), 8.50 (d, 1H), 11.81 (s, 1H)	418,420
39	CH_2OAC	(DMSO-d_6) 2.07 (s, 3H), 2.88 (dd, 1H), 3.23 (dd, 1H), 4.51 (q, 2H), 4.62 (m, 1H), 5.50 (t, 1H), 7.0 (d, IH), 7.18 (m, 5H), 8.50 (t, 2H), 11.81 (s, 1H)	432,434
40		(DMSO-d_6) 1.37 (s, 9H), 2.89 (dd, 1H), 3.05 (m, 2H), 3.57 (m, 1H), 4.24 (m, IH), 5.53 (m, 1H), 5.46 (t, 1H), 6.70 (d, 1H), 6.98 (m, 2H), 7.18 (m, 5H). 8.28 (d, 1H), 8.52 (d, 1H), 11.82 (s, 1H)	568, 570
41	CH_2NHBoc	-	511,513

42	$CH_2C(O)NH_2$	(DMSO-d_6) 2.86 (dd, 1H), 3.07 (m, 2H), 3.23 (dd, 1H), 4.55 (m, 1H), 5.47 (m, 1H), 6.98 (s, 1H), 7.0 (d, 1H), 7.19 (m, 5H), 7.38 (s, 1H), 8.49 (d, 1H), 8.53 (d,1H), 11.82 (s,1H).	417,419
56	CH_2CO_2tBu	(DMSO-d_6) 1.36 (s, 9H), 2.83 (m, 1H), 3.19 (m, 3H), 4.57 (m, 1H), 5.45 (t, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.20 (m, 4H), 8.53 (t, 2H), 11.82 (s, 1H)	474,476
57		(DMSO-d_6) 2.85 (dd, 1H), 3.22 (dd, 1H), 3.45 (m, 1H), 3.57 (m, 4H), 4.51 (m, 3H), 5.48 (m, 1H), 7.0(s-1H), 7.18(m, 5H), 8.25 (d, 1H), 8.5 (d, 1H), 11.80 (s,1H)	433,435 $(M-H)^-$

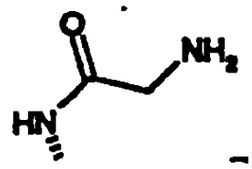
Ejemplo 43: *N*-{(1*R*,2*R*)-1-[((3)-3-Amino-3-carbamoilpropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se disolvió *N*-((1S,2S)-1-{[(2(S)-2-(*tert*-Butoxicarbonilamino)-2-carbamoilacetil] amino}-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5- carboxamida (**Ejemplo 40**,251mg, 0.46 mmol) en ácido trifluoroacético (4 mL) y se revolvió a temperatura ambiente durante 24 horas. Los volátiles se evaporaron bajo presión reducida y el material bruto se destiló mediante destilación azeotrópica con cloroformo (3x5 mL) para obtener una goma. La goma se trituró con éter (5 mL), el sólido se recolectó por filtración, se lavó con éter (2x5 mL) y se secó para obtener la sal de trifluoroacetato del compuesto del título (239 mg, 93%) como un sólido marrón.

^{1}H NMR 2.75 (m, 2H), 2.90 (dd, 1H), 3.23 (dd, 1H), 4.04 (m, 1H), 4.59 (m, 1H), 5.50 (t, 1H), 7.00 (s, 1H), 7.19 (m, 5H), 7.54 (s, 1H), 7.74 (s, 1H), 8.05 (br s, 3H), 8.56 (d, 1H), 8.70 (d, 1H). 11.83 (s, 1H); MS m/z 468,469.

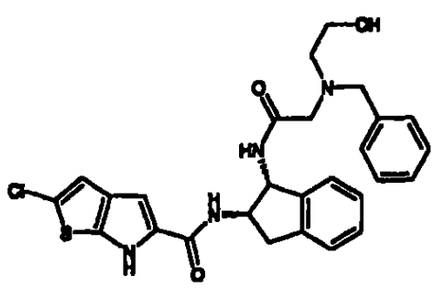
Ejemplo 44: *N*-{(1*R*,2*R*)-1-[(Aminoacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro- 6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se disolvió *N*-((1S,2S)-1-[(2-(*tert*-Butoxicarbonilamino)acetilamino]-2,3-dihidro-1*H*- inden-2-il) -2- cloro-6*H*- tieno[2,3-*b*] pirrol-5-carboxamida (**Ejemplo 41**; 366 mg, 0.75 mmol) en diclorometano (10 mL) y se agregó ácido trifluoroacético (0.5 mL) y la reacción se revolvió a temperatura ambiente durante 7 horas. Los volátiles se evaporaron bajo presión reducida y el sólido bruto se destiló mediante destilación azeotrópica con cloroformo (3x5 mL), se trituró con éter (5 mL), se recolectó para filtración, se lavó con éter (2x5 mL) y se secó para obtener la sal de trifluoroacetato del compuesto del título (200 mg, 53%) como un sólido marrón.

^{1}H NMR 2.90 (dd, 1H), 3.21 (m, 1H), 3.65 (m, 2H), 4.59 (m, 1H), 5.51 (t, 1H), 6.99 (s, 1H), 7.19 (m, 5H), 8.08 (br, 3H), 8.58 (d, 1H), 8.84 (d, 1H); MS m/z 389,391.

Ejemplo 45: 2-Cloro-*N*-[(1*R*,2*R*)-1-({[(2-hidroxietil)(fenilmetil) amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se agregó 2-(Bencilamino)etanol (160 mg, 1.06 mmol) a una solución de 2-cloro-*N*-{(1R,2R)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden-2-ilo }-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida (**Método 23**; 216 mg, 0.53 mmol) y Et_3N (500 µL, 3.60 mmol) en anhidro THF (5 mL) y la reacción se revolvió durante aproximadamente 16 horas a temperatura ambiente y luego durante 16 horas adicionales a 50 °C. Los volátiles se retiraron bajo presión reducida, el residuo se disolvió en EtOAc (10 mL), se lavó con H_2O (2 x 10 mL) y se secó con ($MgSO_4$). El solvente se retiró bajo presión reducida, el residuo se trituró (EtOAc:isohexano, 1:5), se recolectó por filtración, se lavó con isohexano (10 mL) y se secó para obtener el compuesto del título (100 mg, 36%) como un sólido marrón.
^{1}H NMR 2.58 (t, 2H), 2.90 (dd, 1H), 3.09 (dd, 2H), 3.18 (dd, 1H), 3.50 (dd, 2H). 3.68 (dd, 2H), 4.55 (t, 1H), 4.65 (m, 1H), 5.46 (t, 1H), 6.99 (s, 1H), 7.04 (d, 1H), 7.23 (m. 9H), 8.38 (d, 1H), 8.53 (d, 1H), 11.81 (s, 1H); MS m/z 523,525

Los siguientes ejemplos se efectuaron para el proceso del **Ejemplo 45** empleando 2-cloro-*N*-{(1*R*,2*R*)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden -2-ilo } -6*H*-tieno[2,3-*b*]pirrol -5-carboxamida y la amina apropiada disponible en el comercio:

Ejemplo 46: 2-Cloro-*N*-{(1*R*-2*R*)-1-[(morfolin-4-ilacetil)amino]-2,3-dihidro-1*H*-inden -2-ilo } -6*H*-tieno[2,3-*b*]pirrol -5-carboxamida

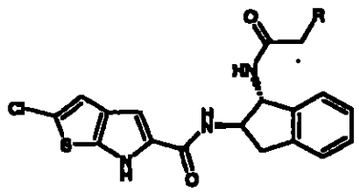
Ejemplo 47: 2-Cloro-*N*-{(1*R*-2*R*)-1-({[(2hidroxietil) (metil)amino] acetil} amino)-2,3-dihidro-1*H*-inden -2-ilo } -6*H*-tieno[2,3-*b*]pirrol -5-carboxamida

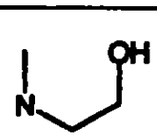
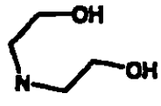
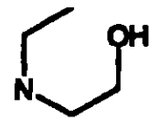
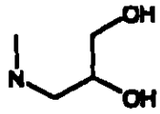
Ejemplo 48: *N*-((1*R*,2*R*)-1-({[Bis(2-hidroxietil) amino]acetil) amino) -2,3-dihidro-1*H*-inden -2-ilo)-2-cloro -6*H*-tieno[2,3-*b*]pirrol -5-carboxamida

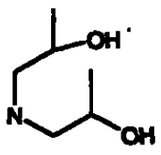
Ejemplo 49: 2-Cloro-*N*-((1*R*-2*R*)-1-({[etil(2-hidroxietil)amino]acetil) amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

Ejemplo 50: 2-Cloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihidroxipropil)(metil) amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

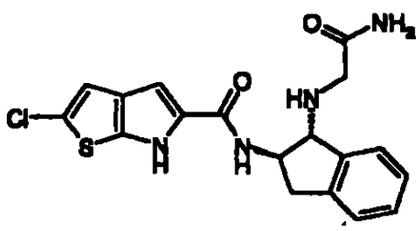
Ejemplo 51: *N*-((1*R*,2*R*)-1-({[Bis(2-hidroxipropil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Ex	R	NMR	M/z
46		(DMSO-d_6) 2.42 (m, 4H), 2.97 (m, 3H), 3.19 (dd, 1H), 3.55 (m, 4H), 4.69 (m, 1H), 5.44 (t, 1H), 6.98 (s, 1H), 7.09 (d, 1H), 7.14 (m, 4H), 8.13 (d, 1H), 8.50 (d, 1H), 11.80 (br s, 1H)	459,461
47		(DMSO-d_6) 2.21 (s, 3H), 2.47 (m, 2H), 2.90 (dd, 1H), 3.03 (dd, 2H), 3.21 (dd, 1H), 3.44 (m, 2H), 4.43 (t, 1H), 4.66 (m, 1H), 5.49 (t, 1H), 6.99 (s, 1H), 7.19 (m, 5H), 8.25 (d, 1H), 8.52 (d, 1H), 11.81 (s, 1H)	447,449
48		(DMSO-d_6) 2.59 (m, 4H), 2.91 (dd, 1H), 3.17 (m, 3H), 3.43 (m, 4H), 4.23 (t, 2H), 4.62 (m, 1H), 5.47 (t, 1H), 6.99 (s, 1H), 7.18 (m, 5H). 8.34 (d, 1H), 8.53 (d, 1H), 11.81 (br s, 1H)	477,479
49		(DMSO-d_6) 0.92 (t, 3H), 2.54 (m, 4H), 2.90 (dd, 1H), 3.07 (dd, 2H), 3.21 (m, 1H), 337 (m, 2H), 4.45 (t, 1H), 4.63 (m, 1H), 5.46 (t, 1H), 6.98 (s, 1H), 7.16 (m ,5H), 8.25 (d, 1H), 8.51 (d, 1H), 11.80 (s, 1H)	461,463
50		(DMSO-d_6) 2.22 (s, 3H), 2.42 (m, 2H), 2.99 (m, 3H), 3.25 (obs m, 3H), 3.56 (m, lH), 4.43 (m, 1H), 4.54 (m, 1H), 4.66 (m, 1H), 5.50 (t, 1H), 6.99 (s, 1H), 7.17 (m, 5H), 8.34 (d, 1H), 8.51 (m, 1H), 11.80 (s, 1H)	477.479

51		(DMSO-d_6) 0.96 (m, 6H), 2.35 (m, 4H), 2.88 (dd, 1H). 3.11 (dd, 1H), 3.67 (m, 2H), 4.49 (m, 2H), 4.60 (m, 1H), 5.47 (t, 1H), 6.99 (s, 1H), 7.17 (m, 5H), 8.69 8.49 (m,2H),11.77(s, 1H)	505,507 *

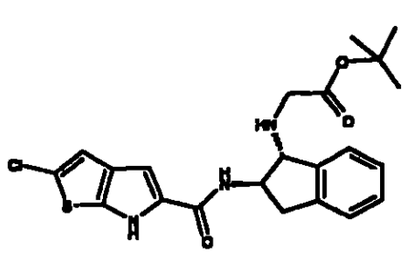
Ejemplo 52: *N*-{(1*R*,2*R*)-1-[(2-Amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se calentó en el microondas N-{(1*R*, 2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-il)-2-carboxamida sal de ácido trifluoroacético (**Método 21**, 225 mg, 0.5 mmol), DIPEA (216 µL, 1.5 mmol) y bromoacetamida (70 mg, 0.5 mmol) a 180°C durante 3 minutos. Se agregó EtOAc (30 mL) y la mezcla se lavó con agua (2 x 10 mL), solución salina (10 mL), se secó con ($MgSO_4$) y se evaporó. El residuo se purificó por medio de una cromatografía en columna (EtOAc:MeOH 19:1) para obtener el compuesto del título (52 mg, 27%) como una espuma blanca.

^{1}H NMR 2.68 (s, 1H), 2.79 (dd, 1H), 3.24 (m, 3H), 4.21 (m, 1H), 4.41 (m, 1H), 7.02 (m, 2H), 7.14 (s, 1H), 7.21 (m, 3H), 7.28 (m, 1H), 7.36 (m, 1H), 8.42 (d, 1H), 11.83 (s, 1H); MS m/z 389,391.

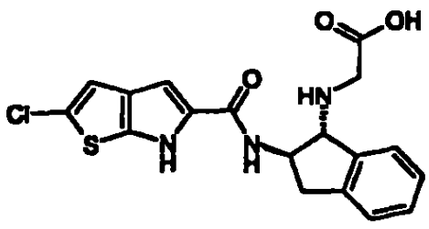
Ejemplo 53: *N*-[(1*R*,2*R*)-1-[*tert*-Butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se agregó DIPEA (350 µL, 2.0 mmol) y *t*-butilo bromoacetato (90 µL, 0.7 mmol) a una solución de *N*-{(1*R*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-il)-2-carboxamida (**Método 21**, 300 mg, 0.7 mmol) en CH_3CN (10 mL). La solución resultante se revolvió a 60°C durante aproximadamente 2 horas. Después de su enfriamiento, los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (10 mL), se lavó con agua (2 x 10 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por cromatografía en columna (EtOAc:isohexano 1:1) para obtener el compuesto del título (30 mg, 10%) como un sólido blanco.

^{1}H NMR 1.45 (s, 9H), 2.11 (br s, 1H), 2.80 (dd, 1H), 3.60 (m, 3H), 4.27 (d, 1H), 4.46 (m, 1H), 6.8 (d, 2H), 7.10 (d, 1H), 7.30 (m, 4H), 11.35 (s, 1H); MS m/z 446,448.

Ejemplo 54: *N*-{(1*R*,2*R*)-1- (Carboximetilamino)-2,3-dihidro-1*H*-inden-2-ilo-2-cloro-6*H*-tieno(3,2-*b*]pirrol-5-carboxamida

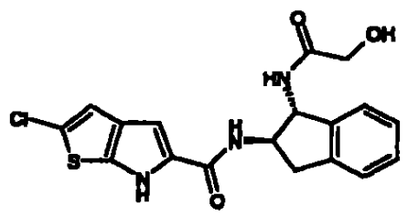


Se disolvió *N*-[(1*R*,2*R*)-1-[(*tert*- Butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida (**Ejemplo 53**, 100 mg, 0.22 mmol), en DCM (5mL). Se agregó TFA (1 mL) y la reacción se revolvió a temperatura ambiente durante 20 horas.

Evaporación bajo presión reducida, co-evaporación con $CHCl_3$ (2 x 10 mL) y el secado produjo una sal de ácido trifluoroacético del compuesto del título (110 mg, 99%) como un polvo gris.

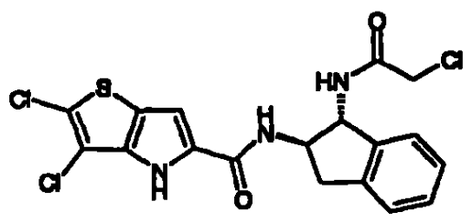
^{1}H NMR 3.1 (dd, 1H), 3.52 (dd, 1H), 4.2 (m, 2H), 4.9 (m, 2H), 7.05 (s, 1H), 7.2 (s. 1H), 7.4 (m, 3H), 7.7 (d, 1H), 8.76 (d, 1H), 9.73 (s, 2H), 12.02 (s, 1H), 13.9 (s, 1H); MS m/z $(M-H)^-$ 388,390.

Ejemplo 58: 2-Cloro-*N*-{(1*R*-2*R*)-1-[(hidroxiacetilamino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



Se disolvió *N*-{(1*R*,2*R*)-1-[(2-Acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida (**Ejemplo 39**; 393 mg, 0.92 mmol) en THF (5 mL), MeOH (5 mL) y luego se agregó K_2CO_3 (50 mg) y la suspensión se revolvió a temperatura ambiente durante 4 horas. Se agregó agua (10 mL) y la fase acuosa se extrajo con EtOAc (3 x 10 mL). Las fases orgánicas combinadas se lavaron con agua (50 mL), solución salina (50 mL) y se secaron con ($MgSO_4$). El solvente se retiró por evaporación bajo presión reducida, el producto bruto se trituró (EtOAc:isohexano, 1:5), se filtró, se lavó con isohexano (5 mL) y se secó para obtener el compuesto del título (257 mg, 72%) como un sólido blanco. ^{1}H NMR 2.86 (dd, 1H), 3.23 (dd, 1H), 3.88 (dd, 2H), 4.70 (m, 1H), 5.39 (t, 1H), 5.50 (t. 1H), 7.00 (s, 1H), 7.18 (m, 5H), 8.10 (d, 1H), 8.51 (d, 1H), 11.81 (s, 1H); MS m/z 391,393.

Ejemplo 59: 2,3-Dicloro-*N*-{(1R,2R)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

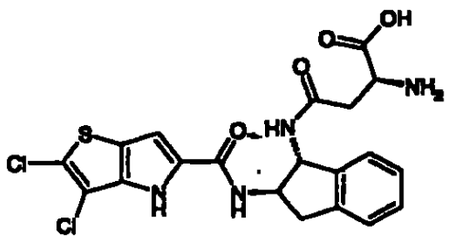


Se disolvió *N*-[(1*R*,2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida (**Método 8**, 602 mg, 1.6 mmol) en diclorometano (30 mL), y a lo anterior se agregó trietilamina (0.25 mL, 1.8 mmol) y cloruro de cloroacetilo (0.14 mL, 1.8 mmol). La

solución se revolvió a temperatura ambiente durante 16 horas, después de lo cual se agregó trietilamina (0.25ml, 1.8mmol) y cloruro de cloroacetilo (0.14ml, 1.8mmol) antes de revolver durante una hora. Se agregó agua (15 mL) a la pasta aguada resultante antes de filtrarla para obtener el producto del título (532 mg, 73%) como un sólido crema.

^{1}H NMR 2.88 (m, 1H), 3.25 (m, 1H), 4.11 (s, 2H), 4.63 (m, 1H), 5.47 (t, 1H), 7.13 (m, 2H), 7.23 (m, 3H), 8.63 (d, 1H), 8.73 (d, 1H), 12.38 (s, 1H); MS m/z 442.

Ejemplo 60: *N*-{(1*R*,2*R*)-1-[((3S)-3-Amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno(3,2-*b*]pirrol-5-carboxamida



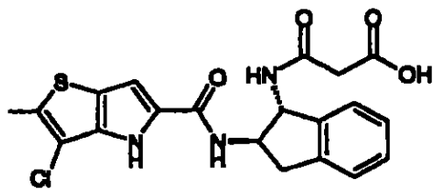
Se agregó *N*-[(1*R*,2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida (**Método 8**, 350 mg, 0.73 mmol) a una solución de *N-alfa-t*-Boc-1-ácido aspártico *alfa-t*- butilo éster (232 mg, 0.80 mmol), 1-hidroxibenzotriazole monohidrato (123 mg, 0.80 mmol), 1-etilo-3-(3-dimetilaminopropil)hidrocloruro carbodiimida (154 mg, 0.80 mmol), 4-metilmorfolina (0.18 mL, 1.6 mmol) in *N,N*-dimetilformamida (20 mL). La mezcla se revolvió a temperatura ambiente durante 16 horas. Los volátiles se retiraron por evaporación y se disolvió el residuo en etilo acetato (20 mL) y agua (10 mL), las capas se separaron antes de lavarlas con 2*M* HCl, luego se saturaron con $NaHCO_3$. La evaporación produjo un sólido blanco que se volvió a disolver en diclorometano (5 mL) y ácido trifluoroacético (5 mL), se dejo revolver la solución a temperatura ambiente durante 2 horas. Los volátiles se retiraron por evaporación y el residuo se trituró con éter, se recolectó por filtración, se lavó con éter (2 x 10 ml) y se secó para obtener el compuesto del título

(210 mg, 48%) como un sólido blanco.

^{1}H NMR 2.85 (m, 2H), 3.25 (m, 2H), 3.94 (t, 1H), 4.56 (m, 1H), 5.45 (t, 1H), 7.11 (s, 1H), 7.23 (m, 4H), 8.64 (d, 1H), 8.73 (d, 1H); MS m/z 481.

Los siguientes ejemplos se prepararon en forma similar a la del **Ejemplo 60** empleando *N*-[(1R,2R)-1 -amino-2,3-dihidro- 1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Método 8**) o *N*-{(1*R*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-il)-2-carboxamida (**Método 21**) como el componente amina y el ácido carboxílico protegido en forma apropiada como el material de inicio, antes de la desprotección.

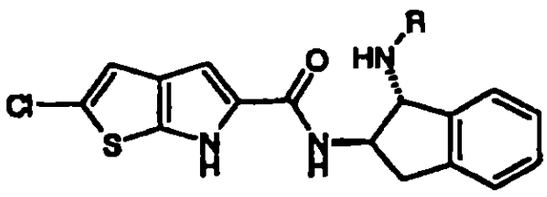
Ejemplo 61: *N*-{(1*R*,2*R*)-1-[(2-Carboxiacetil)amino]2,3-dihidro-1*H*-inden-2-ilo-2,3-dicloro-4*H*-tieno(3,2-*b*]pirrol-5-carboxamida



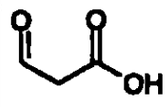
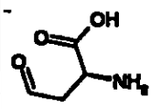
^{1}H NMR 2.84 (m, 1H), 3.25 (m, 3H), 4.56 (m, 1H), 5.47 (t, 1H), 7.11 (s, 1H), 7.20 (m, 4H), 8.59 (m, 1H), 12.36 (s, 1H); MS m/z 452.

Ejemplo 62: *N*-{(1*R*,2*R*)-1-[(2-Carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno(3,2-*b*]pirrol-5-carboxamida

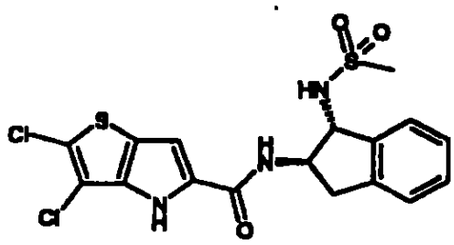
Ejemplo 63; *N*-{(1*R*,2*R*)-1-[((3S)-3-Amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno(3,2-*b*]pirrole-5-carboxamida



143
189

Ex	R	^{1}H NMR	m/z
62		2.84 (m, 1H), 3.17 (m, 3H), 4.55 (m,1H), 5.47 (t, 1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.20 (m, 4H), 8.53 (t, 2H), 11.82 (s. 1H), 12.42(s,1H)	419,421
63		2.64 (m, 1H), 2.85 (m, 2H), 3.23 (m,1H), 4.00(t,1H) 4.56 (m, 1H), 5.45 (t,1H), 7.00 (s, 1H), 7.15 (s, 1H), 7.23 (m, 4H), 8.53 (d, 1H), 8.71 (d, 1H)	447,449

Ejemplo 64: 2,3-Dicloro-*N*-{(1*R*,2*R*)-1-[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

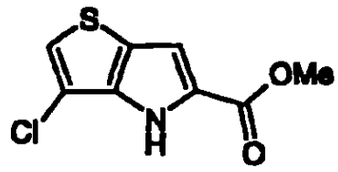


Se disolvió *N*-[(1*R*,2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*- tieno [3,2-*b*]pirrol-5-carboxamida sal de trifluoroacetato (**Método 8**, 223 mg, 0.5 mmol) en THF (4 mL) y la solución se enfrió a 0 °C. Se agregó Et_3N (223 µL, 1.6 mmol) y luego cloruro de metanosulfonilo (43 µL, 0.55 mmol) y la reacción se revolvió 0 °C durante 5 minutos. Se agregó $NaHCO_3$ acuoso (5 mL), las fases se separaron y la fase acuosa se extrajo con EtOAc (3 x 10 mL). Las fracciones orgánicas combinadas se lavaron con H_2O (20 mL), se secaron con ($MgSO_4$) y el solvente se retiró bajo presión reducida. El residuo se sometió a purificación por medio de un preparado de fase reversa HPLC para obtener el compuesto del título (30 mg, 15%) como un sólido blanco.

^{1}H NMR 2.83 (dd, 1H), 2.98 (s, 3H), 3.22 (dd, 1H), 4.55 (m ,1H), 4.96 (t, 1H), 7.01 (s, 1H), 7.23 (m, 5H), 7.87 (d, 1H), 8.57 (d, 1H), 11.90 (s, 1H); MS m/z 410,412.

Método 1

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



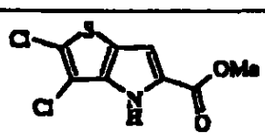
Se diluyó una solución de metóxido sódico metanólico (28%) (5 ml, 25.9 mmol) con MeOH (5 ml) y se enfrió a -25°C bajo nitrógeno. En forma de goteo se agregó una solución de 4-cloro-2-tiofenecarboxaldehído (J Heterocyclic Chem, 1976, 13, 393; 1.1 g, 7.5 mmol) y metil azidoacetato (3.0 g, 26.1 mmol) en MeOH (20 ml), manteniendo la temperatura a -25°C. Una vez se terminó la adición, se dejó tibiar la solución a 5°C durante un periodo de aproximadamente 16 horas. La solución se agregó al cloruro de amonio acuoso saturado (250 ml) y se extrajo la mezcla usando DCM. Las capas orgánicas combinadas se concentraron a 0°C. El residuo se absorbió en xiloeno (30 ml) y esta solución se agregó en forma de goteo al xiloeno (120 ml) bajo reflujo. La solución se calentó a reflujo durante 30 minutos antes de enfriarla y concentrarla. El compuesto del título se purificó mediante una mezcla de cristalización (EtO Ac/isohexano) y cromatografía en una columna Bond Elut levigándolo con un solvente graduado al 5-50% de 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.

Método 2 y 2a

Se prepararon los siguientes compuestos para el proceso del Método 1 empleando los materiales de inicio apropiados.

Método 2: 2,3-Dicloro-5-metoxicarbonilo-4*H*-tieno[3,2-*b*]pirrol

Método 2a: : 2-Cloro-5-metoxicarbonilo-6*H*-tieno[2,3-*b*]pirrol

Método	Compuesto	NMR ($CDCl_3$)	M/z
2		9.2(1H,br), 7.0(1H,s),3.9(3H,s)	248.2

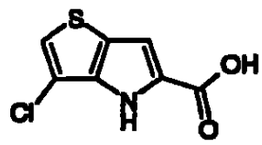
2a[2]		9.4-9.2 (1H, br), 7.0 (1H, s), 6.9(1H, s), 3.9 (3H,s)	214

1 aldehído: DE 2814798

2 aldehído: Gronowitz *y colaboradores*. Tetrahedron Vol.32 1976 p. 1403

Método 3

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



Se absorbió 3-Cloro-5-metoxicarbonilo-4*H*-tieno[3,2-*b*]pirrol (**Método 1**; 0.61 g, 2.83 mmol) en MeOH (10 ml) y se calentó bajo reflujo. Se agrego hidróxido de litio acuoso (2.0 M, 3.0 ml, 6.0 mmol) en forma de porciones durante 45 minutos. La mezcla se calentó bajo reflujo durante 30 minutas antes de enfriarla y concentrarla. Se agregó agua (20 ml) y se neutralizó la solución empleando ácido clorhídrico acuoso (2.0 M, 3.0 ml). Se extrajo la solución utilizando EtOAc, y las capas orgánicas combinadas se concentraron para obtener 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

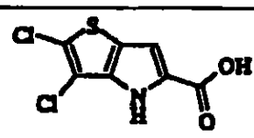
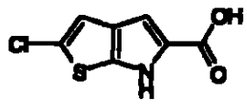
Método 4 y 4a

Se prepararon los siguientes compuestos para el proceso del **Método 3** utilizando los métodos 2 y 2a como los materiales de inicio.

Método 4: 5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol

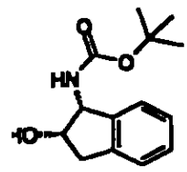
Método 4a: 5-Carboxi-2-cloro-6*H*-tieno[2,3-*b*]pirrol

Método	Compuesto	NMR ($CDCl_3$)	M/z	SM

4		7.0 (1H,s)	234.2	Método 2
4a		12.6-12.7(1H,b), 12.0-12.1(1H,b), 7015(1H,s), 6.9(1H,s)		Método 2a

Método 5

Cis-1-[(1,1-Dimetiletoxi)carbonilamino]-2 hidroxiindan

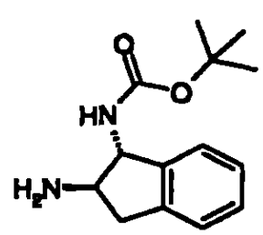


Se disolvió *Cis*-1 -Amino-2-hidroxiindan (12.0g, 80.5mmol) en DCM (500 ml) y trietilamina (22.4 ml, 161mmol). Se agregó di-*tert*-butilo dicarbonato (22.0g, 100mmol) en DCM (50 ml) y la mezcla se revolvió a temperatura ambiente durante 20 horas y luego se evaporó. Se agregó EtOAc (200 ml), la solución se lavó con agua, se secó sobre sulfato de magnesio y se evaporó. El producto bruto se evaporó por cromatografía en sílice con 4:1 *iso*-hexano: EtOAc como fase móvil para obtener el compuesto del título (17.9 g, 90%) como un sólido blanco.

^{1}H NMR 1.42 (s, 9H). 2.78 (dd, 1H), 3.00 (dd, 1H), 4.40 (m, 1H), 4.85 (m, 1H), 4.95 (m, 1H), 6.30 (d,1H), 7.10 (m,4H).

Método 6

Trans-2-Amino-1-[(1,1-dimetiletoxi)carbonilamino]indan



Se disolvió *Cis*-1-[(l,l-Dimetiletoxi)carbonilamino]-2-hidroxiindan

(**Método 5**; 14.0g, 56.2mmol) en DCM (200 ml) y trietilamina (11.8 ml, 84.3 mmol). Se agregó cloruro de metanosulfonilo (7.1g, 61.9mmol) disuelto en DCM (20 ml) y la mezcla se revolvió a temperatura ambiente durante 3 horas. La mezcla se evaporó y se agregó EtOAc (250 ml). Después de lavarla con agua y de secarla sobre sulfato de magnesia, la solución orgánica se evaporó para producir *Cis*-1-[(1,1-dimetiletoxi)carbonilamino]-2-metanosulfoniloxiindan (9.7g, 98%) como un sólido blanco.

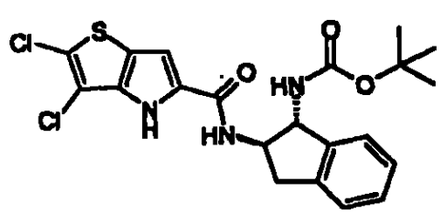
^{1}H NMR 1.45 (5, 9H), 3.15 (m, 2H), 3.18 (s, 3H), 5.20 (m, 1H), 5.35 (m, 1H), 7.15 (m, 4H), 7.45 (d, 1H).

Se disolvió *Cis*-1-[(1,1-dimetiletoxi)carbonilamino]-2-metanosulfoniloxiindan (18.1g, 55.3mmol) en dimetil acetamida seca (100 ml). Se agregó azida sódica (5.4g, 83.0mmol) y la mezcla se calentó a 90°C durante horas. La reacción se enfrió, se diluyó con etilo acetato (150 ml), se lavó con agua (6 x 200 ml) y se secó sobre sulfato de magnesio. Se agregó 10% paladio sobre carbón activado y la mezcla se revolvió bajo una atmósfera de hidrógeno durante 24 horas. La filtración mediante Celite, seguida por evaporación produjo el compuesto del título(2.6g, 98%) como un sólido blanco.

^{1}H NMR: 1.45 (s, 9H), 2.50 (dd, 1H), 3.05 (dd, 1H), 3.30 (m, 3H), 4.55 (m, 1H), 7.1 (m, 5H).

Método 7

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



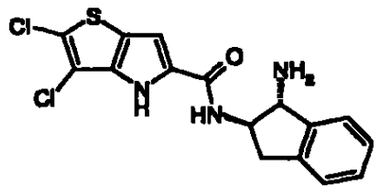
Se revolvió 5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (**Método 4**;

236g, 10.0 mmol), *trans*-2-amino-1-{*N*-[(1,1-dimetiletoxi)]carbonilamino} indan (**Método 6**; 2.5g, 10.0mmol), DIPEA (1.7 ml, 10.0mmol) y HOBT (1.35g, 10.0mmol) en DCM (75 ml) a temperatura ambiente durante 2 minutes. Se agregó EDCI (2.4g, 12.5mmol) y la mezcla se revolvió a temperatura ambiente durante 20 horas, y durante este tiempo se precipitó el producto. La reacción se filtró, se lavó con DCM (2 x 25 ml) y se secó para obtener el compuesto del título (3.7 g, 80%) como un polvo de color verde pálido.

^{1}H NMR 1.40 (s, 9H), 2.81 (dd, 1H), 3.20 (dd, 1H), 4.55 (m, 1H), 5.15 (m, 1H), 7.15 (m, 5H), 7.35 (d, 1H), 8.55 (d, 1H), 12.36 (broad s, 1H); m/z 463.7/465.7.

Método 8

N-[(1*R*,2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

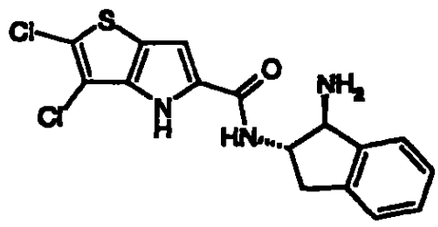


Se disolvió 2,3-Dicloro-5-(*N*-{1-[(1,1-dimetiletoxi) carbonilamino]indan-2-il} carbamoil) -4*H*-tieno[3,2-*b*]pirrol (**Método 7**; 3.7g, 7.9mmol) en DCM (75 ml). Se agregó ácido trifluoroacético (10 ml) y la mezcla se revolvió a temperatura ambiente durante 24 horas. La reacción se filtró y el sólido aislado se lavó con DCM para obtener la sal de ácido trifluoroacético del compuesto del título (3.1g, 82%) como un polvo de color verde pálido.

^{1}H NMR 3.05 (dd, 1H), 3.42 (d, 1H), 4.7 (m, 2H), 7.20 (d, 1H), 7.35 (m, 3H), 7.55 (d, 1H), 8.60 (broad s, 3H), 8.80 (d, 1H), 12.5 (broad s, 1H).

Método 9

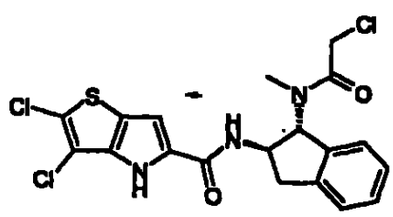
N-[(1*S*,2*S*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*] pirrol-5-carboxamida



El compuesto del título se preparó en forma análoga al **Método 8**.
^{1}H NMR 3.05 (dd, 1H), 3.42 (d, 1H), 4.7 (m, 2H), 7.20(d, 1H), 7.35 (m, 3H), 7.55 (d, 1H), 8.60 (broad s, 3H), 8.80 (d, 1H), 12.5 (broad s, 1H).

Método 10

2,3-Dicloro-*N*-{(1*R*,2*R*)-1-[(cloroacetil)(metil)amino]-2,3-dihidro-1*H*-inden-2-ilo-}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida

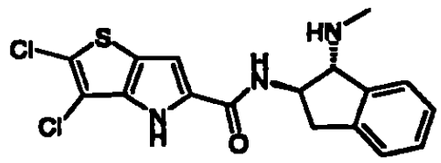


Se disolvió 2,3-Dicloro-*N*-[(1*R*,2*R*)-1-(metilamino)-2,3-dihidro)-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Método 11**; 300 mg, 0.79 mmol) y trietilamina (167 µL, 1.2 mmol) en DCM (5 mL), se agregó cloruro de cloroacetilo (73 µL, 0.9 mmol) y la reacción se revolvió a temperatura ambiente durante 2 horas. Los volátiles se retiraron por evaporación bajo presión reducida y se agregó EtOAc (15 mL). La mezcla se lavó con agua (10 mL), solución salina (10 ml), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (310 mg, 86%) como una espuma de color marrón pálido.
^{1}H NMR 2.73 (d, 3H), 2.98 (m, 1H), 3.24 (m, 1H), 4.45 (m, 2H), 4.82 (m, 1H), 5.77 (dd, 1H), 7.05 (m, 2H), 7.28 (m, 3H), 8.65 (m, 1H); MS m/z 456.

Método 11

2,3-Dicloro-*N*-[(1*R*,2*R*)-1-(metilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-

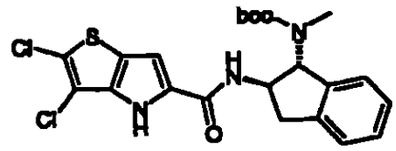
tieno[3,2-*b*]pirrol-5-carboxamida



Se disolvió *tert*-Butilo ((1*R*,2*R*)-2-{ [(2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil]amino}-2,3-dihidro-1*H*-inden-1-il)metilcarbamato (**Método 12**; 900 mg, 1.87 mmol) en DCM (20 mL), se agregó TFA (2 mL) y la reacción se revolvió a temperatura ambiente durante 1 hora. Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por una cromatografía de intercambio de iones (MeOH: Agua 1:1 luego MeOH: Agua.NH_4OH 1:1:0.05) para obtener, después de evaporación el compuesto del título (300 mg, 32%) como un polvo de color blancuzco. ^{1}H NMR 2.75 (s, 3H), 3.01 (dd, 1H), 3.49 (dd, 1H), 4.75 (m, 1H), 4.86 (m, 1H), 7.11 (d, 1H), 7.35 (m, 3H), 7.58 (d, 1H), 8.74 (d, 1H), 9.04 (m, 1H), 12.37 (s, 1H); MS m/z 380.

Método 12

tert-Butilo ((1*R*,2*R*)-2-{[2,3- dicloro- 4*H*-tieno [3,2-*b*]pirrol-5-il)carbonil]amino}-2,3-dihidro-1*H*-inden-1-il)metilcarbamato

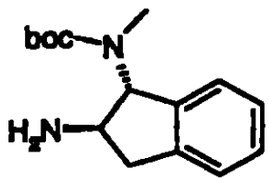


Se disolvió 5-Carboxi-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol (**Método 4**, 472 mg, 2.0 mmol), *tert*-butilo [(1*R*,2*R*)-2-amino-2,3-dihidro-1*H*-inden-1-il]metilcarbamato (Método 13; 524 mg, 2.0 mmol), DIPEA (348 µL, 2.0 mmol), HOBT (270 mg, 2.0 mmol) y EDCI (480 mg, 2.5 mmol) en DCM (10 mL) y se revolvió a temperatura ambiente durante 20 horas. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (50 mL), se lavó con agua (3 x 25 mL), solución salina (25 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (900 mg, 93%)

como una espuma de color marrón pálido.
^{1}H NMR 1.29 (m, 9H), 2.66 (s, 3H), 2.9-3.25 (m, 2H), 4.8 (m, 1H), 5.64 (m, 1H). 6.23-7.34 (m, 4H), 8.65 (m, 1H); MS m/z 480.

Método 13

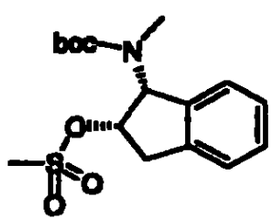
tert-Butilo [(1*R*,2*R*)-2-amino-2,3-dihidro-1*H*-inden-1-il]metilcarbamato



Se calentó (1*R*,2*S*)-1-(*tert*-Butoxicarbonil)(metil)amino]-2,3-dihidro-1*H*-inden-2-ilo metanosulfonato (**Método 14**; 3.0g, 8.8mmol) y azida sódica (2.3 g, 35.2 mmol) en DMA seco (30 mL) a 90°C durante 7 horas. La reacción se enfrió y se agregó etilo acetato (100 mL). La mezcla se lavó con agua (6 x 25 mL), solución salina (50 mL) y se secó con ($MgSO_4$). Se agregó 10% de paladio en el carbono (400 mg) a la solución orgánica que se revolvió bajo una atmósfera de hidrógeno durante 4 horas, se filtró por Celite y se evaporó. El residuo se purificó por medio de una cromatografía en columna (EtOAc y luego DCM:MeOH 9:1) para obtener el compuesto del título (1.2 g, 55%) como un aceite de color marrón pálido.
^{1}H NMR 1.45 (m, 9H), 2.6 (s, 3H), 2.8 (m, 1H), 33 (m, 1H), 4.45 (m, 1H), 5.55 (dd, 1H), 7.26 (m, 4H); MS m/z 264.

Método 14

(1*R*-2*S*)-1-[(*tert*-Butoxicarbonil)(metil)amino]-2,3-dihidro-1*H*-inden-2-ilo metanosulfonato

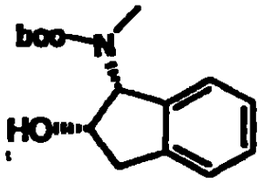


Se disolvió *tert*-Butilo[(1*R*,2*S*)-2- hidroxi-2,3- dihidro-1*H*- inden-1-

il] metilcarbamato (**Método 15**; 3.0 g, 11.4 mmol) en THF seco (40 mL) a 10°C. Se agregó una solución de cloruro de metano sulfonilo (1.44 g, 12.55 mmol) en THF seco (10 mL), se dejó calentar la reacción a temperatura ambiente y se revolvió durante 30 minutos. Los volátiles se retiraron por evaporación bajo presión reducida y se agregó etilo acetato (100 mL). La mezcla se lavó con agua (2 x 50 mL), solución salina (50 mL) y la fase orgánica se secó con ($MgSO_4$), se filtró y evaporó. El residuo se purificó por medio de una cromatografía en columna (EtOAc:Hexano) para obtener el compuesto del título (3.1g, 80%) como un jarabe incoloro.
^{1}H NMR 1.46 (s, 9H), 2.61 (s, 3H), 3.12 (m, 1H), 3.18 (s, 3H), 3.32 (m, 1H), 5.45 (m, 1H), 5.68 (m, 1H), 7.28 (m, 4H); MS m/z 342.

Método 15

tert-Butilo [(1*R*,2*S*)-2-hidroxi-2,3dihidro-1*H*-inden-1-il]metilcarbamato

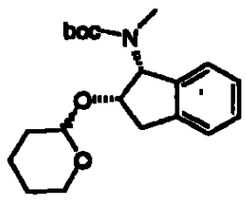


Se disolvió *tert*-Butilo metil[(1*R*,2*S*)-2-(tetrahidro-2*H*-piran-2-iloxi)-2,3-dihidro-1*H*-inden-1-il]carbamato (**Método 16**; 4.0 g, 11.5 mmol) en metanol (50 mL), se agregó 4-tolueno ácido sulfónico y la reacción se revolvió a temperatura ambiente durante 2 horas. Se agregó $NaHCO_3$ saturado (50 mL), agua (100 mL) y se agregó etilo acetato (100 mL) y la mezcla se revolvió durante 30 minutos. La fase orgánica se separó, se lavó con agua (50 mL), solución salina (50 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (3.0 g, 99%) como un aceite.
^{1}H NMR 1.45 (s, 9H), 2.6 (s, 3H), 2.75 (m, 1H), 3.05 (m, 1H), 4.5 (m, 1H), 5.05 (m, 1H), 5.34 (m, 1H), 7.03-7.3 (m, 4H).

Método 16

tert-Butilo metil[(1*R*,2*S*)-2-(tetrahidro-2*H*-piran-2-iloxi)-2,3-dihidro-1*H*-

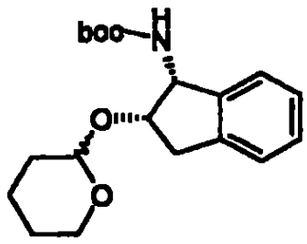
inden-1-il]carbamato



Se disolvió *tert*-Butilo [(1*R*,2*S*)-2-(tetrahidro-2H-piran-2-iloxi)-2,3-dihidro-1*H*-inden-1-il]carbamato (**Método 17**; 4.0 g, 12.0 mmol) en DMA seco (25 mL) a 5°C. Se agregó 60% de hídrido sódico (575 mg, 14.4 mmol) la reacción se revolvió a 5°C durante 30 minutos, se dejó calentar a temperatura ambiente y se revolvió durante 30 minutos adicionales. Se agregó metil iodida (896 µL, 14.4 mmol) y la reacción se revolvió a temperatura ambiente durante 3 horas. La reacción se vertió sobre agua (100 mL) y se extrajo con etilo acetato (2 x 50ml). Los extractos orgánicos se lavaron con agua (6 x 25 mL), solución salina (50 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (4.1 g, 97%) como un aceite.
^{1}H NMR 1.4-1.9 (m, 6H), 1.5 (s, 9H), 2.7 (dd, 3H), 2.85-3.3 (m, 2H), 3.5 (m, 1H), 3.7-4.0 (m, 1H), 4.6-4.9 (m, 2H), 5.5-5.85 (m, 1H), 7.2 (s, 4H).

Método 17

tert-Butilo [(1*R*,2*S*)-2-(tetrahidro-2*H*-piran-2-iloxi)-2,3-dihidro-1*H*-inden-1-il]carbamato



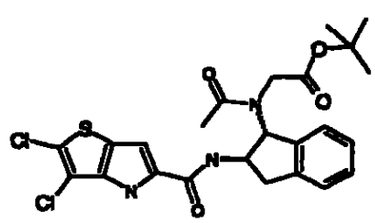
Se disolvió *tert*-Butilo [(1*R*,2*S*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il]carbamato (**Método 15**, 7.0 g, 28.1 mmol) y 3,4-dihidro-2H-piran (4.7 g, 56.2 mmol) en DCM (50 mL). Se agregó 4-Tolueno ácido sulfónico sal de piridinio (100 mg) y la reacción se revolvió durante 4 horas a temperatura ambiente. La reacción se diluyó con etilo acetato (100 mL), se lavó con

agua (2 x 50 mL), solución salina (50 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (8.9 g, 95%) como un aceite.

^{1}H NMR 1.25-1.85 (m, 6H), 1.45 (s, 9H), 2.85-3.1 (m, 2H), 3.4 (m, 1H), 3.8 (m, 1H), 4.35-5.1 (m, 3H), 6.8 (dd, 1H), 7.2(s, 1H).

Método 18

1,1-Dimetiletilo[acetil((1*R*,2*R*)-2-{[(2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil]amino} -2,3-dihidro-1*H*-inden-1-il)amino]acetato

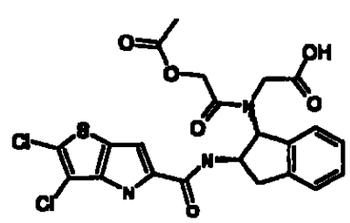


Se agregó cloruro de cetilo (7 µL, 0.1 mmol) a una solución de *N*-(1*R*,2*R*)-1-[(*tert*-butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida (**Ejemplo 29**, 50 mg, 0.1 mmol) en THF (5 mL). La reacción se revolvió a temperatura ambiente durante 1 hora. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (5 mL), se lavó con agua (2x5 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se purificó por cromatografía en columna (EtOAc:isohexano 1:1) para obtener el compuesto del título (168 mg, 76%) como un sólido blanco.

^{1}H NMR 1.40 (s, 9H), 2.75 (dd, 1H), 3.42 (m, 2H), 3.60 (dd, 1H), 3.90 (s, 3H), 4.15 (d, 1H), 4.45 (m, 1H), 6.83 (d, 1H), 7.20 (m, 4H), 7.70 (d, 1H), 9.70 (s, 1H); MS m/z 522.

Método 19

[[(Acetiloxi)acetil]((1*R*,2*R*)-2-{[2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil]amino}-2,3-dihidro-1*H*-inden-1-il)amino]ácido acético

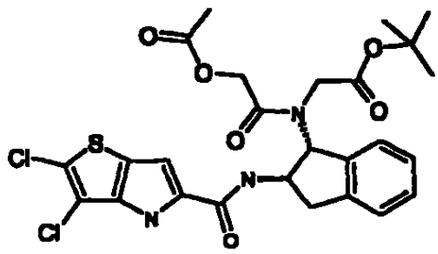


Se agregó TFA (3 mL) a una solución de 1,1 –dimetiletilo [[(acetiloxi)acetil]((1*R*,2*R*)-2-{[(2,3-dicloro-4H-tieno[3,2-*b*]pirrol-5-il) carbonil]amino} -2,3-dihidro-1*H*-inden-1-il)amino]acetato (**Método 20**, 130 mg, 0.25 mmol) en DCM (10 mL) y la reacción se revolvió a temperatura ambiente durante 2 horas. Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (130 mg, 99%) como un sólido blanco.

^{1}H NMR 2.20 (s, 3H), 2.78 (dd, 1H), 3.32 (dd, 1H), 3.97 (m, 2H), 4.35 (d, 1H, 4.68 (m, 2H), 4.90 (d, 1H), 6.42 (d, lH), 6.83 (s, 1H), 7.25 (m, 4H), 11.14, (s, 1H); MS m/z 524.

Método 20

1,1-Dimetiletilo[[(acetiloxi)acetil]((1*R*,2*R*)-2-{[(2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-il)carbonil]amino} -2,3-dihidro-1*H*-inden-1-il) amino] acetato



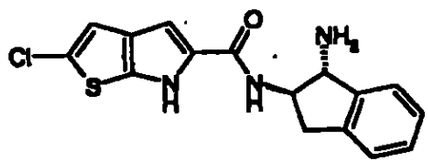
Se agregó ácido acetoxiacético (34 mg, 03 mmol) y DMTMM (81 mg, 03 mmol) a una solución de *N*-(1*R*,2*R*)-1-[tert-butoxicarbonilmetil)amino] -2,3-dihidro-1H-inden-2-il}-2,3- dicloro-4*H*-tieno[3,2-*b*] pirrol-5-carboxamida (**Ejemplo 29**, 140 mg, 0.3 mmol) en THF (10 mL). La reacción se revolvió a temperatura ambiente durante 7 horas. Los volátiles se retiraron por evaporación bajo presión reducida, el residuo se disolvió en EtOAc (10 mL), se lavó con agua (2x5 mL), solución salina (10 mL) y se secó con ($MgSO_4$). Los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (145 mg, 83%)

como un sólido blanco.

^{1}H NMR 1.45 (s, 9H), 2.10 (s, 3H), 2.75 (dd, 1H), 3.50 (m, 3H), 3.90 (m, 2H), 4.15 (d, 1H), 4.50 (m, 1H), 6.83 (s, 1H), 7.20 (m, 4H), 7.70 (d, 1H), 9.70 (s, 1H); MS m/z 580.

Método 21

N-[(1*R*,2*R*)-1-Amino-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida

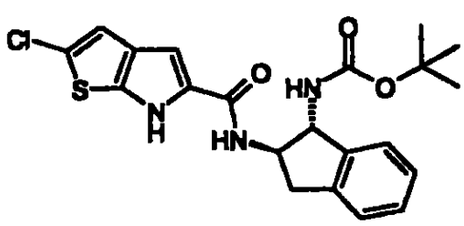


Se suspendió *tert*-Butilo((1*R*,2*R*)-2-{[(2-Cloro-6*H*-tieno[2,3-*b*]pirrol-5-il) carbonil] amino}-2,3-dihidro- 1*H*-inden-1-il)carbamato (**Método 22**, 10.6 g, 24.5 mmol) en DCM (200 mL), se agregó TFA (20 mL) y la reacción se revolvió a temperatura ambiente durante 20 horas. Los volátiles se retiraron por evaporación bajo presión reducida y el residuo se trituró con DCM (50 mL) luego se filtró y se secó para obtener el compuesto del título (10.9 g, 100 %) como la sal de ácido trifluoroacético.

^{1}H NMR 3.03 (dd, 1H), 3.38 (dd, 1H), 4.7 (m, 2H), 7.06 (d, 1H), 7.17 (s, 1H), 7.35 (m, 3H), 7.55 (m, 1H), 8.55 (s, 3H), 8.68 (d, 1H), 11.9 (s, 1H); MS m/z $(M\text{-}NH_3)^+$ 315,317.

Método 22

tert-Butilo ((1*R*,2*R*)-2-{[(2-cloro-6*H*-tieno [2,3-*b*] pirrol-5-il) carbonil] amino} -2,3-dihidro- 1*H*-inden-1-il]carbamato



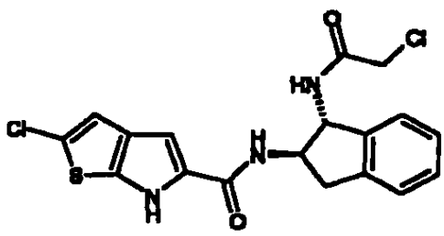
Se disolvió 2-Cloro-5-carboxi-6*H*-tieno[3,2-*b*]pirrol (**Método 4a**, 5.0

g, 25.0 mmol), *trans*-2-amino-1-[(1,1-dimetiletoxi)carbonilamino]indan (**Método 6**, 6.25 g, 25.0 mmol), DIPEA (435 mL, 25.0 mmol) y HOBT (3.4 g, 25.0 mmol) en DCM (200 mL) y se revolvió durante 5 minutos. Se agregó EDCI (6.0 g, 31.0 mmol), la reacción se revolvió durante 24 horas y se evaporó bajo presión reducida. Se agregó EtOAc (150 mL) y la mezcla se filtró, se lavó con agua (2 x 200 mL), solución salina (200 mL), se secó con ($MgSO_4$) y los volátiles se retiraron por evaporación bajo presión reducida para obtener el compuesto del título (10.6g, 98%) como un sólido marrón.

^{1}H NMR 1.38 (s, 9H), 2.81 (dd, 1H), 3.17 (dd, 1H), 4.56 (m, 1H), 5.14 (m, 1H), 7.01 (s, 1H), 7.16 (m, 5H), 7.32 (d, 1H), 8.47 (d, 1H), 11.82 (s, 1H).

Método 23

2-Cloro-*N*-{(1*R*,2*R*)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden-2-y}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida



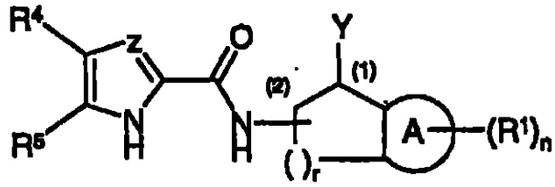
Se agregó Et_3N (3 mL, 21.6 mmol) a una suspensión de *N*-[(1*R*, 2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-il]-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida (**Método 21**, 3.11g, 6.98 mmol) en anhidro diclorometano (55 mL) y se revolvió a temperatura ambiente durante 5 minutos. La suspensión se enfrió a -78 °C y se agregó cloroacetil cloruro (611 |µL, 7.68 mmol) y la reacción se calentó a 0 °C y se revolvió a esta temperatura durante 3 horas. Se agregó $NaHCO_3$ (50 mL), las fases se separaron y la fase acuosa se extrajo con THF (2 x 50 mL). Las fracciones orgánicas combinadas se lavaron con agua (100 mL), se secó con ($MgSO_4$) y el solvente se retiró bajo presión reducida. El residuo se trituró (THF:isohexano, 1:5), se recolectó por filtración, se lavó con hexano (20 mL) y se secó para obtener el compuesto del título (1.92 mg, 68%) como un sólido marrón.

^{1}H NMR 2.88 (dd, 1H), 3.24 (dd, 1H), 4.11 (dd, 2H), 4.61 (m, 1H), 5.46 (t, 1H), 6.99 (s, 1H), 7.20 (m , 5H), 8.55 (d, 2H), 8.73 (d, 1H), 11.84 (s, 1H); MS m/z 408,410.

209
205

Reivindicaciones

1. Un compuesto de la fórmula (1):



(1)

donde:

Z es CH o nitrógeno;

R^4 y R^5 juntos son bien sea -S-C(R^6)=C(R^7)- o -C(R^7)=C(R^6)-S-;

R^6 y R^7 se seleccionan independientemente entre hidrógeno, halo, nitro, ciano, hidroxi, fluorometilo, difluorometilo, trifluorometilo, trifluorometoxi, carboxi, carbamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi y C_{1-4}alcanoilo;

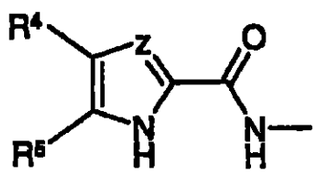
A es fenileno o heteroarileno;

n es 0, 1 o 2;

R^1 se selecciona independientemente entre halo, nitro, ciano, hidroxi, carboxi, carbamoilo, *N*-C_{1-4}alquilcarbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, sulfamoilo, *N*-C_{1-4}alquilsulfamoilo, *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, -S(O)$_b$ C_{1-4}alquilo (donde b es 0, 1, o 2), C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, hidroxi C_{1-4}alquilo, fluorometilo, difluorometilo, trifluorometilo y trifluorometoxi;

o, cuando n es 2, los dos grupos R^1, junto con los átomos de carbono de A a los cuales están adheridos, pueden formar un anillo de 4 a 7 miembros, conteniendo opcionalmente 1 o 2 heteroátomos seleccionados independientemente entre O, S y N, y sustituido opcionalmente por dos grupos metilo;

r es 1 o 2; y cuando r es 1 el grupo



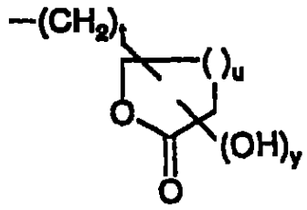
es un radical en el carbono (2) y cuando r es 2 (formando así un anillo de

seis miembros) el grupo mismo es un radical en el carbono (2) o en el carbono (3);

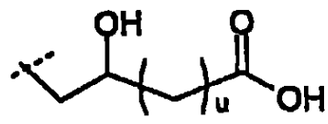
Y es -NR^2R^3 o R^3;

R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcanoilo, carbamoilo, C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, heterociclilo, arilo, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], -COR^8, -SO_bR^8 (donde b es 0, 1 o 2) y

grupos de las fórmulas B y B':



(B)



(B')

donde y es 0 o 1, t es 0, 1, 2 o 3 y u es 1 o 2; siempre que el grupo hidroxi no sea un radical en el anillo de carbono adyacente al anillo de oxígeno; o

donde NR^2R^3 puede formar un anillo saturado, parcialmente saturado o insaturado de 4 a 7 miembros, conteniendo opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados independientemente entre N, O y S, donde cualquier -CH_2- se puede reemplazar opcionalmente por -C(=O)-, y cualquier átomo N o S se puede oxidar opcionalmente para formar un *N*-óxido o un grupo SO o SO_2 respectivamente, y donde el anillo es sustituido opcionalmente por 1 o 2 radicales seleccionados independientemente entre halo, ciano, C_{1-4}alquilo, hidroxi, C_{1-4}alcoxi y C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo, C_{2-4}alquenilo, C_{1-4}alcoxi, ciano(C_{1-4})alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi, hidroxi (C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, -CO_2 C_{1-4}alquilo, arilo y arilo(C_{1-4})alquilo], halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, C_{1-}

$_4$alcoxiC_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo hidroxiC_{1-4}alcoxi, acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, arilo, heterociclilo, (heterociclil)C_{1-4}alquilo, C_{3-7}cicloalquilo (sustituidos opcionalmente con 1 o 2 grupos hidroxi, C_{1-4}alquilo o -C(O)OC_{1-4}alquilo), C_{1-4}alcanoilo, C_{1-4}alquiloS(O)$_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquiloS(O)$_b$- (donde b es 0, 1 o 2), ariloS(O)$_b$- (donde b es 0, 1 o 2), heterociclilo S(O)$_b$- (donde b es 0, 1 o 2), benciloS(O)$_b$- (donde b es 0, 1 o 2), C_{1-4}alquiloS(O)$_c$(C_{1-4})alquilo (donde c es 0, 1 o 2), -N(OH)CHO, -C(=N-OH)NH_2, -C(=N-OH)NHC_{1-4}alquilo, -C(=N-OH)N(C_{1-4}alquil)$_2$, -C(=N-OH)NHC_{3-6}cicloalquilo, -C(=N-OH)N(C_{3-6}cicloalquil)$_2$, -COCOOR^9, C(O)N(R^9)(R^{10}), -NHC(O)R^9, -C(O)NHSO$_2$(C_{1-4}alquilo), - NHSO$_2$R^9, (R^9)(R^{10})N- y –COOR^9, -CH$_2$OR^9, -CH$_2$COOR^9, -CH$_2$OCOR^9, -CH$_2$CH(CO$_2$R^9)OH, -CH$_2$C(O)NR^{9}R^{10}, -(CH$_2$)$_w$CH(NR^{9}R^{10})CO$_2$R$^{9'}$ (donde w es 1, 2 o 3), y -(CH$_2$)$_w$CH(NR^{9}R^{10})CO(NR$^{9'}$R$^{10'}$) (donde w es 1, 2 o 3);

R^9, R$^{9'}$, R^{10} y R$^{10'}$ se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, trihaloalquilo, arilo, heterociclilo, heterociclilo(C_{1-4}alquilo), y -C(=O)O(C_{1-4})alquilo; o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o R$^{9'}$ y R$^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo, C_{1-4}alcoxi y heterociclilo; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por -O-CH$_2$-O- para formar un acetal cíclico donde uno o ambos hidrógenos del grupo -O-CH$_2$-O- se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi,

R^{11} se selecciona independientemente entre hidrógeno, C_{1-4}alquilo e hidroxiC_{1-4}alquilo; o una sal o un profármaco farmacéuticamente aceptable de los mismos; con la salvedad de que el compuesto de fórmula (1) no sea:

i) 2,3-dicloro-5-(*N*-{1-[*N*(1,1-dimetiletoxi)carbonilamino] indan-

2-il}carbamoil)-4*H*-tieno[3,2-*b*]pirrol;

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

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

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

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

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

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

viii) 2-cloro-5-[*N*-(1-hidroxiindan-2-il)carbamoilo-6*H*-tieno[2,3-*b*] pirrol;

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

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

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

2. Un compuesto de la fórmula (1) como se reivindica en la reivindicación 1, donde:

R^2 y R^3 se seleccionan independientemente entre hidrógeno, hidroxi, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], C_{3-7}cicloalquilo (sustituido opcionalmente con 1 o 2 grupos hidroxi), ciano(C_{1-4})alquilo, fenilo, morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo; tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-

oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, y 1,2,4-oxadiazolilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);

R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alcoxiC_{1-4}alcoxi, hidroxiC_{1-4}alcoxi, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, arilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, dihalo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, heterociclilo, heterocicliloC_{1-4}alquilo, arilo, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2), bencilo$S(O)_b$- (donde b es 0, 1 o 2), C_{1-4}alquilo$S(O)_c(C_{1-4})$alquilo (donde c es 0, 1 o 2), $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 R^{13}), C_{3-7}cicloalquilo (sustituido opcionalmente por 1 o 2 grupos hidroxi), $-C(=O)O^tBu$, C_{2-4}alquenilo, ciano(C_{1-4})alquilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano); o

R^9 y R^{10} junto con el nitrógeno al cual están adheridos, y / o $R^{9'}$ y $R^{10'}$ junto con el nitrógeno al cual están adheridos, forman un anillo de 4- a 6-miembros donde el anillo es sustituido opcionalmente en el carbono por 1 o 2 radicales seleccionados independientemente entre oxo, hidroxi, carboxi, halo, nitro, ciano, carbonilo y C_{1-4}alcoxi; o el anillo se puede sustituir opcionalmente en dos carbonos adyacentes por $-O-CH_2-O-$ para formar un acetal cíclico donde uno o ambos hidrógenos del grupo $-O-CH_2-O-$ se pueden reemplazar por un metilo;

R^{13} se selecciona entre halo, trihalometilo y C_{1-4}alcoxi,
o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos.

3. Un compuesto de la fórmula (1) como se reivindica en la reivindicación 1 o la reivindicación 2, donde:
R^2 y R^3 se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo [sustituidos opcionalmente por 1 o 2 grupos R^8], $-COR^8$ y $-SO_bR^8$ (donde b es 0, 1 o 2);
R^8 se selecciona independientemente entre hidrógeno, hidroxi, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo, C_{1-4}alquilo, amino(C_{1-4})alquilo [sustituidos opcionalmente en el nitrógeno por 1 o 2 grupos seleccionados entre C_{1-4}alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, $-CO_2C_{1-4}$alquilo, fenilo y arilo(C_{1-4})alquilo], C_{2-4}alquenilo, C_{3-7}cicloalquilo (sustituidos opcionalmente por $-C(O)OC_{1-4}$alquilo), acetales cíclicos de 5- y 6-miembros y mono y di-metil derivados de los mismos, halo(C_{1-4})alquilo, trihalo(C_{1-4})alquilo, hidroxi(C_{1-4})alquilo, dihidroxi(C_{1-4})alquilo, ciano(C_{1-4})alquilo, furilo (sustituidos opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo (sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), morfolino, furilo(C_{1-4})alquilo (donde el furilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), tienilo(C_{1-4})alquilo (donde el tienilo es sustituido opcionalmente en el carbono por 1 o 2 grupos nitro), 1,2,4-oxadiazolilo, tetrazolilo, imidazolilo, pirrolidinilo, piperidilo, piridilo, tetrahidrofurilo, tetrahidropiranilo, 1-oxo-tetrahidrotiopiranilo, tetrahidrotienilo, fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, ciano, hidroxi y C_{1-4}alquilo), pirazinilo, piperazinilo, 4-metilpiperazino, C_{1-4}alquilo$S(O)_b$- (donde b es 0, 1 o 2), C_{3-6}cicloalquilo$S(O)_b$- (donde b es 0, 1 o 2), arilo$S(O)_b$- (donde b es 0, 1 o 2), heterociclilo$S(O)_b$- (donde b es 0, 1 o 2 $-CH_2CH(NR^9R^{10})CO(NR^{9'}R^{10'})$, $-CH_2OR^9$, $(R^9)(R^{10})N$-, $-COOR^9$, $-CH_2COOR^9$, $-C(O)N(R^9)(R^{10})$, $-CH_2CH(CO_2R^9)OH$, $-CH_2CONR^9R^{10}$, $-CH_2CH(NR^9R^{10})CO_2R^{9'}$ y $-CH_2OCOR^9$;

R^9, $R^{9'}$, R^{10} y $R^{10'}$ se seleccionan independientemente entre hidrógeno, C_{1-4}alquilo (sustituidos opcionalmente por 1 o 2 grupos hidroxi), C_{2-4}alquenilo, y fenilo (sustituidos opcionalmente por 1 o 2 grupos seleccionados entre nitro, halo, hidroxi y ciano);
o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos.

4. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores donde Y es NR^2R^3, o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos.

5. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores de 1 a 3 donde Y es OR^3, o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

6. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores donde R^4 y R^5 juntos son S-C(R^6)=C(R^7)-; o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

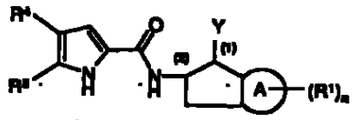
7. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores de 1 a 5 donde R^4 y R^5 juntos son -C(R^7)=C(R^6)-S-; o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

8. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores donde A es fenileno, o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

9. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores de 1 a 7 donde A es heteroarileno, o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

10. Un compuesto como se reivindica en una cualquiera de las reivindicaciones anteriores donde Z es CH, o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos.

11. Un compuesto de la fórmula (1) como se reivindica en una cualquiera de las reivindicaciones anteriores, que es un compuesto de fórmula (IB):



(IB)

o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos.

12. Un compuesto de la fórmula (1) como se reivindica en la reivindicación 1, que es uno cualquiera de:
2,3-dicloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-((1*R*,2*R*)-1-{[(metiloxi)acetil]amino}-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-((1*S*,2*S*)-1-{[(3(*R*)-3-(*tert*-Butoxicarbonilamino-3-carbamoilpropanoil] amino}-2,3-dihidro-1*H*-inden-2-il)-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il] acetil}amino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]-pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{ (1*R*,2*R*)-1-[(trifluoroacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(furan-2-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno [3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(furan-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(3-tienilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(5-nitrofuran-2-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(piridin-3-ilcarbonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*S*,2*S*)-1-(acriloilamino-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(3-hidroxifenil)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*S*,2*S*)-1-(Acetilamino)-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*S*,2*S*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(dimetilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(4-metilpiperazin-1-il)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(etilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-((1*S*,2*S*)-1-{[(prop-2-en-1-ilamino)carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-[(1*S*,2*S*)-1-({[(3,5-dinitrofenil)amino]carbonil]amino}-2,3-dihidro-1*H*-inden-2-il)-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-[(1*S*,2*S*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il]-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoilpropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-(1*R*,2*R*)-1-[((3*R*)-3-carboxi-3-hidroxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2,3-dicloro-*N*-{(1*S*,2*S*)-1-[metil(morfolin-4-ilacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-(1*R*,2*R*)-1-[(tert-butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-(carboximetilamino)-2,3-dihidro-1*H*-inden-2-il]-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-(1*R*,2*R*)-1-[*N*-acetilo-*N*-(carboximetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[acetil(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[*N*-(carboximetil)-*N*-(hidroxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;

2-cloro-*N*-[(1*R*,2*R*)-1-({[(2*S*)-5-oxotetrahidrofuran-2-il]carbonil}amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-[(1*R*,2*R*)-1-(formilamino)-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno [2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-[(metoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-(acetilamino)-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno [2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-[(3-metoxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-[(2-acetoxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*S*,2*S*)-1-{[(2(*S*)-2-(*tert*-butoxicarbonilamino)-2-carbamoilacetil] amino}-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*S*,2*S*)-1-[(2-(*tert*-butoxicarbonilamino)acetilamino}-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-[2-carbamoilacetil)amino]-2,3-dihidro-1*H*-inden-2-il]-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[2-(tert-butoxicarbonil)acetilamino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-{[3-hidroxi-2-(hidroximetil)propanoil]amino}-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoilpropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-(1*R*,2*R*)-1-[(aminoacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-[(1*R*,2*R*)-1-({[(2-hidroxietil)(fenilmetil)amino] acetil}amino)-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-{(1*R*,2*R*)-1-[(morfolin-4-ilacetil)amino-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-((1*R*,2*R*)-1-({[(2-hidroxietil)(metil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*R*,2*R*)-1-({[bis(2-hidroxietil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-((1*R*,2*R*)-1-({[etil(2-hidroxietil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

2-cloro-*N*-((1*R*,2*R*)-1-({[(2,3-dihidroxipropil)(metil)amino]acetil} amino)-2,3-dihidro-1*H*-inden-2-il)-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-((1*R*,2*R*)-1-({[bis(2-hidroxipropil)amino]acetil}amino)-2,3-dihidro-1*H*-inden-2-il)-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-{(1*R*,2*R*)-1-[(2-amino-2-oxoetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;

N-[(1*R*,2*R*)-1-[(tert-butoxicarbonilmetil)amino]-2,3-dihidro-1*H*-inden-2-il}-

2-cloro-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-(carboximetilamino)-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2-cloro-*N*-{(1*R*,2*R*)-1-[(hidroxiacetilamino]-2,3-dihidro-1*H*-inden-2-il}-6*H*-tieno[2,3-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(cloroacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[((3*S*)-3-amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2,3-dicloro-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[(2-carboxiacetil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
N-{(1*R*,2*R*)-1-[((3*S*)-3-amino-3-carboxipropanoil)amino]-2,3-dihidro-1*H*-inden-2-il}-2-cloro-6*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
2,3-dicloro-*N*-{(1*R*,2*R*)-1-[(metilsulfonil)amino]-2,3-dihidro-1*H*-inden-2-il}-4*H*-tieno[3,2-*b*]pirrol-5-carboxamida;
o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos.

13. Una composición farmacéutica que comprende un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12 en asocio con un diluyente o excipiente farmacéuticamente aceptable.

14. Un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12, para el uso en un método de tratamiento de un animal de sangre caliente como el hombre como terapia.

15. Un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12, para el uso como un medicamento.

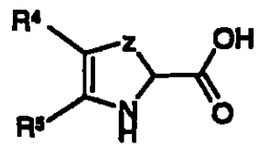
16. Un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12, para el uso como un medicamento en el tratamiento de la diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca u obesidad en un animal de sangre caliente como el hombre.

17. El uso de un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12, en la manufactura de un medicamento para el uso en el tratamiento de la diabetes tipo 2, resistencia a la insulina, síndrome X, hiperinsulinemia, hiperglucagonemia, isquemia cardiaca u obesidad en un animal de sangre caliente como el hombre.

18. El uso de un compuesto de la fórmula (1), o una sal farmacéuticamente aceptable o un éster hidrolisable *in-vivo* de los mismos, como se reivindica en una cualquiera de las reivindicaciones de 1 a 12, en la manufactura de un medicamento para el uso en el tratamiento de la diabetes tipo 2 en un animal de sangre caliente como el hombre.

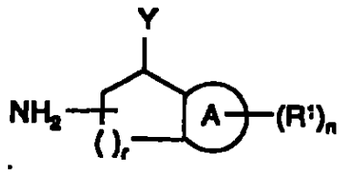
19. Un proceso para la preparación de un compuesto de la fórmula (1) como se reivindica en la reivindicación 1, proceso que comprende:

hacer reaccionar un ácido de la fórmula (2):



(2)

o un derivado activado del mismo; con una amina de fórmula (3):



(3)

y posteriormente si es necesario:

i) convirtiendo un compuesto de la fórmula (1) en otro compuesto de la fórmula (1);

ii) retirando cualquier grupo de protección;

iii) formando una sal farmacéuticamente aceptable o un éster hidrolisable *in vivo*.

PATENT COOPERATION TREATY

CODE	DATE	NTD

ANKOM 03 OCT 2003 PCT

DATA ENTERED

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
TINSLEY, Rachel Maria et al
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
GRANDE BRETAGNE

Registered letter

FINAL CHECK

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

06 OCT 2003

(PCT Rule 71.1)

Applicant's or agent's file reference: 100667-1 WO	Date of mailing (day/month/year): 24/09/2003
	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB 03/00875	04/03/2003	06/03/2002

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.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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	OBERHAUSER A S Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (August 2002) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100667-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/ 00875	04/03/2003	06/03/2002
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 2 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 consists 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 supporting 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
09/09/2003	19/09/2003
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	TZSCHOPPE D A Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 03/00875

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/407 A61K31/4162 A61P3/10

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)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, 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.
P,A	WO 02 20530 A (FREEMAN SUE ;KENNY PETER (GB); MORLEY ANDREW (GB); WHITTAMORE PAUL) 14 March 2002 (2002-03-14) examples	1-19
A	EP 1 088 824 A (PFIZER PROD INC) 4 April 2001 (2001-04-04) claims; examples	1-19
A	EP 0 846 464 A (PFIZER) 10 June 1998 (1998-06-10) claims	1-19
A	ES 2 081 747 A (ESTEVE LABOR DR) 1 March 1996 (1996-03-01) page 2; examples	1-19

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2003	30/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fazzi, R

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 03/00875

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0220530	A	14-03-2002	AU	8283301 A	22-03-2002
			WO	0220530 A1	14-03-2002
EP 1088824	A	04-04-2001	BR	0004582 A	17-04-2001
			CA	2321379 A1	30-03-2001
			EP	1088824 A2	04-04-2001
			JP	2001131181 A	15-05-2001
			US	2002183369 A1	05-12-2002
			US	6399601 B1	04-06-2002
EP 0846464	A	10-06-1998	AU	717547 B2	30-03-2000
			AU	4686997 A	11-06-1998
			CA	2223317 A1	05-06-1998
			EP	0846464 A2	10-06-1998
			HU	9702356 A2	28-08-1998
			JP	3277147 B2	22-04-2002
			JP	10194990 A	28-07-1998
			NZ	329333 A	28-07-2000
			US	5952322 A	14-09-1999
			ZA	9710907 A	04-06-1999
ES 2081747	A	01-03-1996	ES	2081747 A1	01-03-1996
US 3706810	A	19-12-1972	NONE		

PCT REQUEST

100667-1 WO

Original (for SUBMISSION) - printed on 03.03.2003 02:22:49 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	100667-1 WO
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address:	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+44 1625 510752

PCT REQUEST 100867-1 WO

Original (for SUBMISSION) - printed on 03.03.2003 02:22:49 PM

III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address:	15 Stanhope Gate London, Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	WHITTAMORE, Paul, Robert, Owen
III-2-5	Address:	AstraZeneca R&D Alderley Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-2-6	State of nationality	GB
III-2-7	State of residence	GB
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	BENNETT, Stuart, Norman, Lile
III-3-5	Address:	AstraZeneca R&D Alderley Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	SIMPSON, Iain
III-4-5	Address:	AstraZeneca R&D Alderley Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB

IV-1	**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
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address:	Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

PCT REQUEST 100667-1 WO

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V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. 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.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	06 March 2002 (06.03.2002)	
VI-1-2	Number	0205170.4	
VI-1-3	Country	GB	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	115	-
IX-3	Claims	12	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	133	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		

PCT REQUEST

100667-1 WO

Original (for SUBMISSION) - printed on 03.03.2003 02:22:49 PM

IX-20	Language of filing of the international application	English
X-1	Signature of applicant, agent or common representative	
X-1-1	Name	ASTRAZENECA
X-1-2	Name of signatory	AGENT
X-1-3	Capacity	ASTRAZENECA

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

100667-1 WO

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(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)			
0-9	Applicant's or agent's file reference	100667-1 WO			
2	Applicant	ASTRAZENECA AB, et al.			
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (GBP)	
12-1	Transmittal fee	T	⇨	55	
12-2-1	Search fee	S	⇨	592	
12-2-2	International search to be carried out by		EP		
12-3	International fee Basic fee (first 30 sheets)	b1	278		
12-4	Remaining sheets		103		
12-5	Additional amount	(X)	6		
12-6	Total additional amount	b2	618		
12-7	b1 + b2 =	B	896		
12-8	Designation fees Number of designations contained in international application		94		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	60		
12-11	Total designation fees	D	300		
12-12	PCT-EASY fee reduction	R	-86		
12-13	Total international fee (B+D-R)	I	⇨	1,110	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	1,757	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office:		United Kingdom Patent Office (RO/GB)		
12-20-1	Authorization to charge the total fees indicated above.		✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		✓		
12-20-3	Authorization to charge the fee for priority document.		✓		
12-21	Deposit account No.		D02934		
12-22	Date		03 March 2003 (03.03.2003)		

PCT (ANNEX - FEE CALCULATION SHEET) 100667-1 WO

Original (for SUBMISSION) - printed on 03.03.2003 02:22:49 PM

12-23	Name and signature	ASTRAZENECA

VALIDATION LOG AND REMARKS

13-2-3	Validation messages Names	Yellow Applicant 1.:City missing
13-2-7	Validation messages Contents	Green? The abstract appears to be more than 150 words, applicant is reminded that it should be as concise as the disclosure permits (preferably 50 to 150 words if it is in English or when translated into English)
		Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

PCT

100867-1 WO

Original (for SUBMISSION) - printed on 03.03.2003 02:22:49 PM

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

	Names
Yellow	Applicant 1.:City missing
	Contents
Green?	The abstract appears to be more than 150 words, applicant is reminded that it should be as concise as the disclosure permits (preferably 50 to 150 words if it is in English or when translated into English)
Green?	The international application contains no drawings. Please verify.
	Payment
Green?	Please ensure that you have a valid deposit account with the receiving Office selected.

Before submitting the International Application, please carefully verify that:

-the information contained on printed Request form is correct;
-Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
-all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
-the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

A B S T R A C T

CHEMICAL COMPOUNDS

Heterocyclic amides of formula (1)

(A chemical formula should be inserted here - please see paper copy enclosed herewith)

(1)
wherein:
Z is CH or nitrogen;
R4 and R5 together are either -S-C(R6)=C(R7)- or -C(R7)=C(R6)-S- ;
R6 and R7 are selected from for example hydrogen, halo, C1-4alkyl, and C1-4alkanoyl;
A is phenylene or heteroarylene;
n is 0, 1 or 2;
R1 is selected from for example halo, nitro, cyano, hydroxy, carboxy;
r is 1 or 2;
Y is -NR2R3 or -OR3;
R2 and R3 are selected from for example hydrogen, hydroxy, aryl, heterocyclyl and C1-4alkyl(optionally substituted

by 1 or 2 R8 groups);
R4 is selected from for example hydrogen, halo, nitro, cyano, hydroxy, C1-4alkyl, and C1-4alkanoyl;
R8 is selected from for example hydroxy, -COCOOR9, -C(O)N(R9)(R10), -NHC(O)R9 , (R9)(R10)N- and
-COOR9 ;
R9 and R10 are selected from for example hydrogen, hydroxy, C1-4alkyl (optionally substituted by 1 or 2 R13);
R13 is selected from hydroxy, halo, trihalomethyl and C1-4alkoxy;
or a pharmaceutically acceptable salt or pro-drug thereof; 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.

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: 100667/WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB03/00875	04 March 2003 (04.03.2003)	06 March 2002 (06.03.2002)

Title of invention: HETEROCYCLIC AMIDE DERIVATIVES HAVING GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

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.: +44 1625 230148
Facsimile No.: +46 8 553 28820
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.)*
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1K 1LN
GB

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 Robert Owen
AstraZeneca R&D Alderley
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.

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Sheet No. 2.

International application No.
PCT/GB03/00875

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.)*

BENNETT, Stuart Norman Lile
AstraZeneca R&D Alderley
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.)*

SIMPSON, Iain
AstraZeneca R&D Alderley
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:

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.

Sheet No. 3

International application No.
PCT/GB03/00875

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.)*

TINSLEY, Rachel Maria et al
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
GB

Telephone No.
+44 1625 514266

Facsimile No.
+46 8 553 28820

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:

232 80

Sheet No. .4.

International application No.
PCT/GB03/00875

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).

.....

Rachel Maria TINSLEY et al
Global Intellectual Property, Patents, 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:

CHAPTER II

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PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/GB03/00875	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 100667/WO	Date stamp of the IPEA
Applicant: AstraZeneca AB et al	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EURO 1530.00 P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EURO 159.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	EURO 1689.00 TOTAL	

MODE OF PAYMENT

☒ authorization to charge deposit account with the IPEA (see below)	☐ cash
☐ cheque	☐ revenue stamps
☐ postal money order	☐ coupons
☐ bank draft	☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EPO

☒ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 2810 0023

Date:

Name: Jennifer Bennett

Signature:

95.053
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234

100667-1P CO

ASSIGNMENT

The undersigned,

Paul Robert Owen WHITTAMORE
Stuart Norman Lile BENNETT
Iain SIMPSON

domiciled in
Astrazeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom

hereby state under oath to be the sole and true inventor of

HETEROCYCLIC AMIDE DERIVATIVES HAVING GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

state as well that assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

domiciled in

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leyes de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

.....
Paul Robert Owen WHITTAMORE

.....
Iain SIMPSON

.....
Stuart Norman Lile BENNETT

.....

46750

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CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 2004, compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2004 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

NOTARY PUBLIC (Notario Público)

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 2004, compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 30 day of July 2004 personally appeared before me, a Notary Public,
Paul Robert Owen Whittamore
Iain Simpson and
Stuart Norman Gilo Blanott

to me known and known to me to be the person described in and who executed the foregoing document, and they duly acknowledged to me that they executed the same for the uses and purposes therein expressed.

J. L. Chesterjian
Notary Public
Wilmslow
Cheshire
England

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — **John Haig Ekserdjian**
   a été signé par

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

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

5. at London/à Londres — Certified/Attesté 6. the/le **03 August 2004**

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

8. Number/sous No **G481176**

9. Stamp:
   timbre:

10. Signature: **Z. Ahmed**

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

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

Brigard & Castro

BOGOTA - COLOMBIA

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PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
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 JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
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 de 200

Firma

Nombre
Cargo

09 MAR 2004
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SIETE

POWER OF ATTORNEY

I (We) **ASTRAZENECA AB**

domiciled in SE-151 Södertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of 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 vegetables 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 explotation 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 are 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 kind 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. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
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 Macclesfield, Cheshire, England

this 18th day of January 2003

Signature

Name KEVIN BILL
Title Director, IP Services

120816

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

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)

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 precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL
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
ATTORNEY
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 purpose for which this instrument is granted 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 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

NOTARIAL CERTIFICATE
NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me 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.

09 AGO 2004
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SIETE

Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED.

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — J B Hodgson
   a été signé par

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

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

   Certified/Attesté

5. at London/à Londres — 6. the/le 17 February 2004

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

8. Number/sous No **G348987**

9. Stamp/timbre:

10. Signature: J. Ireland

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

COLEGIO NOTARIAL CUARENTA Y SEIS DEL CIRCULO DE SANTAFE DE BOGOTA, HACE CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA D.C. REPUBLICA DE COLOMBIA
09 AGO 2004
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

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

50 238
-242

SUPERINDUSTRIA Y COMERCIO
Radicacion 04007003 00000000 Folios 241
Fecha (AMD): 2004-09-03 18:24:57
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN **MODELO DE UTILIDAD**	( )	(T
Indicación de que se solicita la concesión de una patente	( )	T
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	T
Descripción de la invención	( )	T
Dibujos de ser estos pertinentes.	( )	T
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 o 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 solcitante o de la persona que presenta La solicitud	( )	( )
Representacion gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable

Fecha 3 Sept - 04

Industria y Comercio
SUPERINTENDENCIA

234

Folio 243

2020
Bogotá DC

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)
ASTRAZENECA AB.

REFERENCIA:	Radicación No.	04-87003
	Solicitud Internacional	PCT/GB2003/00875
	Fecha inicio fase nacional	06/10/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1486
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 23 SET. 2004

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

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