INDOLAMID DERIVATIVES WHICH POSSESS GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof. These heterocyclic amide 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.

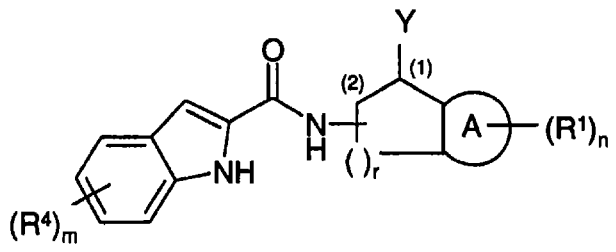
Liver glycogen phosphorylase a activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetalogia 43, 589-597).

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:

A is phenylene or heteroarylene;

n is 0, 1 or 2;

m 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, -$S(O)_bC_{1-4}$alkyl (wherein b is 0,1,or 2), C_{1-4}alkyl, C_{2-4}alkenyl,

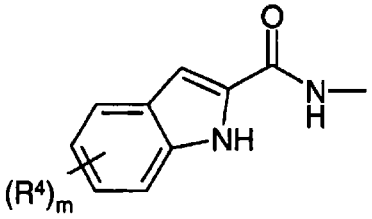
C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy;

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^4 is 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;

r is 1 or 2; and

when r is 1 the group



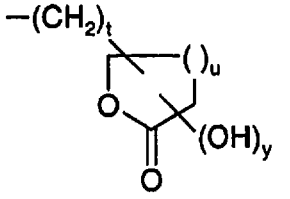
is a substituent on carbon (2) and

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

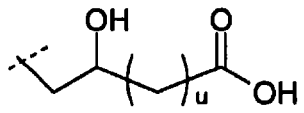
Y is $-NR^2R^3$ or $-OR^3$;

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, $-C(=N\text{-}OH)NH_2$, $-C(=N\text{-}OH)NHC_{1-4}$alkyl, $-C(=N\text{-}OH)N(C_{1-4}\text{alkyl})_2$, $-C(=N\text{-}OH)NHC_{3-6}$cycloalkyl, $-C(=N\text{-}OH)N(C_{3-6}\text{cycloalkyl})_2$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NHSO_2(C_{1-4}\text{alkyl})$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2$-, $-COCH_2OR^{11}$, $(R^9)(R^{10})$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), $-(CH_2)_wCH(NR^9R^{10})CO(NR^{9'}R^{10'})$ (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), $-C(=O)O(C_{1-4})$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

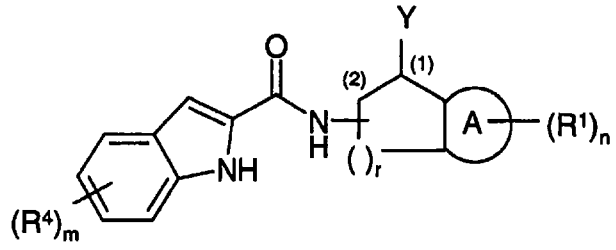
may be optionally substituted on two adjacent carbons by –O-CH_2-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH_2-O- group may be replaced by a methyl;

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.

In another aspect, the present invention provides a compound of formula (1):



(1)

wherein:

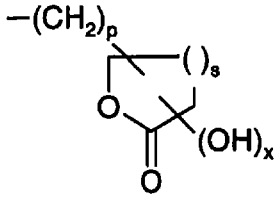
A is phenylene or heteroarylene;

n is 0, 1 or 2;

m is 0, 1 or 2;

wherein 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":



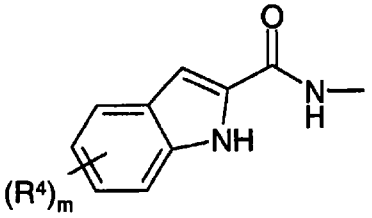
(A')

$-CH_2CH(OH)(CH_2)_uCO_2H$ (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;

wherein R^4 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, and trifluoromethoxy;

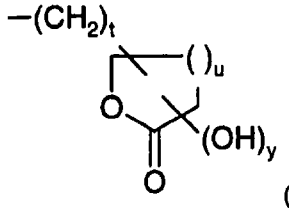
r is 1 or 2; and when r is 1 the group



is a substituent on carbon (2) and when r is 2 (thereby 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 (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, 4-butanolidyl, 5-pentanolidyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, tetrahydrothiopyranyl, 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) $-CH_2CH(OH)(CH_2)_uCO_2H$ (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], halo(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, C_{1-4}alkylS(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_{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, 4-butanolidyl, 5-pentanolidyl, 1-oxo-tetrahydrothiopyranyl, 1,1-dioxo-tetrahydrothiopyranyl, 1,1-dioxo-tetrahydrothiopyranyl, 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}alkylS(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}alkylS(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}alkyl)$_2$amino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_f$(C_{1-4})alkyl (wherein f is 0, 1 or 2), -N(OH)CHO, $(R^{11})(R^{12})NCO-$, $(R^{11})(R^{12})NSO_2-$, $-COCH_2OR^{11}$, $(R^{11})(R^{12})N-$;

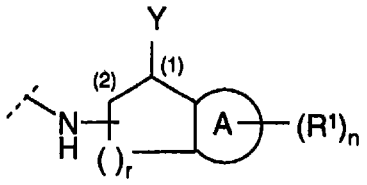
wherein R^{11} and R^{12} are as defined above]};

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

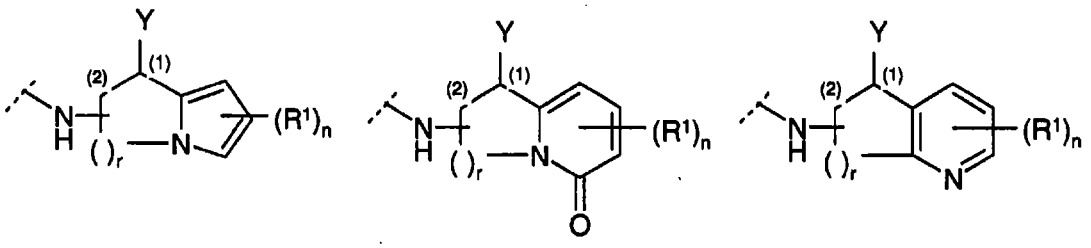
of the formula A' or A" such that a compound of formula (1) can contain only one of A', A", B and B';

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

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, $R^ACO(C_{1-6})$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. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and "C_{2-4}alkynyl" includes ethynyl, 1-propynyl and 2-propynyl.

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_{1-4}alkanoyl" include formyl, acetyl and propionyl. Examples of "C_{1-4}alkanoyloxy" are formyloxy, acetoxy and propionoxy. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. 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*-(C_{1-4}alkyl)carbamoyl" are methylcarbamoyl and ethylcarbamoyl. 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*-(C_{1-4}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. 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 "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.

The term "sulfo" means $HOSO_2$- . The term "sulfino" means HO_2S- .

Examples of "C_{1-4}alkyl$S(O)_b$ (wherein b is 0,1 or 2)", "C_{1-4}alkyl$S(O)_c$ (wherein c is 0 to 2)", "C_{1-4}alkyl$S(O)_d$ (wherein d is 0 to 2)", "C_{1-4}alkyl$S(O)_e$ (wherein e is 0 to 2)", and "C_{1-4}alkyl$S(O)_f$ (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_{1-4}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.

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}alkyl$S(O)_b$ (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}alkyl$S(O)_b$ (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}alkyl$S(O)_b$

(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 susbtituents 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, m 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).

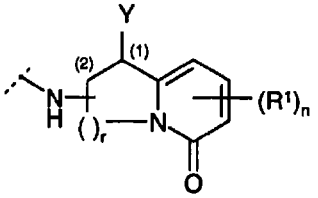
Particular examples of in-vivo hydrolysable esters of compounds of the formula (1) are such esters of compounds of the formula (1) wherein Y comprises a group containing a carboxy group. Suitable esters are those hereinbefore described for carboxy groups.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein 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 present invention m is 1 or 2.

In another aspect of the invention m is 1.

In one aspect of the present invention R^4 is selected from hydrogen, halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl.

In another aspect of the invention R^4 is hydrogen or halo.

Preferably R^4 is selected from hydrogen, chloro or bromo.

More preferably R^4 is chloro.

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.

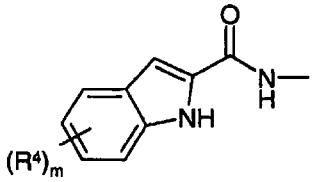
In a further aspect R^1 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, $-S(O)_bMe$ (wherein b is 0, 1 or 2), methyl and methoxy.

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

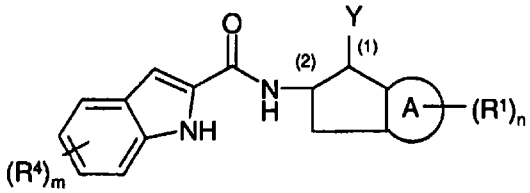
Preferably R^1 is selected from halo and C_{1-4}alkoxy.

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

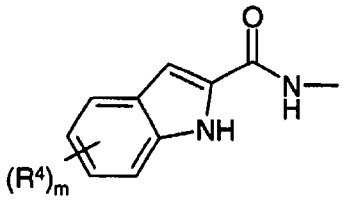
In one aspect of the invention r is 1 and when r is 1 the group



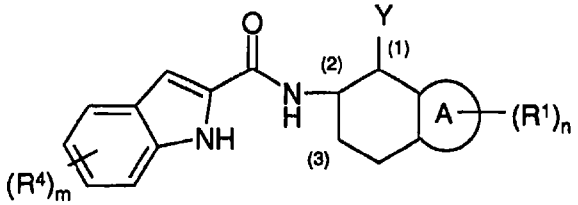
is a substituent on carbon (2) such that an example of when r is 1 is:



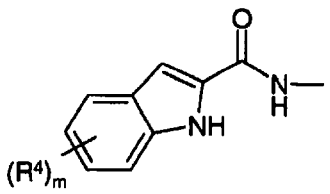
In another aspect of the invention r is 2 and when r is 2 the group



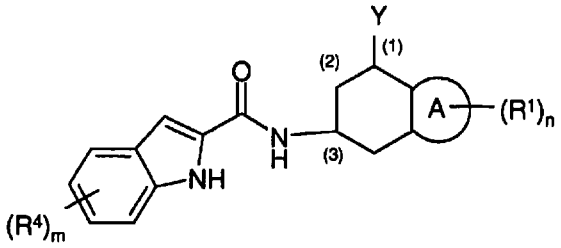
is a substituent on carbon (2) such that an example of when r is 2 is:



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$S(O)_c$(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 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}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^{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}alkylS(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 or 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 invention 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 invention R^3 is selected from hydrogen, 1,3-dihydroxyisopropyl, 1,2-dihydroxypropyl, cyanomethyl, trifluoromethylcarbonyl,

carboxyacetyl, carboxymethyl, acetylmethanesulfonyl, 1-amino-1-carboxyethylcarbonyl, aminoacetyl, 1-amino-1-carboxypropanoyl, chloroacetyl, hydroxyacetyl, *N*-methyl-*N*-hydroxyethylaminoacetyl, *N*-benzyl-*N*-hydroxyethylaminoacetyl, hydroxypiperidinoaminoacetyl, hydroxypyrrolidinylaminoacetyl, chloromethylsulfonyl, trifluoromethylsulfonyl, thienylmethyl, tetrazolylmethyl, carbamoylacetyl, carbamoylmethyl, methoxyacetyl, methoxypropanoyl, acetoxyacetyl, [2-(ethoxycarbonyl)cyclopropyl]methyl, (1-amino-1-carbonylamino)ethylcarbonyl, *N*-(tert-butoxycarbonyl)aminoacetyl and *N*-(aminocarbonyl)-*N*-(tert-butoxycarbonyl)aminoacetyl.

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

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^{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;

m is 1 or 2;

R^4 is hydrogen or halo;

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

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

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], -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;

m is 1;

R^4 is chloro;

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

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

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}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).

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

m is 1;

R^4 is chloro;

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

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

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 selected from optionally substituted morpholino, 2,5-dioxomorpholino, piperidinyl, pyrrolidinyl, pyrazolyl, pyrrolyl, imidazolyl, piperazinyl and thiomorpholinyl;

m is 1;

R^4 is chloro;

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

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

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}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}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);

m is 1 or 2;

R^4 is chloro or bromo;

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

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

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 [substituted by 1 or 2 R^8 groups], -COR^8 and –SO_bR^8 (wherein b is 0, 1 or 2);

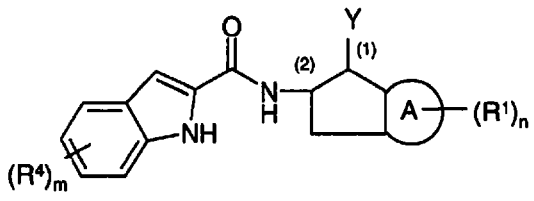
R^8 is independently selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl, amino(C_{1-4})alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, -CO_2C_{1-4}alkyl, phenyl and aryl(C_{1-4})alkyl], 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);

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

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



(1A)

wherein

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;

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

R^3 is selected from C_{1-4}alkyl [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;

A is heteroarylene;

n is 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;

m is 1 or 2;

R^4 is hydrogen or halo;

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

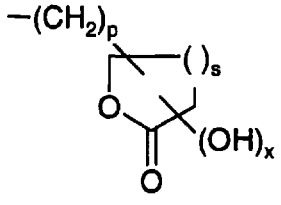
A preferred class of compound is of the formula (1) wherein;

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

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



(A') -$CH_2CH(OH)(CH_2)_uCO_2H$ (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, hydroxyC_{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, 1-oxo-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}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, 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, 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, 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)]};

m is 1 or 2;

R^4 is hydrogen or halo;

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

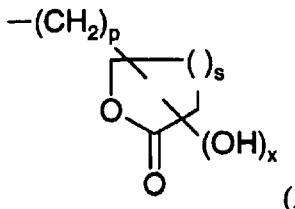
A further preferred class of compound is of the formula (1) wherein;

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

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



(A') -$CH_2CH(OH)(CH_2)_uCO_2H$ (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;

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

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

R^3 is selected from 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, 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, C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(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 C_{1-4}alkenyl or phenyl (optionally substituted by nitro, halo or cyano)]};

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

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

5-chloro-2-[*N*-(1-hydroxyindan-2-yl)carbamoyl]indole;

5-chloro-*N*-{(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

N-{(1*R**, 2*R**)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

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

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

5-chloro-*N*-[(1*R*,2*R*)-1-(*tert*-butoxycarbonylaminoacetamido)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide;

N-((1*R*,2*R*)-1-{[3-(*tert*-butoxycarbonylamino)-4-oxopentanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

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

5-chloro-*N*-{(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

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

5-chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypiperidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypyrrolidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

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

N-{1-[(aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide;

N-{1-[((3*S*)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(chloromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{[(trifluoromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[(cyanomethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{(1*R*,2*R*)-1-[(1*H*-tetrazol-5-ylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

N-[(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

N-{(1*S*,2*S*)-1-[acetyl(2-thienylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide;

N-{(1*S*,2*S*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-[(1*S*,2*S*)-1-{*N*-acetyl-*N*-[2-(ethoxycarbonyl)cycloprop-1ylmethyl]amino}-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[bis-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

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

N-{(1*R*,2*R*)-1-[*N*-(2-acetoxyacetyl)-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(2*R*)-2,3-dihydroxypropyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

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

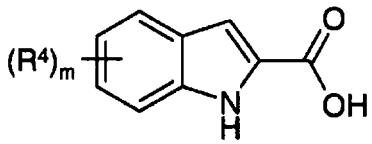
In another aspect of the invention, preferred compounds of the invention are any one of:

5-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

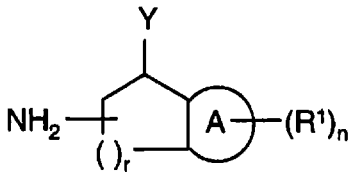
Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein A, Y, R^1, R^4, m, r and n are, unless otherwise specified, as defined in formula (1)) comprises of:

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.

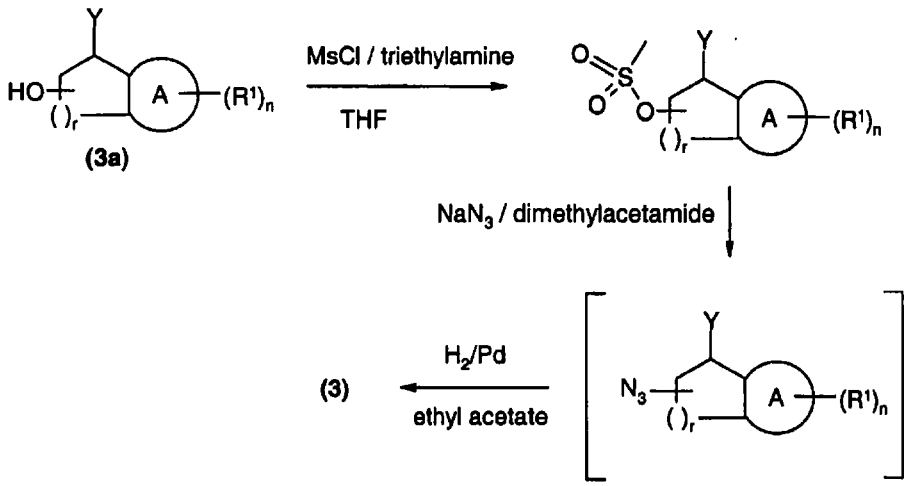
Process a) Acids of formula (2) and amines of formula (3) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide 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.

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

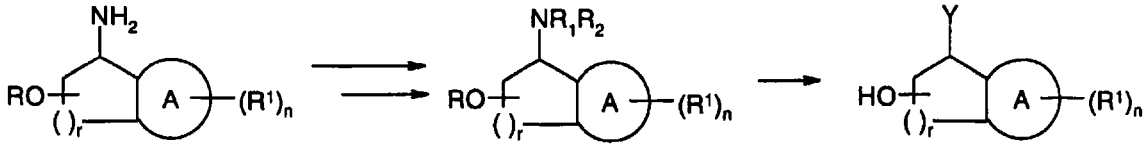
Compounds of formula (3) where Y is OR^3 are commercially available or they are known compounds or they are prepared by processes known in the art. When Y is NR^2R^3, the amines of formula (3) may be prepared according to Scheme 1:



Scheme 1

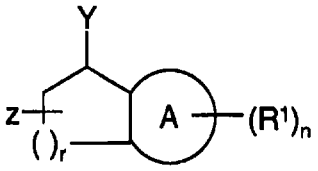
Compounds of formula (3a) are commercially available or they are known compounds or they are prepared by processes known in the art. For example, starting from primary amines of formula (4), in which R is H or a suitable protecting group, one or both of R^1 and/or R^2 may be introduced by acylation, (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).



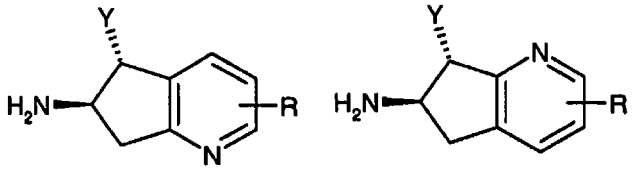
(4) (3a)

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 (5) in which Z is NH_2 or a nitrogen atom with one or two suitable protecting groups.



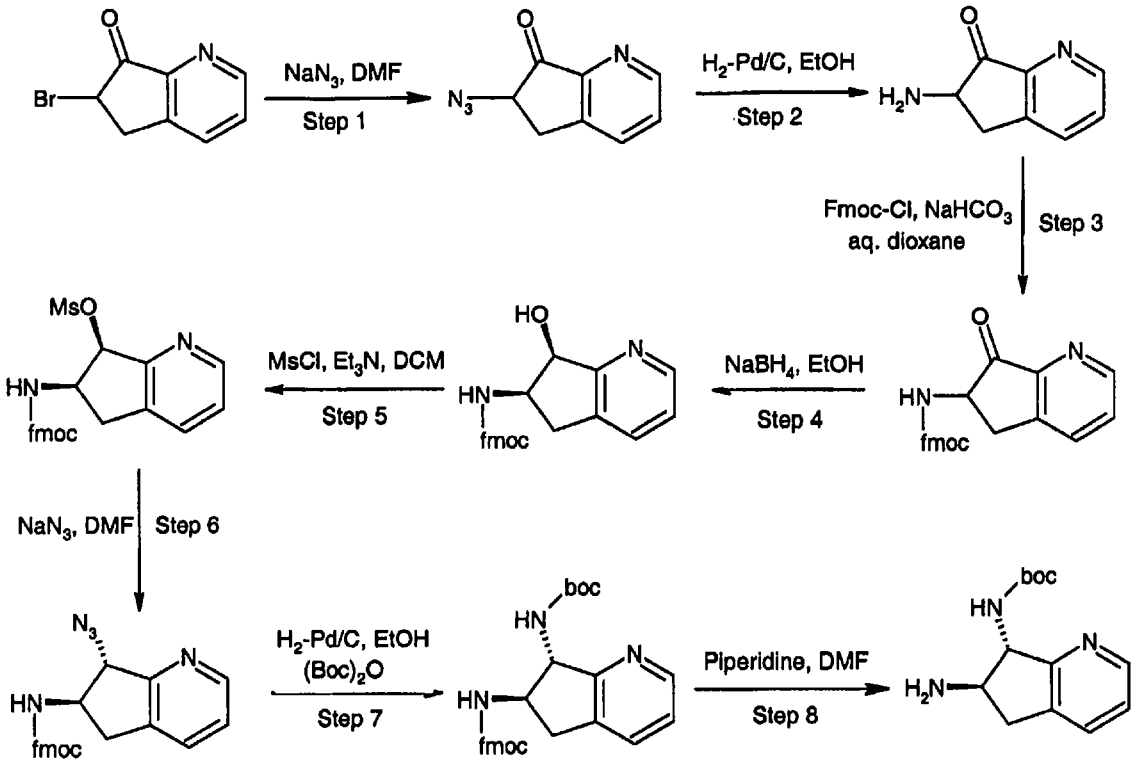
(5)

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)

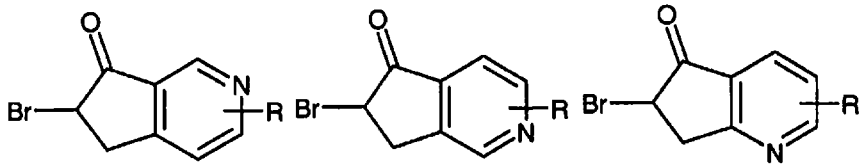
compounds of formula (3b) and (3c) may be prepared from the corresponding pyrindinone regioisomer according to Scheme 2 :-



Scheme 2

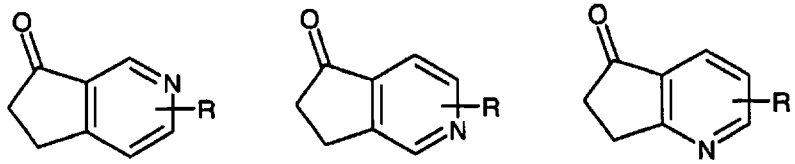
Step1 is performed on a compound known in the literature (*Jpn. Kokai Tokkyo Koho*, **1995**, 14. JP 07070136). Steps 2, 3, 4, 5, 6, 7 and 8 are performed using standard techniques known in the art.

It will be appreciated that the bromopyrindinone isomers (6a, 6b and 6c) could



(6a) **(6b)** **(6c)**

be converted to the corresponding heterocylic version of (3) by the means described in Scheme 2. The bromopyrindinones can be prepared from the corresponding pyrindinone by standard techniques known in the art. The pyrindinones (7a, 7b, 7c) are known in the literature or they are prepared by processes known in the art.



(7a) **(7b)** **(7c)**

The process described above and shown in Scheme 2 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 and R^4, 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.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds in the direction of glycogen synthesis, the conversion of glucose-1-phosphate into glycogen with the release of inorganic phosphate, as described in EP 0 846 464 A2. The reactions were in 96well microplate format in a volume of 100µl. The change in optical density due to inorganic phosphate formation was measured at 620nM in a Labsystems iEMS Reader MF by the general method of (Nordlie R.C and Arion W.J, Methods of Enzymology, 1966, 619-625). The reaction is in 50mM HEPES (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 17 was found to have an IC_{50} of 7.4μm.

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;

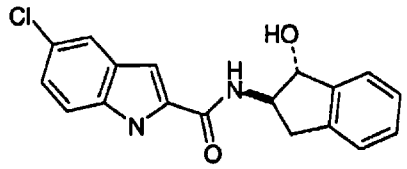
(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) The following abbreviations are used:

EtOAc	ethyl acetate;
MeOH	methanol;
EtOH	ethanol;
DCM	dichloromethane;
HOBT	1-hydroxybenzotriazole;
DIPEA	di-isopropylethylamine;
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide 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

Certain intermediates described hereinafter within the scope of the invention may also possess useful activity, and are provided as a further feature of the invention.

Example 1: 5-Chloro-2-[*N*-(1-hydroxyindan-2-yl)carbamoyl]indole

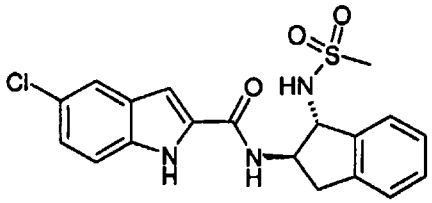


5-Chloro-1*H*-indole-2-carboxylic acid (116mg, 0.67mmol) was dissolved in DCM (10 ml) containing DIPEA (0.21 ml, 1.19mmol) and 2-aminoindan-1-ol (**Method 1**; 101mg, 0.67mmol) and HATU (247mg, 0.67mmol). The reaction mixture was stirred at room temperature for approximately 18 hours. The resulting solution was washed with water (20

ml) and the aqueous layer extracted with DCM (2 x 20 ml). The organic extracts were combined, dried over magnesium sulphate and concentrated under reduced pressure to give the title compound (195mg, 100%) as a white solid.

^{1}H NMR 2.83 (dd, 1H), 3.22 (dd, 1H), 4.40 (quin, 1H), 5.14 (d, 1H), 7.40 (m, 8H), 8.80 (d, 1H), 12.37 (s, 1H); m/z 325.

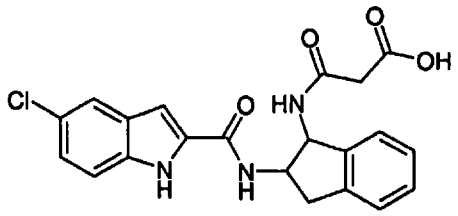
Example 2: 5-Chloro-*N*-{(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



5-Chloro-1*H*-indol-2-carboxylic acid (196mg, 1.0mmol), *N*-[(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methanesulfonamide (**Method 2**; 226mg, 1.0mmol), DIPEA (0.17 ml, 1.0mmol), and HOBT (130mg, 1.0mmol) was stirred in DCM (10 ml) for one minute. EDCI (240mg, 1.25mmol) was added and the mixture stirred at room temperature for 20 hours. The mixture was diluted with EtOAc, washed with water (2 x 25 ml), dried over magnesium sulphate and evaporated to give the title compound (320mg, 79%) as a foam.

^{1}H NMR 2.85 (dd, 1H), 3.25 (dd, 1H), 4.60 (m, 1H), 5.00 (m, 1H), 7.20 (m, 6H), 7.42 (d, 1H), 6.70 (s, 1H), 7.90 (d, 1H), 8.90 (d, 1H), 11.80 (broad s, 1H); m/z 402.4.

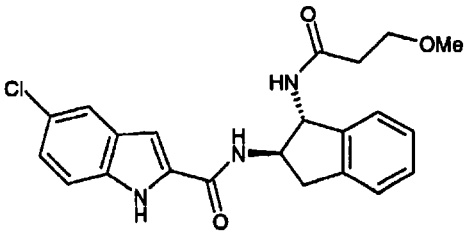
Example 3: *N*-[(1*R, 2*R**)-1-[(2-Carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide**



rac-*N*-(1-Amino-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide (**Method 4**; 440mg, 1.0mmol) was suspended in a solution of DCM (10 ml), mono-tert-butyl malonate (160mg, 1.0mmol), DIPEA (0.35 ml, 2.0mmol) and HOBT (135mg, 1.0mmol) and stirred for 2 mins. EDCI (240mg, 1.25mmol) was added and the reaction stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate and washed with water and brine. Drying over magnesium sulphate followed by evaporation gave the t-butyl ester as a white foam which was dissolved in DCM (10 ml) and trifluoroacetic acid and stirred at room temperature for 6 hours. The mixture was evaporated and co-evaporated with chloroform (2 x 10 ml). Trituration with Et_2O followed by filtration and drying gave the title compound (380mg, 92%) as a beige powder.

m/z 411.9.

Example 4: 5-Chloro-*N*-{(1*R*,2*R*)-1-[(3-methoxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



DIPEA (180 µL, 1.05 mmol), HOBT (68 mg, 0.5 mmol), 3-methoxypropanoic acid (46 µL, 0.5 mmol) 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]-5-chloro-1*H*-indole-2-carboxamide (**Method 5**, 220 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 (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 triturated (DCM), collected by filtration, washed with hexane (2 x 5 mL) and dried to give the title compound (84 mg, 41%) as a brown solid.

^{1}H NMR 2.38 (m, 2H), 2.88 (dd, 1H), 3.19 (s, 3H), 3.26 (obs m, 1H), 3.55 (m, 2H), 4.61 (m, 1H), 5.51 (t, 1H), 7.17 (m, 5H), 7.44 (d, 1H), 7.70 (s, 1H), 8.36 (d, 1H), 8.84 (d, 1H), 11.73 (s, 1H); MS m/z 413, 415

The following examples were made by a similar process to **Example 4** using -[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide (**Method 5**) and the appropriate commercially available carboxylic acid.

Example 5: *N*-[(1*R*,2*R*)-1-(Acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide

Example 6: 5-Chloro-*N*-[(1*R*,2*R*)-1-(*tert*-butoxycarbonylaminoacetamido)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide

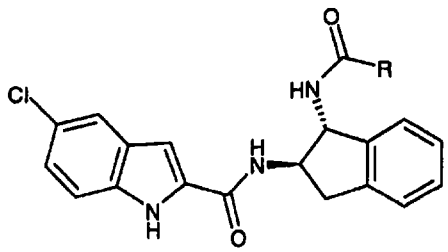
Example 7: *N*-((1*R*,2*R*)-1-{[3-(*tert*-Butoxycarbonylamino)-4-oxopentanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide

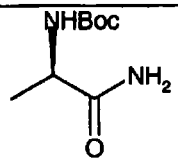
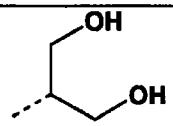
Example 8: *N*-{(1*R*,2*R*)-1-[(2-Carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide

Example 9: *N*-{(1*R*,2*R*)-1-[(2-Carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide

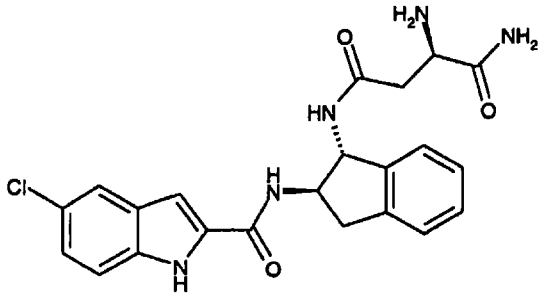
Example 10: 5-Chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide

Example 11: 2-Chloro-*N*-((1*R*,2*R*)-1-{[3-hydroxy-2-(hydroxymethyl)propanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide



Ex	R	NMR	M/z
5	Me	(DMSO-d_6) 1.88 (s, 3H), 2.87 (dd, 1H), 3.23 (obs m, 1H), 4.59 (m, 1H), 5.48 (t, 1H), 7.18 (m, 5H), 7.43 (d, 1H), 7.70 (s, 1H), 8.35 (d, 1H), 8.84 (d, 1H), 11.74 (s, 1H)	368, 370
6	CH_2NHBoc	-	505, 507 $(M+Na)^+$
7		-	562, 564 $(M+Na)^+$
8	$CH_2C(O)NH_2$	(DMSO-d_6) 2.89 (dd, 1H), 3.08 (m, 2H), 3.26 (m, 1H), 4.60 (m, 1H), 5.51 (m, 1H), 6.98 (s, 1H), 7.21 (m, 6H), 7.38 (s, 1H), 7.44 (d, 1H), 7.7 (d, 1H), 8.52 (d, 1H), 8.87 (d, 1H), 11.74 (s, 1H)	411, 413
9	CH_2CO_2H	(DMSO-d_6) 2.88 (dd, 1H), 3.19 (m, 2H), 3.26 (m, 1H), 4.6 (m, 1H), 5.51 (m, 1H), 7.17 (m, 6H), 7.43 (d, 1H), 7.7 (d, 1H), 8.58 (d, 1H), 8.86 (d, 1H), 11.74 (s, 1H)	412, 414
10	CH_2OH	(DMSO-d_6) 2.89 (dd, 1H), 3.25 (m, 1H), 3.89 (m, 2H), 4.76 (m, 1H), 5.39 (m, 1H), 5.54 (m, 1H), 7.17 (m, 6H), 7.43 (d, 1H), 7.69 (d, 1H), 8.13 (d, 1H), 8.84 (d, 1H), 11.73 (s, 1H)	-
11		(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 $(M-H)^-$

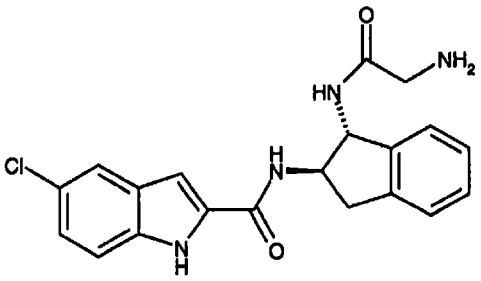
Example 12: *N*-{(1*R*,2*R*)-1-[((3*R*)-3-Amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide



N-((1*R*,2*R*)-1-{[3-(*tert*-Butoxycarbonylamino)-4-oxopentanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide (**Example 7**; 276 mg, 0.51 mmol) was dissolved in TFA (3 mL) and stirred at ambient temperature for 1 hour. The volatiles were removed under reduced pressure and the crude product was azeotroped with chloroform (3 x 5 mL), triturated (Et_2O), filtered and dried to give the trifluoroacetate salt of the title compound (242 mg, 86%) as a yellow solid.

^{1}H NMR 2.75 (m, 2H), 2.95 (dd, 1H), 3.25 (dd, 1H), 4.04 (br s, 1H), 4.64 (m, 1H), 5.53 (t, 1H), 7.19 (m, 6H), 7.44 (d, 1H), 7.54 (s, 1H), 7.73 (d, 2H), 8.06 (br, 3H), 8.73 (d, 1H), 8.90 (d, 1H), 11.75 (s, 1H); MS m/z 440, 442.

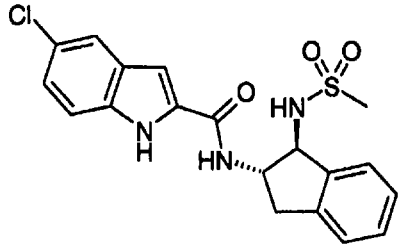
Example 13: *N*-{(1*R*,2*R*)-1-[(Aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide



5-Chloro-*N*-[(1*R*,2*R*)-1-(*tert*-butoxycarbonylaminoacetamido)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide (**Example 6**; 330 mg, 0.75 mmol) was dissolved in DCM (10 mL), TFA (0.5 mL) was added and the reaction was stirred at ambient temperature for 8 hours. The volatiles were removed under reduced pressure and the crude product was azeotroped with chloroform (3 x 5 mL), triturated (Et_2O), filtered and dried to give the trifluoroacetate salt of the title compound (264 mg, 71%) as a yellow solid.

^{1}H NMR 2.94 (dd, 1H), 3.27 (dd, 1H), 3.62 (dd, 2H), 4.65 (m, 1H), 5.56 (t, 1H), 7.20 (m, 6H), 7.39 (d, 1H), 7.70 (s, 1H), 8.89 (m, 2H), 11.76 (s, 1H); MS m/z 383, 385.

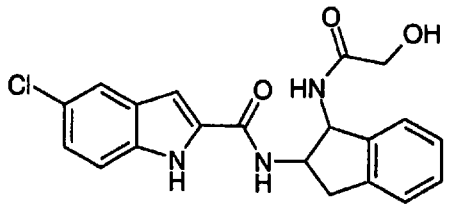
Example 14 5-Chloro-*N*-{(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



Prepared by a process similar to **Example 2** using (1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (see **Method 4a**) and 5-Chloro indole-2-carboxylic acid.

^{1}H NMR 2.86 (m, 1H), 2.99 (s, 3H), 3.24 (m, 1H), 4.6 (m, 1H), 4.99 (m, 1H), 7.09-7.37 (m, 6H), 7.42 (d, 1H), 7.71 (d, 1H), 7.89 (d, 1H), 8.9 (d, 1H), 11.8 (s, 1H); MS m/z $(M-H)^-$ 402, 404.

Example 15: 5-Chloro-*N*-{1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



5-Chloro-*N*-{1-[(iodoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide (**Method 7a**; 60mg, 0.12mmol) and sodium carbonate (100 mg) were dissolved in 1:1 dioxane:water (5 mL) and heated to reflux for 20 hours. The reaction was cooled, water (10 mL) added, filtered and the filter cake washed with water (3 x 1mL) and dried to give the title compound (40mg, 85%) as a white powder.

^{1}H NMR 2.9 (dd, 1H), 3.25 (m, 1H), 3.87 (m, 2H), 4.77 (m, 1H), 5.4 (m, 1H), 5.55 (m, 1H), 7.15 (m, 6H), 7.42 (d, 1H), 7.68 (s, 1H), 8.15 (d, 1H), 8.85 (d, 1H), 11.74 (s, 1H); MS m/z 384, 386.

Examples 16-20 were made by the following method:

5-Chloro-*N*-{1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide (**Method 7**, 200 mg, 0.5 mmol), Et_3N (418 µl, 3.0 mmol) and the corresponding amine (1.0mmol) were dissolved in THF (5mL) and stirred at ambient temperature for 24 hours. EtOAc (20 mL) was added and the mixture washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and the volatiles removed under reduced pressure to give the title compounds.

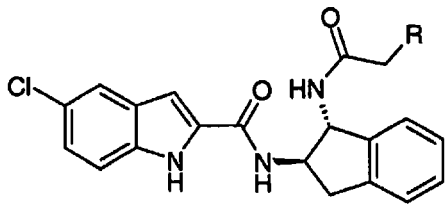
Example 16: 5-Chloro-*N*-[(1*R*,2*R*)-1-({[(2-hydroxyethyl)(methyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide

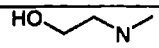
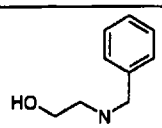
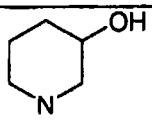
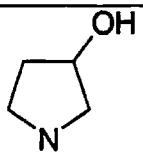
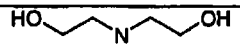
Example 17: 5-Chloro-*N*-[(1*R*,2*R*)-1-({[(2-hydroxyethyl)(phenylmethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide

Example 18: 5-Chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypiperidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide

Example 19: 5-Chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypyrrolidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide

Example 20: *N*-[(1*R*,2*R*)-1-({[Bis(2-hydroxyethyl)amino]acetyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide



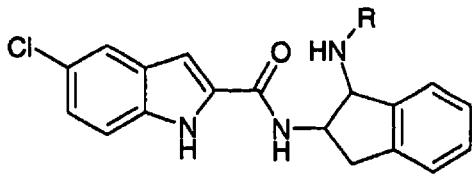
Ex	R	M/z
16		441, 443
17		455, 457
18		467, 469
19		453, 455
20		471, 473

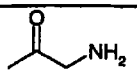
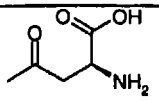
Examples 21 and **22** were prepared by the following method:

rac-N-[1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide trifluoroacetic acid salt (**Method 4,** 440 mg, 1.0 mmol), the corresponding carboxylic acid (1.0 mmol), DIPEA (350 µL, 2.0 mmol) and HOBT (135 mg, 1.0 mmol) were dissolved in DCM (10 mL) and stirred for 5mins. EDCI (240 mg, 1.25 mmol) was added and the mixture stirred at ambient temperature for 24h and the volatiles removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (25 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 dissolved in DCM (20 mL) and TFA (2 mL), stirred at ambient temperature for 4 hours, evaporated and co-evaporated with chloroform (2 x 10 mL) under reduced pressure and dried to give the title compound as a foam.

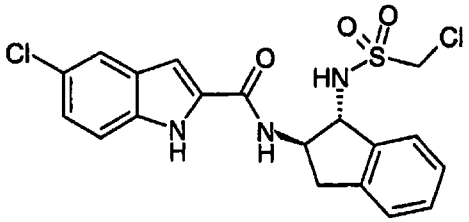
Example 21: *N*-{1-[(Aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide

Example 22: *N*-{1-[((3*S*)-3-Amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide



Ex	R	M/z
21		383, 385
22		441, 443

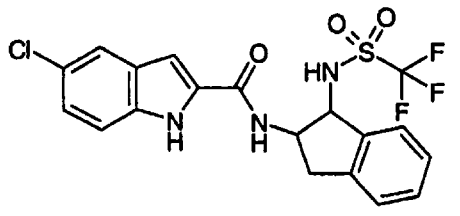
Example 23: 5-Chloro-*N*-((1*R*,2*R*)-1-{[(chloromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide



N-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide trifluoroacetic acid salt (**Method 5**, 2.2 g, 5.0 mmol) and Et_3N (2.1 mL, 15.0 mmol) dissolved in dry THF (30 mL) at 5°C, chloromethyl sulphonyl chloride (820 mg, 5.5 mmol) in dry THF (5 mL) was added and the reaction allowed to warm to ambient temperature for 2 hours. The volatiles were removed by evaporation under reduced pressure and the residue dissolved in EtOAc (75 mL), washed with water (2 x 25 mL), brine (25 mL) and dried ($MgSO_4$). Removal of the volatiles under reduced pressure gave the title compound (2.16 g, 98%) as a buff powder.

^{1}H NMR 2.84 (dd, 1H), 3.28 (m, 1H), 4.59 (m,1H), 5.02 (m, 3H), 7.26 (m, 7H), 7.71 (s, 1H), 8.53 (d, 1H), 8.82 (d, 1H), 11.79 (s, 1H); MS m/z 438.3/440.3.

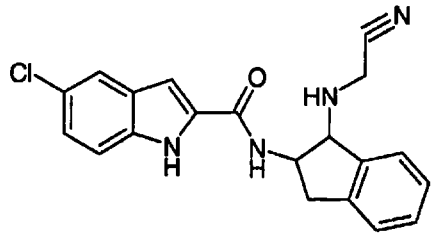
Example 24: *rac*-5-Chloro-*N*-(1-{[(trifluoromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide



rac-*N*-(1-Amino-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide (**Method 4,** 440 mg, 1.0mmol) suspended in DCM (6 mL) at 5°C. Et_3N (420 µL, 3.0 mmol) and trifluoromethane sulphonic anhydride (200 µL, 1.2 mmol) were added and the reaction stirred at ambient temperature for 2 hours. EtOAc (25 mL) was added and the mixture was washed with saturated sodium bicarbonate (5 mL), water (2 x 5 mL), brine (10 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (400mg, 87%) as a off-white powder.

^{1}H NMR 3.0 (dd, 1H), 3.3 (m, 1H), 4.85 (m, 1H), 5.55 (m, 1H), 7.12 (m, 2H), 7.18 (dd, 1H), 7.28 (m, 3H), 7.43 (d, 1H), 7.71 (d, 1H), 8.91 (d,1H), 9.96 (d, 1H), 11.77 (s. 1H); MS m/z 558, 460.

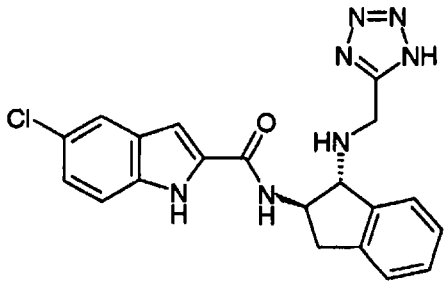
Example 25: *rac*-5-Chloro-*N*-{1-[(cyanomethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



N-[1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide trifluoroacetic acid salt (**Method 4,** 220 mg, 0.5 mmol), DIPEA (260 µL, 1.5 mmol) and bromoacetonitrile (37 µL, 0.55 mmol) in acetonitrile (5 mL) were heated in a microwave to 180°C for 1 min. 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:Hexane 1:1) to afford the title compound (110mg, 60%) as a white foam.

^{1}H NMR 2.93 (dd, 1H), 3.17 (m,1H), 3.23 (dd, 1H), 3.80 (m, 2H), 4.30 (m, 1H), 4.48(m, 1H), 7.21 (m, 5H), 7.35 (m, 1H), 7.43 (d, 1H), 7.68 (d, 1H), 8.8 (d, 1H), 11.77 (s, 1H); MS m/z 365, 367.

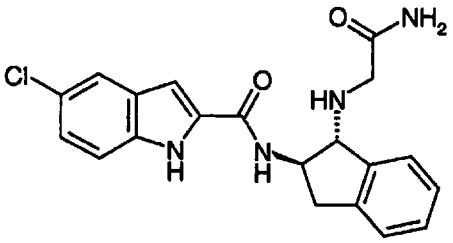
Example 26: 5-Chloro-*N*-{(1*R*,2*R*)-1-[(1*H*-tetrazol-5-ylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide



5-Chloro-*N*-{1-[(cyanomethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide (**Example 25**; 182 mg, 0.5 mmol), sodium azide (195 mg, 3.0 mmol) and ammonium chloride (163 mg, 3.05 mmol) in DMA (5 mL) were heated in a microwave at 180°C for 1 min. EtOAc (50 mL) was added and the mixture washed with water (6 x 10 mL), brine (25 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure. The desired component was isolated by preparative HPLC (CH_3CN:water) to give the title compound (35 mg, 14%) as a pale orange powder.

^{1}H NMR 2.9 (dd, 1H), 3.42 (dd, 1H), 4.25 (m, 2H), 4.47 (m, 1H), 4.69 (m, 1H), 7.16 (m, 2H), 7.27 (m, 3H), 7.42 (d, 1H), 7.49 (m, 1H), 7.68 (d, 1H); MS m/z $(M-H)^-$ 407, 409.

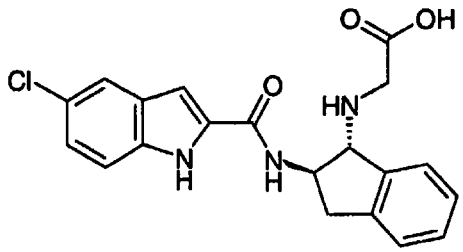
Example 27: *N*-{(1*R*,2*R*)-1-[(2-Amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide



Prepared in a similar manner to **Example 25** using *N*-[(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide trifluoroacetic acid salt (**Method 5**) as the amine and 2-bromoacetamide as electrophile.

^{1}H NMR 2.71 (s, 1H), 2.83 (dd, 1H), 3.26 (m, 3H), 4.25 (m, 1H), 4.47 (m, 1H), 7.03 (s, 1H), 7.19 (m, 5H), 7.29 (s, 1H), 7.38 (s, 1H), 7.43 (d, 1H), 7.68 (d, 1H), 8.75 (d, 1H), 11.75 (s, 1H); MS m/z $(M-H)^-$ 382, 384.

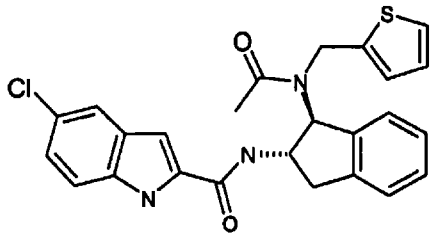
Example 28: *N*-[(1*R*,2*R*)-1-(Carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide



tert-Butyl *N*-((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)glycinate (**Method 8**, 230 mg, 0.52 mmol) was dissolved in DCM (10 mL). TFA (1 mL) was added and the reaction stirred at ambient temperature for 3 hours. Evaporation under reduced pressure, co-evaporation with $CHCl_3$ (2 x 10 mL) and crystallization from EtOAc gave the title compound (85 mg, 36%) as a powder.

^{1}H NMR 2.93 (dd, 1H), 3.41 (dd, 1H), 3.69 (m, 2H), 4.55 (m, 1H), 4.66 (m, 1H), 7.13 (s, 1H), 7.31 (m, 4H), 7.5 (d, 1H), 8.64 (d, 1H), 12.43 (s, 1H); MS m/z $(M-H)^-$ 382, 384.

Example 29: *N*-{(1*S*,2*S*)-1-[Acetyl(2-thienylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide



2-Thiophenecarboxaldehyde (80 µL, 0.8 mmol) and potassium acetate (90 mg, 0.9 mmol) were added to a solution of *N*-{(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (**Method 5b**, 400 mg, 0.9 mmol) in MeOH (10 mL). The reaction was stirred at ambient temperature for approximately 5 mins then macroporous triethylammonium methyl polystyrene cyanoborohydride (540 mg, 0.9 mmol) was added and the reaction stirred at ambient temperature for a further 3 h. The reaction was then filtered and the volatiles were removed by evaporation under reduced pressure to afford *N*-{(1*S*,2*S*)-1-[(2-thienylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide which was used crude in the next stage.

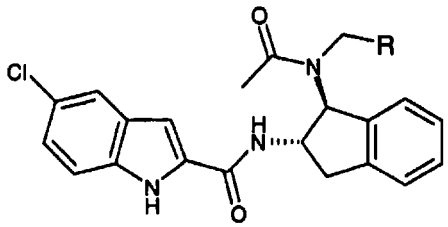
DIPEA (90 μL, 0.5 mmol) and acetyl chloride (40 μL, 0.5 mmol) were added to a solution of *N*-{(1*S*,2*S*)-1-[(2-thienylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (210 mg, 0.5 mmol) in anhydrous THF (7 mL). The reaction was stirred at ambient temperature for approximately 3 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 (SCX-2, MeOH:EtOAc 1:10) to afford the title compound (100 mg, 43%) as a white solid.

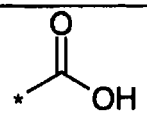
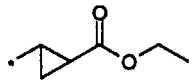
^{1}H NMR 2.45 (s, 3H), 2.90 (dd, 1H), 3.35 (dd, 1H), 4.35 (d, 1H), 4.50 (m, 1H), 4.90 (m, 2H), 7.5 (m, 11H), 8.80 (d, 1H), 11.80 (s, 1H); MS m/z 464.

The following examples were made by the process of **Example 29** using *N*-{(1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (**Method 5b**) and the appropriate commercially available aldehyde:

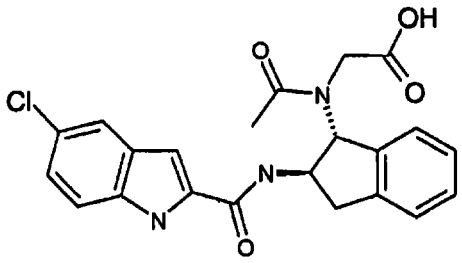
Example 30: *N*-{(1*S*,2*S*)-1-[*N*-Acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide

Example 31: *N*-[(1*S*,2*S*)-1-{*N*-Acetyl-*N*-[2-(ethoxycarbonyl)cycloprop-1ylmethyl]amino}-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide



Ex	R	NMR	M/z
30		(DMSO-d_6) 2.45 (s, 3H), 2.95 (dd, 1H), 3.15 (dd, 1H), 3.30 (s, 2H), 4.60 (m, 1H), 5.45 (t, 1H), 7.15 (m, 5H), 7.40 (d, 1H), 7.7 (s, 1H), 8.35 (s, 1H), 8.85 (d, 1H), 11.75 (br s, 1H)	424 (M-H)
31		(DMSO-d_6) 1.11 (t, 3H), 2.44 (s, 3H), 2.95 (dd, 1H), 3.05 (m, 2H), 3.36 (m, 5H), 3.94 (m, 2H), 4.85 (br m, 1H), 5.45 (br m, 1H), 7.15 (m, 5H), 7.42 (d, 1H), 7.69 (s, 1H), 8.35 (s, 1H), 8.86 (d, 1H), 11.80 (br s, 1H)	494

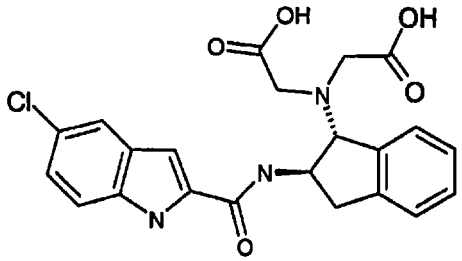
Example 32: *N*-{(1*R*,2*R*)-1-[*N*-Acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide



TFA (5 mL) was added to a solution of 1,1-dimethylethyl [acetyl((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (**Method 9**, 138 mg, 0.3 mmol) in DCM (10 mL) and the reaction was stirred at ambient temperature for 1h. The volatiles were removed by evaporation under reduced pressure to afford the title compound (100 mg, 83%) as a white solid.

^{1}H NMR 2.42 (s, 3H), 2.97 (dd, 1H), 3.20 (dd, 1H), 3.90 (m, 2H), 4.60 (m, 1H), 5.45 (d, 1H), 7.25 (m, 8H), 8.80 (d, 1H), 11.73, (s, 1H); MS m/z 426.

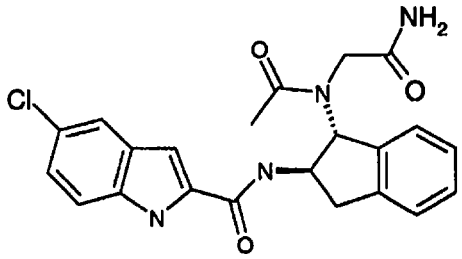
Example 33: *N*-{(1*R*,2*R*)-1-[Bis-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide



TFA (5 mL) was added to a solution of 1,1-dimethylethyl [((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]diacetate (**Method 10**, 280 mg, 0.5 mmol) in DCM (10 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 (150 mg, 68%) as a white solid.

^{1}H NMR 2.85 (dd, 1H), 3.63 (m, 4H), 3.71 (dd, 1H), 4.30 (m, 1H), 4.51 (d, 1H), 7.30 (m, 7H), 7.60 (s, 1H), 8.67 (s, 1H), 10.22 (s, 1H); MS m/z 442, 309.

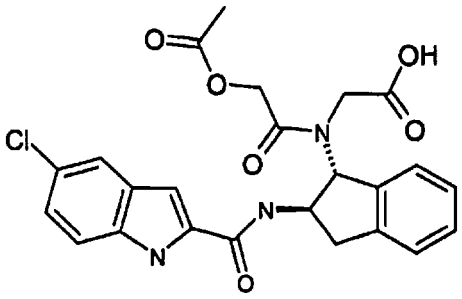
Example 34: *N*-{(1*R*,2*R*)-1-[Acetyl(2-amino-2-oxoethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide



Acetyl chloride (20 µL, 0.32 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}-5-chloro-1*H*-indole-2-carboxamide (**Example 27**, 122 mg, 0.32 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 to afford the title compound (40 mg, 29%) as a white solid.

^{1}H NMR 2.49 (s, 3H), 2.98 (dd, 1H), 3.20 (dd, 1H), 3.29 (brs, 2H), 4.05 (m, 2H), 4.45 (m, 1H), 5.70 (d, 1H), 7.28 (m, 8H), 8.80 (d, 1H), 11.78, (s, 1H); MS m/z 447 $(M+NH4)^+$ 309.

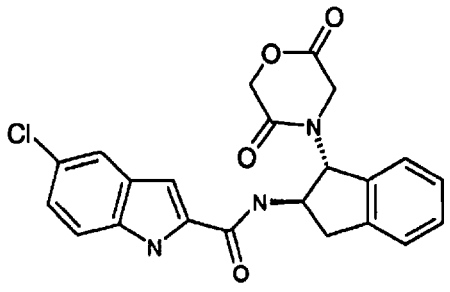
Example 35: *N*-{(1*R*,2*R*)-1-[*N*-(2-Acetoxyacetyl)-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide



TFA (3ml) was added to a solution of 1,1-dimethylethyl [[(acetyloxy)acetyl]((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino }-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (**Method 11**, 200 mg, 0.4 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 2.49 (s, 3H), 3.14 (dd, 1H), 3.26 (dd, 1H), 3.94 (d, 1H), 4.28 (d, 1H), 4.80 (m, 3H), 5.98 (d, 1H), 7.20 (m, 6H), 7.45 (d, 1H), 7.65 (s, 1H), 8.71 (brd, 1H), 11.52, (s, 1H); MS m/z 484.

Example 36: 5-Chloro-*N*-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide

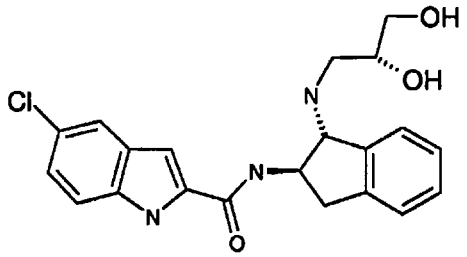


Potassium carbonate (20 mg) and MeOH (1 mL) were added to a solution of *N*-{(1*R*,2*R*)-1-[*N*-(2-acetoxyacetyl)-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide (**Example 35**, 184 mg, 0.38 mmol) in THF (5 mL) and the reaction was stirred at ambient temperature for 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 and the residue purified by column chromatography (EtOAc:isohexane 1:4) to afford the title compound (50 mg, 31%) as a white solid.

^{1}H NMR 3.07 (dd, 1H), 3.22 (dd, 1H), 3.94 (d, 1H), 4.27 (d, 1H), 4.82 (m, 3H), 5.96 (d, 1H), 7.18 (m, 6H), 7.42 (d, 1H), 7.71 (s, 1H), 8.90 (d, 1H), 11.77 (s, 1H); MS m/z(M-H)$^-$ 422.

Example 37: 5-Chloro-*N*-((1*R*,2*R*)-1-{[(2*R*)-2,3-dihydroxypropyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide



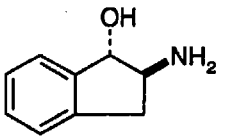
2,3-*O*-(*S*)-Isopropylidene-*L*-glyceraldehyde (98 mg, 0.75 mmol) and potassium acetate (75 mg, 0.75 mmol) were added to a solution of *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (**Method 5**, 328 mg, 0.75 mmol) in MeOH (10 mL). The reaction was stirred at ambient temperature for approximately 5 mins then macroporous triethylammonium methyl polystyrene cyanoborohydride (352 mg, 0.9 mmol) was added and the reaction stirred at ambient temperature for a further 5 h. The reaction was then filtered and the volatiles were removed by evaporation under reduced pressure to 5-chloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide which was used crude in the next stage.

TFA (3 mL) was added to a solution of 5-chloro-*N*-[(1*R*,2*R*)-1-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide (100 mg, 0.23 mmol) in DCM (10 mL) and the reaction was stirred at ambient temperature for 24 h. The volatiles were removed by evaporation under reduced pressure to afford the title compound (90 mg, 100%) as a white solid.

^{1}H NMR 2.94 (dd, 1H), 3.15 (m, 2H), 3.38 (m, 1H), 3.53 (q, 1H), 4.35 (m, 3H), 4.77 (br s, 1H), 4.96 (br s, 1H), 6.80 (s, 1H), 7.30 (m, 7H), 7.50 (s, 1H), 10.01 (s, 1H); MS m/z 400.

Method 1:

(+/-)-*trans*-2-Aminoindan-1-ol



Isoamyl nitrite (15 ml, 108mmol) was added to a solution of indan-1,2-dione (12g, 90mmol) in MeOH (380 ml) at 45°C followed by concentrated HCl (12 ml) dropwise over 5 minutes. The reaction mixture was stirred for 3 hours at room temperature. Excess isoamyl nitrite (1 ml) and concentrated HCl (1 ml) was added and the suspension stirred for a further 15 minutes. On cooling to room temperature a white precipitate formed. The precipitate was filtered off and washed with cold MeOH (40 ml) followed by Et_2O (40 ml) to afford indan-1,2-dione-2-oxime (6.2g, 43%) as a white solid.

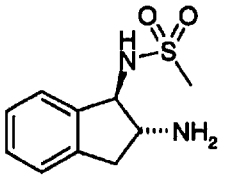
^{1}H NMR 3.80 (s, 2H), 7.43 (t, 1H), 7.60 (d, 1H), 7.70 (t, 2H); m/z 162.

A solution of indan-1,2-dione-2-oxime (6.2g, 39mmol) in EtOH (470 ml) and 4MHCl/Dioxane (36 ml) was hydrogenated at room temperature and 40 psi. The reaction mixture was filtered through celite, washed with EtOH (30 ml) and concentrated under reduced pressure to give 10g of an off-white solid which was recrystallised from EtOH to give the title compound (5g, 86%) as a white solid.

^{1}H NMR: 2.80 (dd, 1H), 3.25 (dd, 1H), 3.73 (q, 1H), 5.12 (t, 1H), 6.04 (d, 1H), 7.2 (m, 4H), 8.60 (s, 2H).

Method 2

N-[(1*R*,2*R*)-2-Amino-2,3-dihydro-1*H*-inden-1-yl]methanesulfonamide



(1*R*,2*S*)-1-Amino-2-hydroxyindan (3.0g, 20mmol) was dissolved in dry THF (40 ml) and triethylamine (8.4 ml, 60.0mmol) at 10°C. Methane sulphonyl chloride (5.0g, 44.0mmol) dissolved in THF (10ml) was added at such a rate that the internal temperature remained below 15°C. Following the addition the mixture was stirred at room temperature for 20hours

and then evaporated. To the residue was added EtOAc (100 ml) and the mixture washed with saturated aqueous sodium bicarbonate and then water. The organic solution was dried over magnesium sulphate and evaporated to give (1*R*,2*S*)-1-methanesulphonamido-2-methylsulphonyloxyindan (5.7g, 93%) as a pale yellow solid.

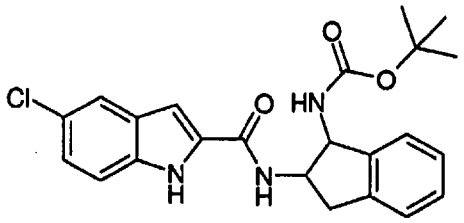
^{1}H NMR: 3.25 (m, 2H), 3.10 (s, 3H,), 3.20 (s, 3H), 5.15 (m, 1H), 5.35 (m, 1H), 7.3 (m, 4H), 7.90 (m, 1H); m/z 304.2.

(1*R*,2*S*)-1-Methanesulphonamido-2-methylsulphonyloxyindan (2.0g, 6.56mmol) was dissolved in dry dimethyl acetamide (20 ml). Sodium azide (1.7g, 26.2mmol) was added and the mixture heated to 90°C for 1 hour. The reaction was cooled, diluted with EtOAc (100 ml), washed with water (6 x 50 ml), dried over magnesium sulphate and filtered. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 3 hours. Filtration through celite followed by evaporation gave the title compound (1.25 g, 83%) as a pale green solid.

^{1}H NMR 1.70 (broad s, 2H), 2.72 (dd, 1H), 3.20 (s, 3H), 3.25 (dd, 1H), 4.55 (m, 1H), 4.70 (m, 1H), 7.20 (m, 4H); m/z 227.4.

Method 3

5-Chloro-2-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl) indole

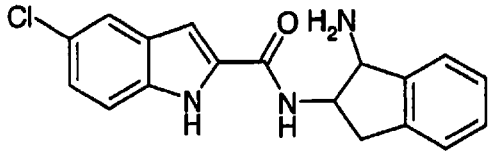


5-Chloro-indole-2-carboxylic acid (5.0g, 25.6mmol), (+/-)-*trans*-2-amino-1-{*N*-[(1,1-dimethylethoxy)]carbonylamino}indan (6.3g, 25.6mmol), DIPEA (4.5 ml, 25.6mmol) and HOBT (3.5g, 25.6mmol) was stirred in DCM (100 ml) at room temperature for 2 minutes. EDCI (6.1g, 32.0mmol) was added and the mixture stirred at room temperature for 20 hours. The mixture was diluted with EtOAc (250 ml) and washed with water and brine. Drying over magnesium sulphate followed by evaporation gave the crude material which was purified by silica chromatography with hexane:EtOAc to give the title compound (9.1 g, 83%) as a pale pink foam.

^{1}H NMR 2.85 (dd, 1H), 3.20 (dd, 1H), 4.50 (m, 1H), 5.10 (m, 1H), 7.15 (m, 6H), 7.35 (d, 1H), 7.45 (d, 1H), 7.70 (s, 1H), 8.80 (d, 1H), 11.78 (broad s, 1H).

Method 4

rac-N-(1-Amino-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide

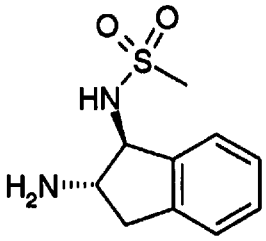


5-Chloro-2-(*N*-{1-[*N*-(1,1-dimethylethoxy)carbonylamino]indan-2-yl}carbamoyl) indole (**Method 3**; 5.0g, 11.74mmol) was dissolved in DCM (50 ml). Trifluoroacetic acid (10 ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was evaporated then co-evaporated with chloroform (2 x 50 ml) and triturated with Et_2O to give the trifluoroacetic acid salt of the title compound (5.0 g, 96%) as a beige powder.

^{1}H NMR 3.04 (dd, 1H), 3.40 (dd, 1H), 4.80 (m, 2H), 7.15 (m, 2H), 7.30 (m, 3H), 7.55 (d, 1H), 7.60 (d, 1H), 7.75 (d, 1H), 8.60 (broad s, 3H), 9.00 (d, 1H), 11.82 (broad s, 1H).

Method 4a

N-[(1*S*,2*S*)-2-Amino-2,3-dihydro-1*H*-inden-1-yl]methanesulfonamide



This compound was prepared according to the process of Method 2, starting from (1*S*,2*R*)-1-amino-2-hydroxyindan to give the intermediate (1*S*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate:

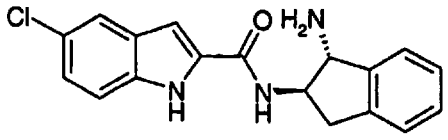
^{1}H NMR 3.1 (s, 3H), 3.23 (s, 3H), 3.07-3.33 (m, 2H), 5.13 (s, 1H), 5.37 (m, 1H), 7.30 (m, 4H), 7.95 (s, 1H); MS m/z $(M-H)^-$ 304.

and then the required final product:

^{1}H NMR 1.96 (s, 2H), 2.56 (m, 1H), 3.01 (m, 1H), 3.14 (s, 3H), 3.32 (m, 1H), 4.36 (d, 1H), 7.1-7.3 (m, 4H), 7.56 (s, 1H); MS m/z 227.

Method 5

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

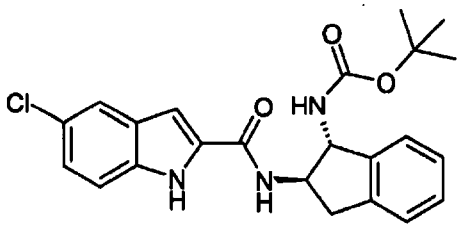


tert-Butyl ((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)carbamate (**Method 5a**; 1.0g, 2.35mmol) was dissolved in DCM (10 mL), TFA (2 mL) was added and the mixture stirred for approximately 70 hours. Evaporation under reduced pressure followed by co-evaporation with chloroform (2 x 10 mL) and drying gave the title compound as the trifluoroacetate salt (1.0 g, 100%) as a pale brown amorphous powder.

^{1}H NMR 3.03 (dd, 1H), 3.4 (dd, 1H), 4.75 (m, 2H), 7.17 (d, 1H), 7.2 (d, 1H), 7.36 (m, 3H), 7.46 (d, 1H), 7.55 (m, 1H), 7.72 (d, 1H), 8.57 (s, 3H), 8.99 (d, 1H); MS m/z 326, 328.

Method 5a

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

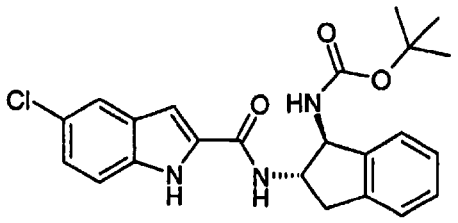


5-Chloroindole-2-carboxylic acid (391 mg, 2 mmol), *tert*-Butyl [(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]carbamate (497 mg, 2 mmol), DIPEA (350 µL, 2 mmol) and HOBT (270 mg, 2 mmol) were dissolved in DCM (10 mL), stirred for 5 mins, then EDCI (479mg, 2.5 mmol) was added and the reaction stirred for 3 hours. The volatiles were removed by evaporation under reduced pressure, EtOAc (25 mL) was added and the organic solution washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (800 mg, 94%) as a pale brown foam.

^{1}H NMR 1.47 (s, 9H), 2.9 (dd, 1H), 3.27 (dd, 1H), 4.7 (m, 1H), 5.25 (m, 1H), 7.24 (m, 6H), 7.5 (m, 2H), 7.79 (s, 1H), 8.91 (d, 1H), 11.85 (s, 1H), MS m/z 426, 428.

Method 5b

tert-Butyl ((1*S*,2*S*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)carbamate

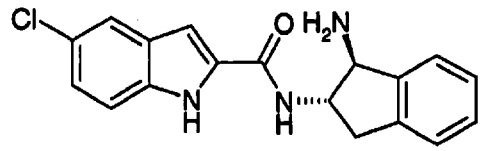


5-Chloroindole-2-carboxylic acid (2.8g, 14 mmol), *tert*-Butyl [(1*S*,2*S*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]carbamate (3.47g, 14mmol), DIPEA (4.9ml, 28mmol) and HOBT (1.89g, 14mmol) were dissolved in DCM (100 mL), stirred for 5 mins, then EDCI (3.2g, 16.7mmol) was added and the reaction stirred for 3 hours. The volatiles were removed by evaporation under reduced pressure, EtOAc (125 mL) was added and the organic solution washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (5.7g, 93%) as a pale brown foam.

^{1}H NMR 1.47 (s, 9H), 2.9 (dd, 1H), 3.27 (dd, 1H), 4.7 (m, 1H), 5.25 (m, 1H), 7.24 (m, 6H), 7.5 (m, 2H), 7.79 (s, 1H), 8.91 (d, 1H), 11.85 (s, 1H), MS m/z 426, 428.

Method 6

N-[(1*S*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide

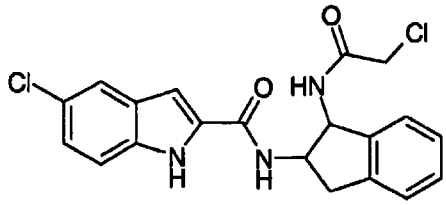


tert-Butyl ((1*S*,2*S*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)carbamate (**Method 5b**; 5.7g, 2.35mmol) was dissolved in DCM (70 mL), TFA (13 mL) was added and the mixture stirred for approximately 20 hours. Evaporation under reduced pressure followed by co-evaporation with chloroform (2 x 50 mL) and drying gave the title compound as the trifluoroacetate salt (5.5 g, 97%) as a pale brown amorphous powder.

^{1}H NMR 3.03 (dd, 1H), 3.4 (dd, 1H), 4.75 (m, 2H), 7.17 (d, 1H), 7.2 (d, 1H), 7.36 (m, 3H), 7.46 (d, 1H), 7.55 (m, 1H), 7.72 (d, 1H), 8.57 (s, 3H), 8.99 (d, 1H); MS m/z 326, 328.

Method 7

rac-5-Chloro-*N*-{1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide

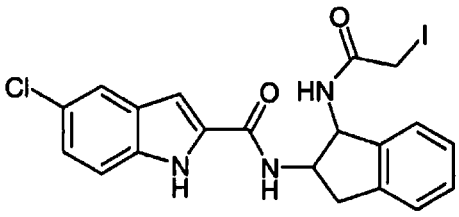


N-[1-Amino-2,3-dihydro-1H-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide trifluoroacetic acid salt (12.8 g, 29.1 mmol) and Et_3N (11.8 g, 116.4 mmol) were dissolved in DCM (500 mL) at 10°C. Chloroacetyl chloride (6.6 g, 58.2 mmol) in DCM (25 mL) was added, the reaction allowed to warm to ambient temperature, stirred for 1 hours, filtered and the filter cake washed with DCM (3 x 50 mL) and dried to give the title compound (9.0 g, 77%) as a white powder.

^{1}H NMR 2.9 (dd, 1H), 3.26 (m, 1H), 4.11 (m, 2H), 4.67 (m, 1H), 5.5 (m, 1H), 7.19 (m, 6H), 7.43 (d, 1H), 7.7 (d, 1H), 8.75 (d, 1H), 8.87 (d, 1H), 11.74 (s, 1H); MS m/z 402, 404.

Method 7a

5-Chloro-*N*-{1-[(iodoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide

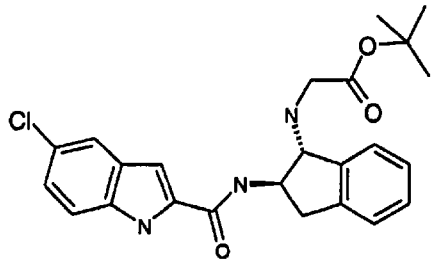


5-Chloro-*N*-{1-[(chloroacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide (**Method 7**; 2.0 g, 5.0 mmol) and potassium iodide (2.0 g, 12.0 mmol) in acetone (50 mL) was heated at reflux for 6 hours and then cooled and the volatiles removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (50 mL) washed with 1M aqueous sodium thiosulphate (2 x 25 mL), water (25 mL), brine (25 mL), dried ($MgSO_4$) and the volatiles removed by evaporation under reduced pressure to give the title compound (2.3 g, 92%) as a pale yellow powder.

^{1}H NMR 2.87 (dd, 1H), 3.25 (m, 1H), 3.69 (m, 2H), 4.6 (m, 1H), 5.45 (m, 1H), 7.2 (m, 6H), 7.42 (d, 1H), 7.7 (d, 1H), 8.77 (d, 1H), 8.87 (d, 1H), 11.73 (s, 1H); MS m/z $(M-H)^-$.492, 494.

Method 8

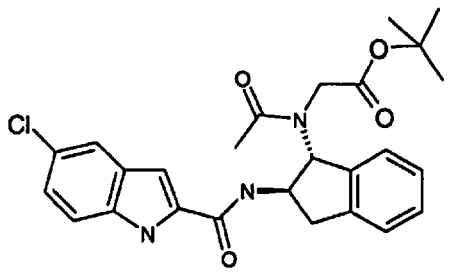
1,1-Dimethylethyl [((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate



DIPEA (2.4 mL, 14 mmol) and *t*-butyl bromoacetate (610 µL, 4.0 mmol) were added to a solution of *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (**Method 5**, 2 g, 4.6 mmol) in CH_3CN (50 mL). The resulting suspension was stirred at 60°C for approximately 2 hours. Upon cooling the volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (50 mL), washed with water (2 x 20 mL) and brine (50 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 (600 mg, 34%) as a white solid. ^{1}H NMR 1.36 (s, 9H), 2.95 (dd, 1H), 3.30 (br s, 1H), 3.38 (dd, 1H), 3.67 (br t, 2H), 4.45 (br s, 1H), 4.60 (m, 1H), 7.15 (s, 2H), 7.18 (d, 1H), 7.28 (s, 2H), 7.45 (d, 2H), 7.68 (s, 1H), 8.82 (d, 1H), 11.8 (s, 1H); MS m/z 439.

Method 9

1,1-Dimethylethyl [acetyl((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate



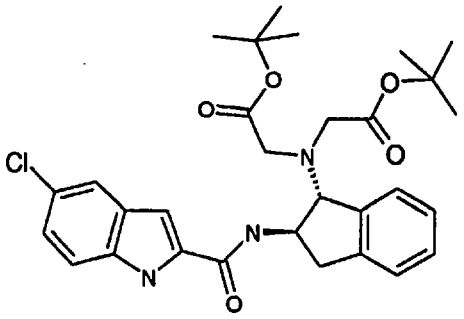
DIPEA (80 µL, 0.5 mmol) and acetyl chloride (30 µL, 0.5 mmol) were added to a solution of 1,1-dimethylethyl [((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (**Method 8**, 200 mg, 0.5 mmol) in THF (10 mL). The

reaction was stirred at ambient temperature for approximately 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 1:1) to afford the title compound (168 mg, 76%) as a white solid.

^{1}H NMR 1.34 (s, 9H), 2.99 (dd, 1H), 3.25 (dd, 1H), 3.28 (s, 3H), 3.38 (q, 2H), 4.67 (m, 1H), 5.53 (d, 1H), 7.50 (m, 8H), 8.50 (d, 1H), 11.75, (s, 1H); MS m/z 504 $(M+NH4)^+$ 426.

Method 10

1,1-Dimethylethyl [((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]diacetate

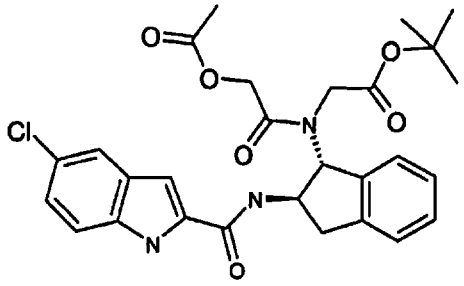


DIPEA (2.4 mL, 14 mmol) and *t*-butyl bromoacetate (610 µL, 4.0 mmol) were added to a solution of *N*-{(1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide (**Method 5**, 2 g, 4.6 mmol) in CH_3CN (50 mL). The resulting suspension was stirred at 60°C for approximately 2 h. Upon cooling the volatiles were removed by evaporation under reduced pressure, the residue dissolved in EtOAc (50 mL), washed with water (2 x 20 mL), brine (50 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 (300 mg, 14%) as a white solid.

^{1}H NMR 1.45 (s, 9H), 1.50 (s, 9H), 2.85 (dd, 1H), 3.63 (m, 4H), 3.71 (dd, 1H), 4.30 (m, 1H), 4.51 (d, 1H), 7.30 (m, 7H), 7.60 (s, 1H), 8.67 (s, 1H), 10.22 (s, 1H); MS m/z 554, 309.

Method 11

1,1-Dimethylethyl [[(acetyloxy)acetyl]((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate

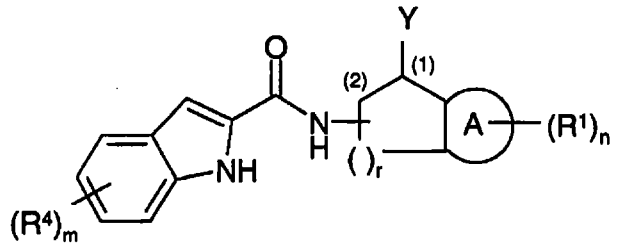


Acetoxyacetic acid (54 mg, 0.5 mmol) and DMTMM (130 mg, 0.5 mmol) were added to a solution of dimethylethyl [((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)amino]acetate (**Method 8**, 200 mg, 0.5 mmol) in THF (10 mL). The reaction was stirred at ambient temperature for approximately 18 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 (215 mg, 80%) as a white solid.

^{1}H NMR 1.40 (s, 9H), 2.50 (s, 3H), 2.75 (m, 1H), 3.36 (dd, 1H), 3.69 (m, 2H), 3.88 (d, 2H), 4.72 (m, 1H), 4.86 (brd, 1H), 7.09 (s, 1H), 7.15 (dd, 1H), 7.28 (m, 4H), 7.45 (d, 1H), 7.65 (s, 1H), 8.55 (s, 1H), 11.47 (s, 1H); MS m/z 562.

Claims

1. A compound of formula (1):



(1)

wherein:

A is phenylene or heteroarylene;

n is 0, 1 or 2;

m is 0, 1 or 2;

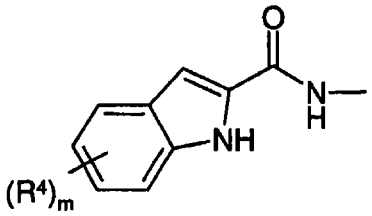
R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, -S(O)$_b$$C_{1-4}$alkyl (wherein b is 0,1,or 2), C_{1-4}alkyl, C_{2-4}alkenyl,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

r is 1 or 2; and

when r is 1 the group



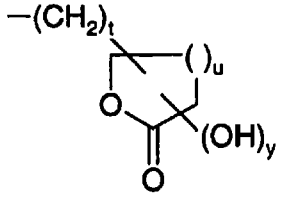
is a substituent on carbon (2) and

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

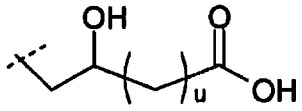
Y is $-NR^2R^3$ or $-OR^3$;

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}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^9R^{10}, -(CH_2)$_w$CH(NR^9R^{10})C$O_2R^{9'}$ (wherein w is 1, 2 or 3), -(CH_2)$_w$CH(NR^9R^{10})CO(N$R^{9'}R^{10'}$) (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), -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.

2. A compound of 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}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_{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 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 an in-vivo hydrolysable ester thereof.

3. A compound of 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}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); or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

4. A compound of the formula (1) as claimed in any preceding claim, wherein Y is NR^2R^3; or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

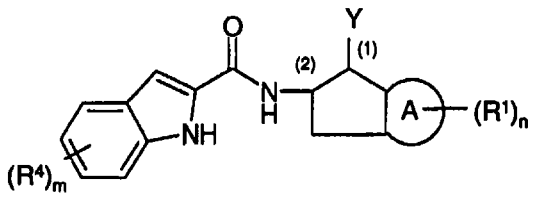
5. A compound of the formula (1) as claimed in any one of claims 1 to 3, wherein Y is OR^3; or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

6. A compound of the formula (1) as claimed in any preceding claim wherein m is 1 and R^4 is chlorine; or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

7. A compound of the formula (1) as claimed in any preceding claim wherein A is phenylene; or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

8. A compound of the formula (1) as claimed in any one of claims 1 to 7 wherein A is heteroarylene; or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

9. A compound of the formula (1) as claimed in any preceding claim, which is a compound of formula (1A):



(1A)

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

10. A compound of the formula (1) as claimed in claim 1, which is any one of:

5-chloro-2-[*N*-(1-hydroxyindan-2-yl)carbamoyl]indole;

5-chloro-*N*-{(1*R*,2*R*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

N-{(1*R**, 2*R**)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

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

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

5-chloro-*N*-[(1*R*,2*R*)-1-(*tert*-butoxycarbonylaminoacetamido)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide;

N-((1*R*,2*R*)-1-{[3-(*tert*-butoxycarbonylamino)-4-oxopentanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-5-chloro-1*H*-indole-2-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carbamoylacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[(2-carboxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-{(1*R*,2*R*)-1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

N-{(1*R*,2*R*)-1-[((3*R*)-3-amino-3-carbamoylpropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

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

5-chloro-*N*-{(1*S*,2*S*)-1-[(methylsulfonyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[(hydroxyacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

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

5-chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypiperidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(3-hydroxypyrrolidin-1-yl)acetyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

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

N-{1-[(aminoacetyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide;

N-{1-[((3*S*)-3-amino-3-carboxypropanoyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(chloromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{[(trifluoromethyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[(cyanomethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{(1*R*,2*R*)-1-[(1*H*-tetrazol-5-ylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-1*H*-indole-2-carboxamide;

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

N-[(1*R*,2*R*)-1-(carboxymethylamino)-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

N-{(1*S*,2*S*)-1-[acetyl(2-thienylmethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloro-1*H*-indole-2-carboxamide;

N-{(1*S*,2*S*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-[(1*S*,2*S*)-1-{*N*-acetyl-*N*-[2-(ethoxycarbonyl)cycloprop-1ylmethyl]amino}-2,3-dihydro-1*H*-inden-2-yl]-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[*N*-acetyl-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

N-{(1*R*,2*R*)-1-[bis-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

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

N-{(1*R*,2*R*)-1-[*N*-(2-acetoxyacetyl)-*N*-(carboxymethyl)amino]-2,3-dihydro-1*H*-inden-2-yl}-5-chloroindole-2-carboxamide;

5-chloro-*N*-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide;

5-chloro-*N*-((1*R*,2*R*)-1-{[(2*R*)-2,3-dihydroxypropyl]amino}-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole-2-carboxamide;

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

11. 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 10 in association with a pharmaceutically-acceptable diluent or carrier.

12. 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 10, for use in a method of treatment of a warm-blooded animal such as man by therapy.

13. 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 10, for use as a medicament.

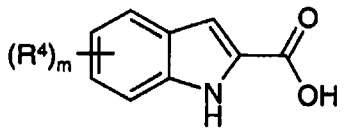
14. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 10, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

15. 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 10, 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.

16. 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 10, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

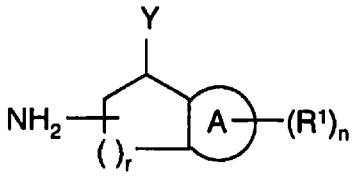
17. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

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.