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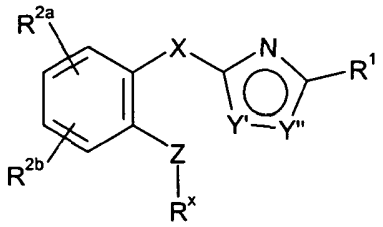
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(54) Title: OXAZOLE AND THIAZOLE COMPOUNDS AND THEIR USE IN THE TREATMENT OF PGE2 MEDIATED DISORDERS



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutiically acceptable derivative thereof: wherein X, Z, Y', Y", R1 ,R2a, R2b, and Rx are as defined in the specification, a process for the preparation of such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.

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OXAZOLE AND THIAZOLE COMPOUNDS AND THEIR USE IN THE TREATMENT OF PGE2 MEDIATED DISORDERS

This invention relates to heterocyclic compounds, more specifically thiazole and oxazole compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of conditions mediated by the action of PGE_2 at the EP_1 receptor.

Prostaglandin receptors, including the EP_{1-4}, DP, FP IP and TP receptors are the effector proteins for the products (prostaglandins) downstream of COX-1/2 activation (PGE_2, PGD2, PGF2a, PGI2 and thromboxane respectively). The NSAIDS (non-steroidal anti-inflammatory drugs) are indiscriminate cyclooxygenase inhibitors and reduce the levels of these prostaglandins. This in turn reduces the action of the prostaglandins at their respective receptors. In view of the relatively large number of receptors affected, the pharmacology of the NSAIDS is complex.

The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion.

We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor. These compounds are antagonists of the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S. Narumiya *et al*, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology,*1994, 112, 735- 740 suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar *et al* in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP_1 receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. In The American Physiological Society (1994, 267, R289-R-294), studies

suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor.

The TP (also known as TxA_2) receptor is a prostanoid receptor subtype stimulated by the endogenous mediator thromboxane. Activation of this receptor results in various physiological actions primarily incurred by its platelet aggregatory and smooth muscle constricting effects, thus opposing those of prostacyclin receptor activation.

TP receptors have been identified in human kidneys (G.P. Brown *et al*, *Prostaglandins and other lipid mediators*,1999, 57 ,179-188) in the glomerulus and extraglomerular vascular tissue. Activation of TP receptors constricts glomerular capillaries and suppresses glomerular filtration rates (M.D. Breyer *et al*, *Current Opinion in Nephrology and Hypertension*, 2000, 9, 23-29), indicating that TP receptor antagonists could be useful for renal dysfunction in glomerulonephritis, diabetes mellitus and sepsis.

Activation of TP receptors induces bronchoconstriction, increase in microvascular permeability, formation of mucosal oedema and mucus secretion, typical characteristic features of bronchial asthma (T. Obata *et al*, *Clinical Review of Allergy*, 1994, 12(1), 79-93). TP antagonists have been investigated as potential asthma treatments resulting in, for example, orally active Seratrodast (AA-2414) (S. Terao *et al*, *Yakugaku Zasshi*, 1999, 119(5), 377-390). Ramatroban is another TP receptor antagonist currently undergoing phase III clinical trials as an anti-asthmatic compound.

Antagonists at the TP receptor have been shown to have a gastroprotective effect. In rats it has been shown that SQ 33961 and BM 13505 inhibit gastric lesions induced by taurocholate acid, aspirin or indomethacin (E.H. Ogletree *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1992, 263(1), 374-380.

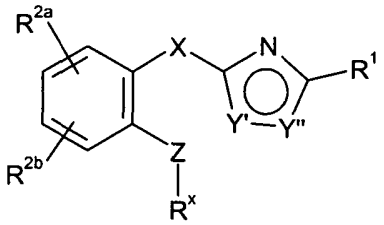
Certain compounds of the present invention also exhibit antagonism at the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of thromboxane at the TP receptor. Such conditions include those disclosed in WO 2004/039807 (Merck Frosst Canada & Co) which is incorporated herein by reference, and include respiratory diseases e.g. asthma, allergic diseases, male erectile dysfunction, thrombosis, renal disorders and gastric lesions.

WO 96/06822 (7 March 1996), WO 96/11902 (25 April 1996), EP 752421-A1 (8 January 1997), WO 01/19814 (22 March 2001), WO 03/084917 (16 October 2003), WO 03/101959 (11 December 2003), WO 2004/039753 (13 May 2004), WO 2004/083185 (30 September 2004), WO 2005/037786 (28 April 2005), WO 2005/037793 (28 April 2005), WO 2005/037794 (28 April 2005), WO 2005/040128 (6 May 2005), WO 2005/054191 (16 June 2005) and WO2005/108369 (17 November 2005) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

A. Hall *et al*, *Bioorg. Med. Chem. Lett.*, 2006, 16, 2666-2671 discloses biaryl heterocyclic EP_1 receptor agonists.

P. Lacombe *et al* (220th National Meeting of The American Chemical Society, Washington D.C., USA, 20-24 August, 2000) disclosed 2,3-diarylthiophenes as ligands for the human EP_1 prostanoid receptor. Y. Ducharme *et al* (18th International Symposium on Medicinal Chemistry; Copenhagen, Denmark and Malmo, Sweden; 15th-19th August 2004) disclosed 2,3-diarylthiophenes as EP_1 receptor antagonists. Y. Ducharme *et al, Biorg. Med. Chem. Lett.*, 2005, 15(4): 1155 also discloses 2,3-diarylthiophenes as selective EP_1 receptor antagonists.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:
either Y' is CH and Y" is O or S, or Y' is O or S and Y" is CH thus forming an oxazole or a thiazole ring;
X is CR^7R^8, O, NR^4, S, SO, or SO_2, or X is a bond;
Z is O, S, SO or SO_2;
R^x is optionally substituted C_{3-10}alkyl, optionally substituted C_{3-10}alkenyl, optionally substituted C_{3-10}alkynyl, optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl, or optionally substituted CQ^aQ^b-aryl;
R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, $NR^4CO_2R^6$, NR^4COR^6 or 1,2,4-triazol-3-yl optionally substituted on a ring carbon; or R^1 represents imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;
R^{2a} and R^{2b} independently represents hydrogen, halo, CN, SO_2alkyl, SR^4 or NO_2; or optionally substituted alkyl or optionally substituted alkoxy;
R^4 is hydrogen or optionally substituted alkyl;
R^5 is hydrogen or optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heterocyclyl, optionally substituted CQ^aQ^baryl, or optionally substituted CQ^aQ^bheterocyclyl; or
R^4 and R^5 together with the nitrogen to which they are attached form a heterocyclic or bicyclic heterocyclic ring;
R^6 is optionally substituted alkyl or optionally substituted aryl;

R^7 is hydrogen, fluorine or alkyl;
R^8 is hydrogen, hydroxy, fluorine or alkyl;
or R^7 *and* R^8 *together with the carbon to which they are attached form a cycloalkyl ring,* optionally containing up to one heteroatom selected from O, S, NH and N-alkyl; or R^7 and R^8 together with the carbon to which they are attached form a carbonyl group; and
Q^a and Q^b are each independently selected from hydrogen, CH_3 and fluorine;
Q^c and Q^d are each independently selected from hydrogen and CH_3;
and derivatives thereof;
provided that:
when X is a bond, then R^1 is $CQ^cQ^dCO_2H$;
when X is CR^7R^8, then R^1 is not $CQ^cQ^dCO_2H$;
when R^1 is benzimidazolyl it is unsubstituted on the 1-position; and
when R^1 is benzimidazole optional substituents on the 4 or 7 position are selected from CH_2OH or CO_2H.

Preferably when Y' or Y" is O, then R^1 *is not* $CQ^cQ^dCO_2H$.

Preferably the compound of formula (I) is not [2-(5-chloro-2-{[(2,4-difluorophenyl)-methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetic acid (Example 79), [2-(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetic acid (Example 80) or [2-(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetic acid (Example 81).

Preferably the compound of formula (I) is not 4-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]-oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide (Example 7).

Preferably the compound of formula (I) is not 1,1-Dimethylethyl [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]carbamate (Example 161)

Suitably X is CR^7R^8, NR^4, or a bond.

Suitably Z is O.

In one aspect R^1 is not $NR^4CO_2R^6$.

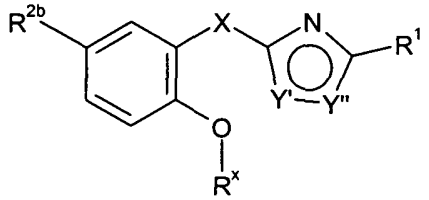
Suitably R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, NR^4COR^6 or 1,2,4-triazol-3-yl *optionally substituted on a ring carbon; or* R^1 *represents* imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;

In one aspect R^{2a} is hydrogen.

Suitably R^{2b} is selected from halogen, e.g. Cl or Br, or CF_3.

Preferably R^{2b} is positioned 1,4- relative to the Z substituent and 1,3- relative to the thiazole/oxazole moiety.

In one aspect the compound of formula (I) is a compound of formula (IA):



(IA)

wherein:

either Y' is CH and Y" is O or S, or Y' is O or S and Y" is CH thus forming an oxazole or a thiazole ring;

X is CR^7R^8, or NR^4, or X is a bond;

R^x is optionally substituted $C_{3\text{-}10}$alkyl, optionally substituted $C_{3\text{-}10}$alkenyl, optionally substituted $C_{3\text{-}10}$alkynyl, optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl, or optionally substituted CQ^aQ^b-aryl;

R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, NR^4COR^6 or 1,2,4-triazol-3-yl optionally substituted on a ring carbon; or R^1 represents imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;

R^{2b} is Cl, Br, or CF_3.

R^4 is hydrogen or optionally substituted alkyl;

R^5 is hydrogen or optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heterocyclyl, optionally substituted CQ^aQ^baryl, or optionally substituted CQ^aQ^bheterocyclyl; or

R^4 and R^5 together with the nitrogen to which they are attached form a heterocyclic or bicyclic heterocyclic ring;

R^6 is optionally substituted alkyl or optionally substituted aryl;

R^7 is hydrogen, fluorine or alkyl;

R^8 is hydrogen, hydroxy, fluorine or alkyl;

or R^7 and R^8 together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH and N-alkyl; or R^7 and R^8 together with the carbon to which they are attached form a carbonyl group; and

Q^a and Q^b are each independently selected from hydrogen, CH_3 and fluorine;

Q^c and Q^d are each independently selected from hydrogen and CH_3;

and derivatives thereof;

provided that:

when X is a bond, then R^1 is $CQ^cQ^dCO_2H$;

when X is CR^7R^8, then R^1 is not $CQ^cQ^dCO_2H$;
when Y' or Y" is O, then R^1 is not $CQ^cQ^dCO_2H$;
when R^1 is benzimidazolyl it is unsubstituted on the 1-position; and
when R^1 is benzimidazole optional substituents on the 4 or 7 position are selected from CH_2OH or CO_2H.

In one aspect R^1 is CO_2H, $CQ^cQ^dCO_2H$, 1,2,4-triazol-3-yl, 5-methyl-1,2,4-triazolyl, tetrazolyl, $CONHR^5$, $NHCOR^6$ or imidazolyl wherein optionally the imidazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system.

When R^1 is $CQ^cQ^dCO_2H$, suitably it is CH_2CO_2H, $C(CH_3)_2CO_2H$, or $CH(CH_3)CO_2H$.

Examples of fused imidazole groups include benzimidazole, imidazo[1,2-a]pyridine, imidazo[4,5-b]pyridine, imidazo[4,5-c]pyridine, imidazo[4,5-b]pyrazine, and 1,5-dihydroimidazo[4,5-f]indazole all of which may be optionally substituted. Suitable optional substituents include halogen e.g. F and Cl, CO_2H, CH_2OH, CH_2CH_2OH, piperazinylalkyl e.g. piperazinylmethyl, pyrrolidinyl, piperidinyl, morpholinyl, $CH_2NR^aR^b$, $CH_2CH_2NR^aR^b$; wherein R^a is hydrogen or methyl and R^b is methyl; or R^a and R^b together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinylalkyl, e.g. piperazinylmethyl group.

When R^1 is substituted benzimidazole, preferably it is substituted on the 5 and/or 6 positions.

When R^1 is benzimidazole, in one aspect it is attached to the thiazole or oxazole ring ring through the 2-position carbon atom.

Suitably when R^x represents optionally substituted C_{3-10}alkyl this group is C_{3-8}alkyl, for example propyl, butyl, pentyl, 2-methylpropyl, 3-methylbutyl, cyclopropylmethylene, cyclobutylmethylene, cyclopentylmethylene, and cyclohexylmethylene. In one aspect the alkyl group is unsubstituted.

When R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl, suitably R^x includes optionally substituted CH_2-heterocyclyl, optionally substituted CH_2-bicyclic heterocyclyl or optionally substituted CH_2-aryl e.g optionally substituted CH_2-phenyl. Optional substituents for CH_2-phenyl include one, two or three substituents each independently selected from Cl, Br and F.

In one aspect R^x represents C_{3-8}alkyl or optionally substituted CH_2phenyl.

Suitably R^4 includes hydrogen and C_{1-6}alkyl. In one aspect R^4 is hydrogen.

Suitably R^5 includes hydrogen, C_{1-6}alkyl, phenyl, pyridyl, tetrazolyl, SO_2phenyl, SO_2C_{1-6}alkyl, optionally substituted SO_2isoxazole, CH_2pyridyl, and optionally substituted CH_2phenyl.

Suitable substituents for R^5 when optionally substituted CH_2phenyl include $CH_2NR^cR^d$ wherein R^c methyl and R^d is methyl; or R^c and R^d together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or optionally substituted piperazinyl group, e.g. oxopiperazinyl.

Suitably R^6 includes optionally substituted C_{1-4}alkyl, e.g. methyl, ethyl, isopropyl and benzyl, and optionally substituted phenyl, e.g. $PhCH_2OH$ and $PhCH_2$piperidine.

Suitably R^7 includes C_{1-3}alkyl, e.g. CH_3, and hydrogen.

Suitably R^8 includes C_{1-3}alkyl, e.g. CH_3, and hydrogen.

Suitably Q^a is hydrogen.

Suitably Q^b is hydrogen.

Compounds of formula (I) include the compounds of examples 1 to 183 and derivatives thereof.

Derivatives of the compound of formula (I) include salts, solvates (including hydrates), solvates (including hydrates) of salts, esters and polymorphs of the compound of formula (I). Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The present invention also includes isotopically-labelled compounds, which are identical to the compounds of formula (I), except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of

the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable derivatives (e.g. salts) of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and/or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. ^{3}H and ^{14}C are considered useful due to their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are considered useful in PET (positron emission tomography), and ^{125}I isotopes are considered useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Substitution with heavier isotopes such as ^{2}H can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, are considered useful in some circumstances. Isotopically labelled compounds of formula (I) of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The following definitions are used herein unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester, or solvate of salt or ester of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I). In one aspect the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate or solvate of salt. In an alternative aspect the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt.

It will be appreciated that, for pharmaceutical use, the derivatives referred to above will be pharmaceutically acceptable derivatives, but other derivatives may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; and cyclic amines. Particular pharmaceutically acceptable

organic bases include arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tris(hydroxymethyl)aminomethane (TRIS, trometamol) and the like. Salts may also be formed from basic ion exchange resins, for example polyamine resins. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, ethanedisulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic alkyl group or combinations thereof. Unless hereinbefore defined, examples of alkyl include C_{1-8}alkyl, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclopropylmethylene, cyclohexylmethylene and cyclopentylmethylene.

When used herein the term "cycloalkyl" means a cyclic alkyl group comprising up to eight carbon atoms in a ring.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. C_{3-8}alkenyl, for example, includes 2-methyl-2-propenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-8}alkynyl, for example, includes propynyl and the like.

The term "alkoxy" as a group or as part of a group means a straight, branched or cyclic chain alkoxy group. Unless hereinbefore defined "alkoxy" includes C_{1-8}alkoxy, e.g. *methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, iso-butoxy, t-butoxy,* pentoxy, hexyloxy, cyclopentoxy or cyclohexyloxy. In one aspect "alkoxy" is C_{1-6} alkoxy.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents. Examples of 5-membered heterocycles include furan, tetrahydrofuran, thiophene, tetrahydrothiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, and tetrazole. Examples of 6-membered heterocycles include pyran, tetrahydropyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, and triazine.

The term "heterocyclyloxy" as a group or as part of a group refers to an "-O-heterocyclyl" group, wherein the term "heterocyclyl" is as defined above.

The term "aliphatic heterocyclyl" as a group or as part of a group means an aliphatic five or six membered ring which contains 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur and is unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents.

The term "aryl" as a group or part of a group means a 5- or 6-membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is phenyl.

The term "aryloxy" as a group or as part of a group refers to an "-O-aryl" group, wherein the term "aryl" is as defined above.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2 substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl,

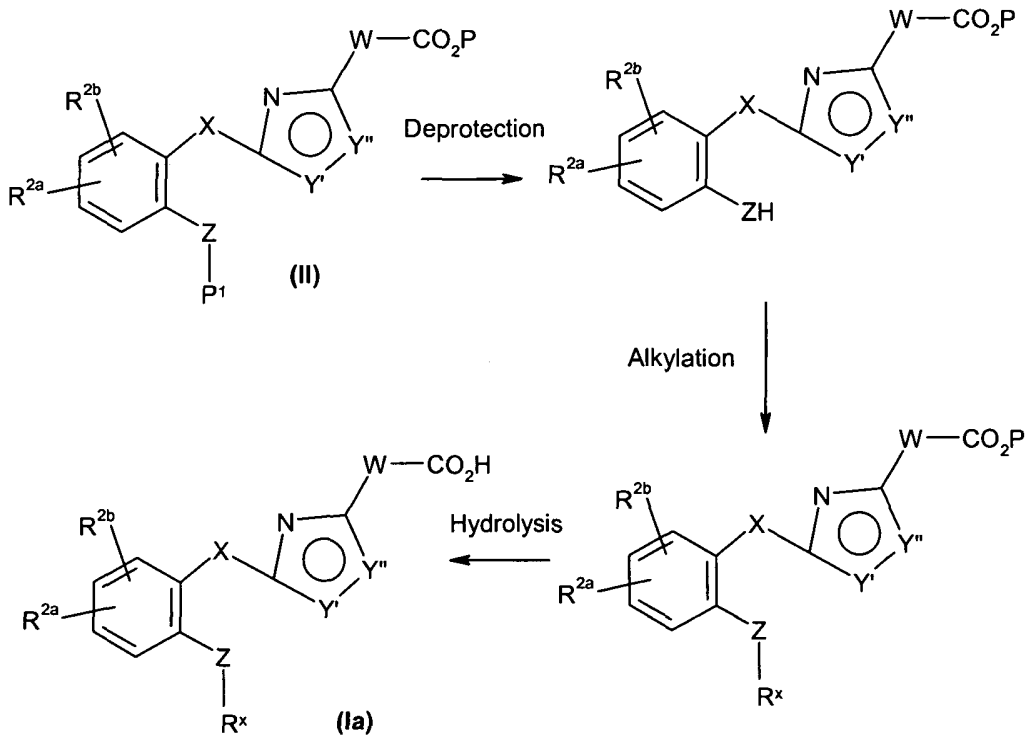
thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-8}alkyl, preferably hydrogen and C_{1-6}alkyl, more preferably hydrogen.

Compounds of formula (I) can be prepared as set forth in the following schemes and in the Examples. The following processes form another aspect of the present invention.

Compounds of formula (I) wherein R^1 is CO_2H or $CQ^cQ^dCO_2H$, hereinafter referred to as compounds of Formula (Ia), may be prepared by the general route below:



wherein X, Z, R^{2a}, R^{2b} and R^x are as defined for compounds of formula (I);
W is CQ^cQ^d [wherein Q^c and Q^d are as defined for compounds of formula (I)] or a bond, and P and P^1 are protecting groups.

Compounds of formula (Ia) may be prepared from an intermediate of formula (II) by removal of P^1 followed by reaction with a suitable source of R^x wherein R^x is as defined for a compound of formula (I). Suitable sources of R^x include R^xBr. Suitable reaction conditions when the source of R^x is R^xBr include heating in the presence of a base, e.g. potassium carbonate, in a suitable solvent, e.g. acetone or N,N-dimethylformamide, followed by removal of protecting group P.

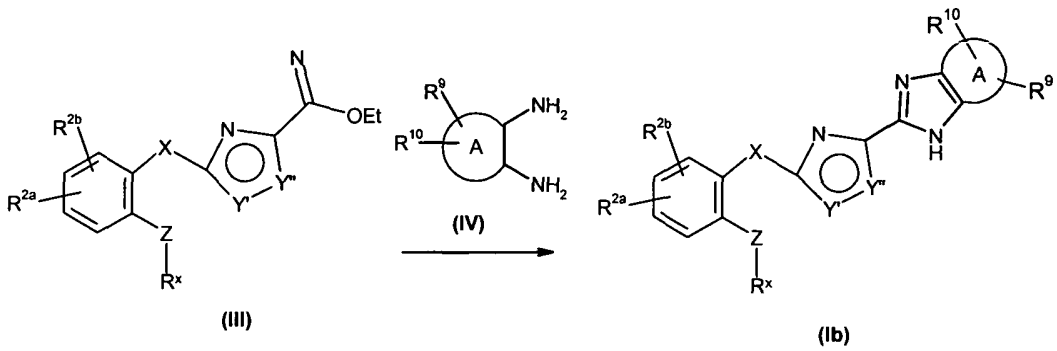
Suitable protecting groups will be known to the skilled person. Suitably P is C_{1-4}alkyl or optionally substituted benzyl. Suitable protecting groups when Z is O include C_{1-4}alkyl or benzyl.

Suitable deprotection methods will be known to the skilled person. Conditions for the deprotection of an ester to give the corresponding carboxylic acid are known to those skilled in the art and include heating in the presence of a suitable base, e.g. aqueous sodium hydroxide, in a solvent e.g. an alcohol.

Removal of the protecting group P^1 can be achieved for example through treatment with boron tribromide in a suitable solvent, for example dichloromethane at reduced temperature.

It will be recognised to those skilled in the art that the compounds of formula (I) wherein R^1 is other than CO_2H can be derived from the carboxylic acid (Ia). Compounds wherein R^1 is $CONR^4R^5$, such as amides or acylsulfonamides, can be prepared by activation of the carboxylic acid, for example by forming the acid chloride (for example by reaction of the carboxylic acid with thionyl chloride) followed by reaction with an amine or a sulfonamide respectively. Other derivatives may be accessed by using the Curtius reaction (P.A.S. Smith, *Org. React.* 3, 337-449 (1946) and J.H. Saunders, R. J. Slocombe, *Chem. Rev.* 43, 205 (1948)), followed by deprotection of the resulting carbamate and reaction with a carboxylic acid derivative such as an acid chloride. It will be recognised to those skilled in the art that a carboxylic acid group may be converted to a pyrazole, triazole or imidazole group by a sequence of well known functional group transformations such as those described in the Examples. Tetrazoles may be formed from carboxylic acids by converting the carboxylic acid to the primary amide, for example by reaction with thionyl chloride followed by ammonia, followed by dehydration of the amide to the nitrile, for example by heating in phosphorous oxychloride, followed by reaction with azide.

Compounds of formula (I) wherein R^1 is an imidazole moiety fused to give an optionally substituted bicyclic or tricyclic ring system [hereinafter referred to as compounds of formula (Ib)] may be prepared from compounds of formula (III) in accordance with the following scheme:



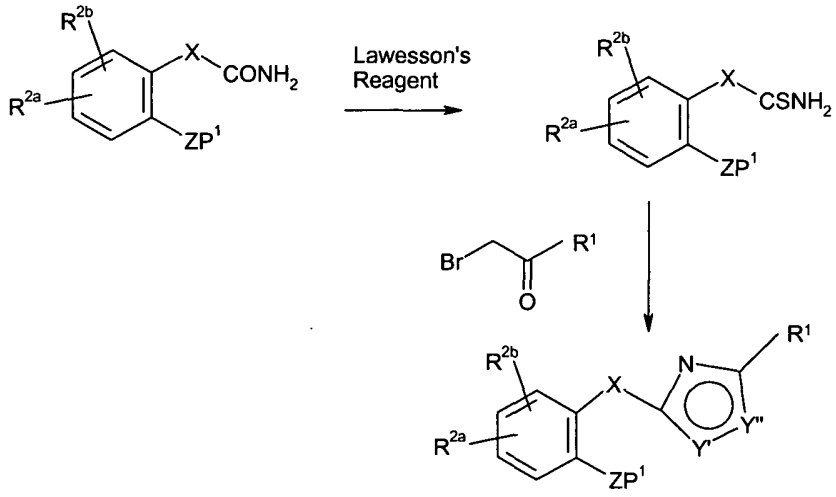
wherein X, Z, R^{2a}, R^{2b}, Y', Y" and R^x are as defined for compounds of formula (I); A represents e.g. phenyl, pyridine, quinoline, or thiophene, and R^9 and R^{10} each represent hydrogen or a substituent.

Suitable reaction conditions for the preparation of a compound of formula (Ib) include heating the intermediates together in a suitable solvent e.g. ethanol.

Diamines of formula (IV) are commercially available, or may be prepared by known methods.

Compounds of formula (Ib) wherein R^1 is a benzimidazole may also be prepared from the reaction of a diamine of formula (IV) with a compound of formula (I) wherein R^1 is CO_2H.

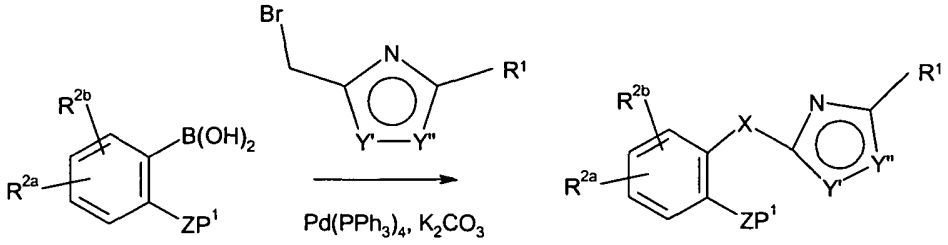
Compounds of formula (II) when X is CH_2 or a bond, R^1 is CO_2P or $CQ^cQ^dCO_2P$, Y' is S and Y" is CH may be prepared by known methods. Suitable methods include for example the Hantsch thiazole synthesis comprising the reaction of an α-haloketone with a thioamide as described by the following scheme:



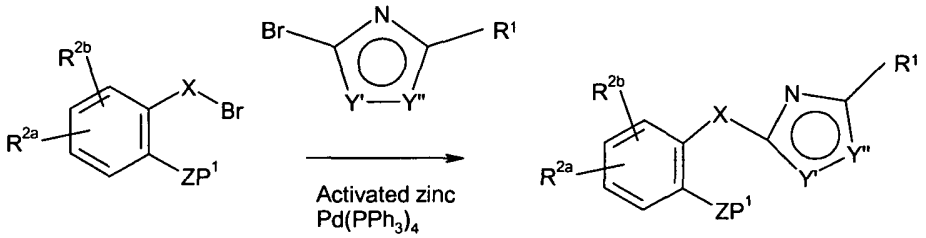
wherein Z, R^{2a}, R^{2b}, P and P^1 are as defined for compounds of formula (I); and P and P^1 are protecting groups as defined above.

Suitable reaction conditions include carrying out the reaction in a suitable solvent such as 1,2-dimethoxyethane in the presence of potassium hydrogen carbonate, trifluoroacetic anhydride and pyridine as described in the examples (Bredekamp, *Synth. Comm.* 20 (1990) 2235). α-Haloketones are commercially available or can be prepared by known methods. Suitable amide starting materials are commercially available or may be readily prepared from commercially available starting materials by known functional group tranformations.

Compounds of formula (II) when X is CH_2, R^1 is CO_2P or $CQ^cQ^dCO_2P$, Y' is CH and Y" is S may be prepared by the following scheme:

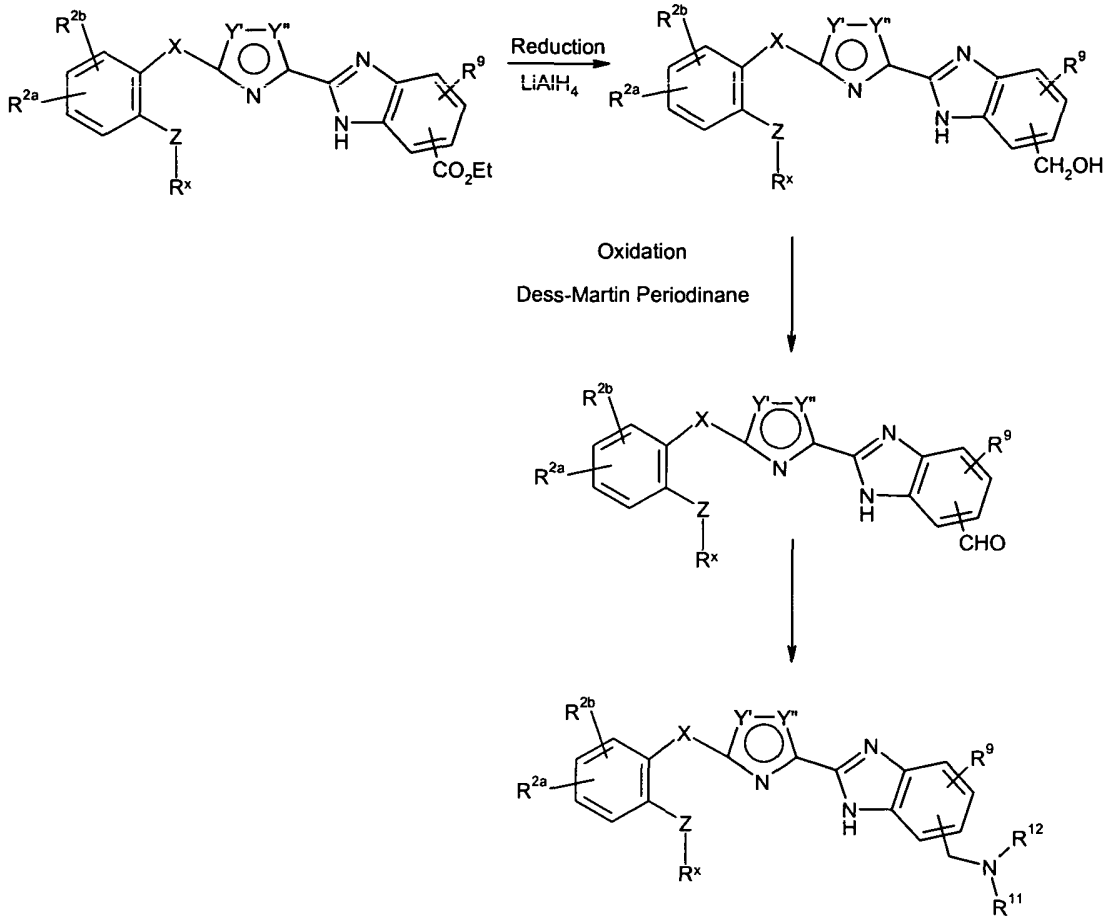


Compounds of formula (II) when X is CH_2 or a bond, R^1 is CO_2P or $CQ^cQ^dCO_2P$, Y' is O and Y" is CH may be prepared by the following scheme:



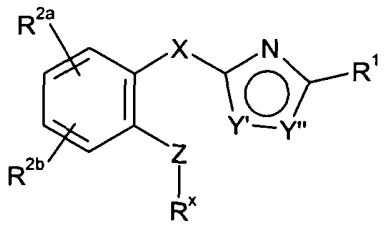
Compounds of formula (III) may be prepared from the corresponding carboxylic acid of formula (Ia) by known methods, for example as described in the Examples. Suitable methods include the reaction of a compound of formula (Ia) with thionyl chloride then ammonia, then phosphorus oxychloride then sodium methoxide in methanol.

Compounds of formula (Ib) wherein R^1 is benzimidazole may be functionalised on the benzimidazole ring using methods described in the Examples and in the scheme below:



wherein X, Z, R^{2a}, R^{2b}, and R^x are as hereinbefore defined for compounds of formula (I) and R^{11} and R^{12} are independently selected from hydrogen, and optionally substituted C_{1-4}alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a heterocyclyl ring optionally containing another heteroatom selected from O, NH, NC_{1-4}alkyl, or S.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:

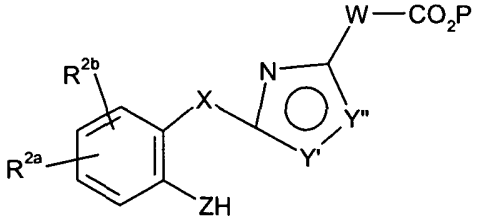


(I)

wherein:

either Y' is CH and Y" is O or S, or Y' is O or S and Y" is CH thus forming an oxazole or a thiazole ring;

X is CR^7R^8, O, NR^4, S, SO, or SO_2, or X is a bond;
Z is O, S, SO or SO_2;
R^x is optionally substituted C_{3-10}alkyl, optionally substituted C_{3-10}alkenyl, optionally substituted C_{3-10}alkynyl, optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl, or optionally substituted CQ^aQ^b-aryl;
R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, $NR^4CO_2R^6$, NR^4COR^6 or 1,2,4-triazol-3-yl optionally substituted on a ring carbon; or R^1 represents imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;
R^{2a} and R^{2b} independently represents hydrogen, halo, CN, SO_2alkyl, SR^4 or NO_2; or optionally substituted alkyl or optionally substituted alkoxy;
R^4 is hydrogen or optionally substituted alkyl;
R^5 is hydrogen or optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heterocyclyl, optionally substituted CQ^aQ^baryl, or optionally substituted CQ^aQ^bheterocyclyl; or
R^4 and R^5 together with the nitrogen to which they are attached form a heterocyclic or bicyclic heterocyclic ring;
R^6 is optionally substituted alkyl or optionally substituted aryl;
R^7 is hydrogen, fluorine or alkyl;
R^8 is hydrogen, hydroxy, fluorine or alkyl;
or R^7 and R^8 together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH and N-alkyl; or R^7 and R^8 together with the carbon to which they are attached form a carbonyl group; and
Q^a and Q^b are each independently selected from hydrogen, CH_3 and fluorine;
Q^c and Q^d are each independently selected from hydrogen and CH_3;
provided that:
when X is a bond, then R^1 is $CQ^cQ^dCO_2H$;
when X is CR^7R^8, then R^1 is not $CQ^cQ^dCO_2H$;
when R^1 is benzimidazolyl it is unsubstituted on the 1-position; and
when R^1 is benzimidazole optional substituents on the 4 or 7 position are selected from CH_2OH or CO_2H;
comprising:
alkylating a compound:



with a source of R^x;
wherein R^{2a}, R^{2b}, Y', Y'', R^x, Z, X are as defined above for a compound of formula (I), W is CH_2 or a bond, and P is a protecting group; and

in any order:
effecting deprotection; and
if necessary, converting WCO_2H or WCO_2P to another group R^1; and
if necessary forming a derivative thereof.

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of such transformations include the hydrolysis of esters and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

The compounds of the invention bind to the EP_1 receptor and are antagonists of this receptor. They are therefore considered useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors.

One condition mediated by the action of PGE_2 at EP_1 receptors is pain, including acute pain, chronic pain, chronic articular pain, musculoskeletal pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer, pain associated with migraine, tension headache and cluster headaches, pain associated with functional bowel disorders, lower back and neck pain, pain associated with sprains and strains, sympathetically maintained pain; myositis, pain associated with influenza or other viral infections such as the common cold, pain associated with rheumatic fever, pain associated with myocardial ischemia, post operative pain, headache, toothache and dysmenorrhea.

Chronic articular pain conditions include rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

Pain associated with functional bowel disorders includes non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome.

Neuropathic pain syndromes include: diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and pain resulting from physical trauma, amputation,

cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful sensations such as "pins and needles" (*paraesthesias and dysesthesias*), *increased sensitivity to touch* (*hyperesthesia*), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

Other conditions mediated by the action of PGE_2 at EP_1 receptors include fever, inflammation, immunological diseases, abnormal platelet function diseases (e.g. occlusive vascular diseases), impotence or erectile dysfunction; bone disease characterised by abnormal bone metabolism or resorbtion; hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors, cardiovascular diseases; neurodegenerative diseases and neurodegeneration, neurodegeneration following trauma, tinnitus, dependence on a dependence-inducing agent such as opiods (e.g. *morphine*), CNS *depressants* (e.g. *ethanol*), *psychostimulants* (e.g. *cocaine*) and nicotine; complications of Type I diabetes, kidney dysfunction, liver dysfunction (e.g. hepatitis, cirrhosis), gastrointestinal dysfunction (e.g. diarrhoea), colon cancer, overactive bladder and urge incontinence..

Inflammatory conditions include skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis), ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis), inflammatory lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation and other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendonitis, bursitis, and Sjogren's syndrome.

Immunological diseases include autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the *latency of HIV infection*

Bone diseases characterised by abnormal bone metabolism or resorbtion include osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia,

osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendonitis and bursitis.

Cardiovascular diseases include hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

Neurodegenerative diseases include dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also considered useful in the treatment of neuroprotection and in the treatment of neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

Complications of Type 1 diabetes include diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma, nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

Kidney dysfunction includes nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome.

The compounds of formula (I) are also considered useful for the preparation of a drug with diuretic action.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1

receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 80 mg/kg body weight, more particularly 0.01 to 30 mg/kg body weight per day, for example 0.1 to 10 mg/kg body weight per day, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 4000

mg/day, more particularly from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, for example 35 to 200 mg/day.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may be formulated for administration by inhalation or for oral, topical, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 (cyclooxygenase-2) inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib, COX-189 or 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (WO99/012930); 5-lipoxygenase inhibitors; NSAIDs (non-steroidal anti-inflammatory drugs) such as diclofenac,

indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARDs (disease modifying anti-rheumatic drugs) such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA (N-methyl-D-aspartate) receptor modulators, such as glycine receptor antagonists; ligands for the $\alpha_2\delta$-subunit of voltage gated calcium channels, such as gabapentin and pregabalin; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B subtype; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 agonists and EP_2 agonists; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands; vanilloid receptor ligand; and purinergic receptor ligands, including antagonists at $P2X_3$, $P2X_{2/3}$, $P2X_4$, $P2X_7$ or $P2X_{4/7}$. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

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

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

In addition to activity at the EP_1 receptor, certain compounds of the present invention and pharmaceutically acceptable derivatives thereof exhibit antagonism of the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of

thromboxane at the TP receptor. Conditions mediated by the action of thromboxane at the TP receptor include renal disorders, asthma, or gastric lesions.

In certain situations it is envisaged that the administration of a compound exhibiting antagonism of TP receptors in combination with a compound exhibiting antagonism of EP_1 receptors may be advantageous.

Certain compounds of the invention are selective for EP_1 over EP_3.

No toxicological effects have currently been observed with the compounds of the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLES

It will be appreciated to those skilled in the art that where compounds are named as hydrochloride salts the stoichiometry of the isolated reaction products is undetermined due to the nature of their preparation. Compounds have therefore been named as hydrochlorides and denoted as xHCl, where x is 0-3 and represents the stoichiometry of said salt.

Abbreviations

AcOH, acetic acid, Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl, ethyl), DMSO (dimethyl sulfoxide), DCM/MDC (dichloromethane), DME (ethylene glycol dimethyl ether), DMF (N,N-dimethylformamide), EDAC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride), EDTA (ethylenediaminetetraacetic acid), EtOAc (ethyl acetate), EtOH (ethanol), HOBt (1-Hydroxybenzotriazole), HPLC (High pressure liquid chromatography), IPA (isopropanol), LCMS (Liquid chromatography/Mass spectroscopy), MDAP (Mass Directed Auto Preparation), MeOH (methanol), ML (mother liquor), NMR (Nuclear Magnetic Resonance (spectrum)), NMP (n-methyl pyrrolidone), Ph (phenyl), pTSA (para-toluene sulphonic acid), RT/Rt (retention time),SM (starting material), SPE (Solid Phase Extraction – silica cartridge chromatography), TBAF (tetrabutylammonium fluoride), TBME (tertiary butyl methyl ether), THF (tetrahydrofuran), s, d, dd, t, q, m, br (singlet, doublet, double doublet, triplet, quartet, multiplet, broad.).

Purification of Reaction Products

Conventional techniques may be used herein for work up of reactions and purification of the products of the Examples.

References in the Examples below relating to the drying of organic layers or phases may refer to drying the solution over magnesium sulfate or sodium sulfate and filtering off the drying agent in accordance with conventional techniques. Products may generally be obtained by removing the solvent by evaporation under reduced pressure.

Purification of the Examples may be carried out by conventional methods such as chromatography and/or recrystallisation using suitable solvents. Chromatographic methods are known to the skilled person and include e.g. column chromatography, flash chromatography, HPLC (high performace liquid chromatography), and MDAP (mass directed autopreparation, also referred to as mass directed LCMS purification). MDAP is described in e.g. W. Goetzinger *et al*, *Int. J. Mass Spectrom.*, 2004, 238, 153-162.

Flash Master II is an automated chromatography system using commercial prepacked columns. *Biotage* is a chromatography system using commercial pre-packed silica gel cartridges. The term FLEX (Parallel Flex) when used herein refers to a parallel HPLC purification system.

LCMS

The following conditions were used for LCMS in the preparation of the examples.

- Column: 3.3cm x 4.6mm ID, 3μm ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5μl
- Temp: Room temperature
- UV Detection Range: 215 to 330nm
-

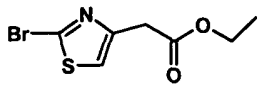
Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

All retention times are measured in minutes.

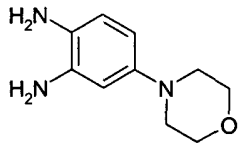
PREPARATION OF INTERMEDIATES

Ethyl (2-bromo-1,3-thiazol-4-yl)acetate



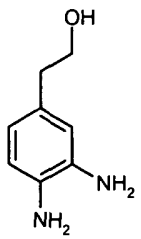
Ethyl 2-amino-4-thiazoleacetate (5g, 26.8mmol) was added under nitrogen to a solution of copper(II) bromide (6.77g, 30mmol) and *t*-butyl nitrite (4.79ml, 40mmol) in acetonitrile (20ml) at -20°C. The reaction mixture was slowly warmed to room temperature and stirred for two hours. The solution was then diluted with diethyl ether and washed with 25ml of 10% hydrochloric acid solution; the aqueous phase was extracted with 20ml of diethyl ether. The combined organic phases were dried and evaporated to dryness. The residue was purified by flash chromatography with 20% of ethyl acetate in iso-hexane to yield the title compound as a yellow liquid (2.2g, 32%).
LC/MS Rt = 2.33, [MH^+] 252.

4-(4-Morpholinyl)-1,2-benzenediamine



A solution of 5-(4-morpholinyl)-2-nitroaniline (1g, 4.5mmol) in DMF (20ml) with ~50mg of 5% Pd/charcoal was hydrogenated over the weekend. Catalyst was filtered off, the filtrate was evaporated and the residue was chromatographed using 15%of methanol in dichloromethane and triturated with diethyl ether to give a brown solid.
LC/MS Rt = 0.39, [MH^+] 194.2, 195.2

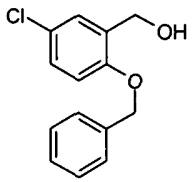
2-(3,4-Diaminophenyl)ethanol



Zinc dust (13.63g, 208.8mmol) was added in portions to a stirred solution of 2-(4-amino-3-nitrophenyl)ethanol (3.8g, 20.88mmol) in acetic acid (80ml) with water bath cooling and the mixture stirred for one hour then filtered and evaporated. The residue was re-evaporated with toluene, dissolved in methanol and triethylamine (20ml) added. The solution was evaporated and purified by flash chromatography on silica eluting with

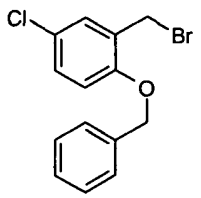
methanol/dichloromethane (8:92) and triturated with ether to give the title compound as an off-white solid which darkened on standing.
LC/MS Rt = 0.32 min, [MH^+] 153.08.

{5-Chloro-2-[(phenylmethyl)oxy]phenyl}methanol



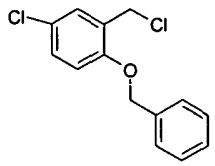
4-Chloro-2-(hydroxymethyl)phenol (5g, 31mmol) was dissolved in acetone (30ml), potassium carbonate (4.78g, 34mmol) and benzyl bromide (3.74ml, 31mmol) were added. The resulting mixture was refluxed for 2 hours. The reaction was then cooled and the solid was filtered off. The solution was concentrated *in vacuo* to give the title compound as colorless oil (~8.2g).
^{1}H NMR ($CDCl_3$)δ: 2.29 (1H, t), 4.68 (2H, d), 5.07 (2H, s), 6.84 (1H, d), 7.6 (1H,d), 7.30-7.39(6H, m).

2-(Bromomethyl)-4-chlorophenyl phenylmethyl ether



A solution of {5-chloro-2-[(phenylmethyl)oxy]phenyl}methanol (8.2g, 33mmol) in dichloromethane (30ml) was stirred under nitrogen and cooled to -10°C. A solution of phosphorous tribromide (3.12ml, 33mmol) in dichloromethane (15ml) was added slowly at -10°C and the mixture stirred for 15 minutes at -10°C. The reaction was then allowed to warm to room temperature and was stirred overnight under nitrogen. The reaction mixture was cooled (ice/water bath) and saturated sodium hydrogen carbonate solution was then added slowly and the mixture diluted with dichloromethane and water, brine was added to help the separation of the two phases. The organic phase was separated, washed with water twice then dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography with 5% of ethyl acetate in iso-hexane to yield the title compound as a white solid (8.1g, 79%).
^{1}H NMR ($CDCl_3$)δ: 4.53 (2H, s), 5.14 (2H, s), 6.84 (1H, d, J = 8.8Hz), 7.21 (1H,dd, J = 8.8, 2.6Hz), 7.32-7.47 (6H, m).

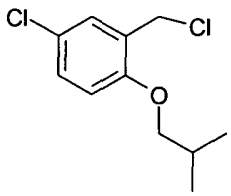
4-Chloro-2-(chloromethyl)phenyl phenylmethyl ether



Thionyl chloride (3.37ml, 50.9mmol) was added to a solution of {5-chloro-2-[(phenylmethyl)oxy]phenyl}methanol (11.5g, 46.2mmol) in DCM (150ml) and stirred at room temperature for 3 h. Solvent was evaporated and azeotroped with toluene to give 11.5g of the title compound.

^{1}H NMR ($CDCl_3$)δ: 4.63 (2H, s), 5.11(2H, s), 6.85 (1H, d, J=8.8Hz), 7.21-7.44 (7H, m)

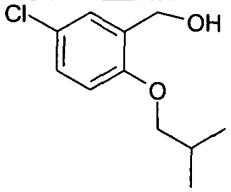
4-Chloro-2-(chloromethyl)phenyl 2-methylpropyl ether



The title compound was prepared in a similar manner to 4-chloro-2-(chloromethyl)phenyl phenylmethyl ether using {5-chloro-2-[(2-methylpropyl)oxy]phenyl}methanol.

^{1}H NMR ($CDCl_3$)δ: 1.05 (6H, d, J=6.8Hz), 2.1-2.16 (1H,m), 3.75 (2H, d, J=6.4Hz), 4.6(2H, s), 6.78 (1H, d, J=8.8Hz), 7.16-7.34 (2H, m)

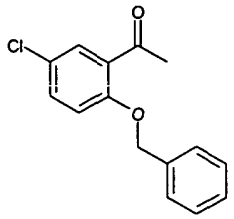
{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methanol



Sodium borohydride (760mg, 20mmol) was added to a stirred solution of 5-chloro-2-[(2-methylpropyl)oxy]benzaldehyde (3.8g, 17.88mmol) in 50ml of ethanol and stirred for 1h. Solvent was evaporated and residue was partitioned between water and ethyl acetate, organic phase was dried and evaporated to give 3.71g of a pale yellow oil.

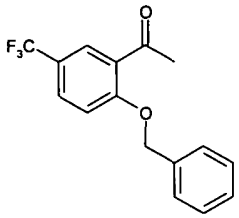
^{1}H NMR ($CDCl_3$)δ: 1.03 (6H, d, J=6.8Hz), 2.07-2.14 (1H,m), 2.3-2.4 (1H,bs), 3.75 (2H, d, J=6.4Hz), 4.66(2H, s), 6.76 (1H, d, J=8.8Hz), 7.18 (1H, dd, J=8.8, 2.8Hz), 7.28 (1H, d, J=2.8Hz).

1-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}ethanone



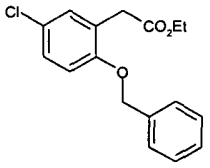
A solution of 1-(5-chloro-2-hydroxyphenyl)ethanone (17.1g, 100mmol) in acetone (100ml) was treated with benzyl bromide (13.08ml, 110mmol) and potassium carbonate (16.56g, 120mmol). The mixture was stirred and heated to reflux under nitrogen for 2h. After cooling, the solid was filtered, washed with acetone and the filtrate evaporated. The residue was triturated with iso-hexane and the white solid filtered and dried *in vacuo.* (24.6g).
^{1}H NMR ($CDCl_3$) δ: 2.59 (3H,s), 5.15 (2H, s), 6.96 (1H, d), 7.35-7.42 (6H, m), 7.71 (1H, d).

1-[2-[(Phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]ethanone



2-[(Phenylmethyl)oxy]-5-(trifluoromethyl)benzoic acid (10g, 33.8mmol) was dissolved in dry diethyl ether (100ml) under nitrogen and 1.4M methyl lithium solution in diethyl ether (72.3ml, 101.3mmol) was added dropwise with stirring. A little ice cooling was necessary to stop the ether boiling. The mixture was heated to reflux for 1.5h, cooled then poured onto a mixture of ice and 2M hydrochloric acid (200ml). The organic layer was washed with water and 5% sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography, eluting with 1:1 dichloromethane and iso-hexane to leave a yellow oil (4.1g).
^{1}H NMR ($CDCl_3$) δ: 2.61 (3H,s), 5.23 (2H, s), 7.11 (1H, d), 7.36-7.45 (5H, m), 7.68 (1H, dd), 8.03 (1H, d).

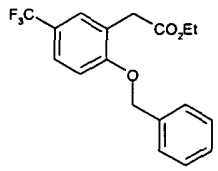
Ethyl {5-chloro-2-[(phenylmethyl)oxy]phenyl}acetate



A stirred mixture of 1-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanone (15.64g, 60mmol), triethyl orthoformate (30ml) and silver nitrate (21.4g, 126mmol) in ethanol (120ml) under nitrogen was treated with iodine (15.94g, 63mmol) and the suspension heated to reflux for 16h. After cooling, the mixture was filtered and the filtrate evaporated. The residue was dissolved in diethyl ether and the solution washed with water and brine, dried ($MgSO_4$) and

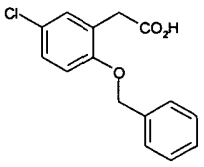
evaporated. The residue was flash chromatographed, eluting with 3-5% ethyl acetate in isohexane to leave a pale yellow solid. (11.58g).
^{1}H NMR ($CDCl_3$) δ: 1.20 (3H,t), 3.62 (2H, s), 4.10 (2H, q), 5.06 (2H, s), 6.83 (1H, d), 7.18 (2H, m), 7.32-7.40 (5H, m).

Ethyl [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetate



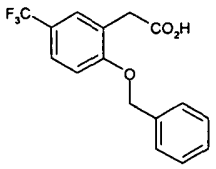
The title compound was prepared in a similar manner to ethyl {5-chloro-2-[(phenylmethyl)oxy]phenyl}acetate using 1-[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]ethanone.
^{1}H NMR ($CDCl_3$) δ: 1.22 (3H,t), 3.69 (2H, s), 4.12 (2H, q), 5.13 (2H, s), 6.97 (1H, d), 7.32-7.42 (5H, m), 7.47-7.51 (2H, m).

{5-Chloro-2-[(phenylmethyl)oxy]phenyl}acetic acid



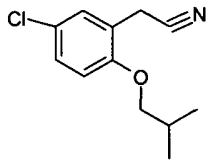
A solution of ethyl {5-chloro-2-[(phenylmethyl)oxy]phenyl}acetate (11.58g, 38mmol) in ethanol (60ml) and water (20ml) was treated with sodium hydroxide (6.08g, 152mmol) and the mixture stirred and heated at 90°C for 1.5h. After cooling, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with 2M sodium hydroxide solution (50ml) and the combined aqueous phases acidified (concentrated hydrochloric acid) and extracted with ethyl acetate (2 x 100ml). The combined organic phases were washed with water, dried ($MgSO_4$) and evaporated to an orange oil (6.86g).
LC/MS Rt = 3.30 min, [MH^+] 277, 279.

[2-[(Phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetic acid



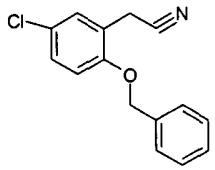
The title compound was prepared in a similar manner to {5-chloro-2-[(phenylmethyl)oxy]phenyl}acetic acid using ethyl [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetate.
LC/MS Rt = 3.37 min.

{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}acetonitrile



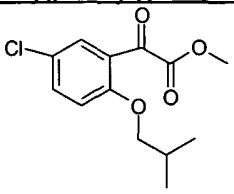
4-Chloro-2-(chloromethyl)phenyl 2-methylpropyl ether (14.7g, 63.3mmol) and sodium cyanide (3.41g, 69.6mmol) in DMSO (100ml) were stirred at 60°C for 1h.
More sodium cyanide (500mg) was added, stirred at 60°C for another 40 minutes. Cooled, diluted with water and diethyl ether, the organic phase was washed with water (x3), dried ($MgSO_4$) and evaporated to give the title compound as yellow oil (13g).
LC/MS Rt = 3.39, [MH^+] 224.

{5-Chloro-2-[(phenylmethyl)oxy]phenyl}acetonitrile



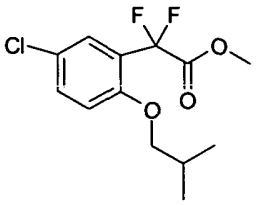
The title compound was prepared in a similar manner to {5-chloro-2-[(2-methylpropyl)oxy]phenyl}acetonitrile using 4-chloro-2-(chloromethyl)phenyl phenylmethyl ether and 1.2 equivalents of sodium cyanide.
^1H NMR ($CDCl_3$)δ: 3.69 (2H,s), 5.1(2H,s), 6.87(1H,d, J=8.8Hz), 7.24-7.43 (7H,m).

Methyl {5-chloro-2-[(2-methylpropyl)oxy]phenyl}(oxo)acetate



$AlCl_3$ (2.65g, 19.9mmol) was slowly added to a solution of 4-chlorophenyl 2-methylpropyl ether (3g, 16.6mmol) and methyl chlorooxoacetate (1.8ml, 19.9mmol) in 20 ml of DCM under argon. The reaction mixture was stirred at room temperature for 3h. Quenched carefully with water and extracted with DCM, the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed using 20% of DCM in hexane to give the title compound as a yellow solid (1.87g). LC/MS Rt = 3.44 min, [MH^+] 271.1.

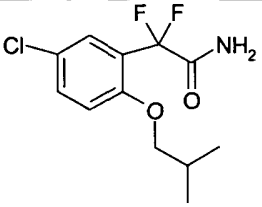
Methyl {5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)acetate



Methyl {5-chloro-2-[(2-methylpropyl)oxy]phenyl}(oxo)acetate (1.67g, 6.17mmol) was dissolved in DCM (16ml) under argon and (diethylamino)sulphur trifluoride (0.97ml, 7.4mmol) was added, the mixture was stirred at room temperature overnight. More (diethylamino)sulphur trifluoride (0.3ml) was added and the mixture was stirred for other 24 h. Quenched with saturated bicarbonate solution and extracted with DCM. The organic phase was dried ($MgSO_4$) and evaporated to give the title compound as a yellow oil (1.53g).

^1H NMR ($CDCl_3$) δ: 1.0 (6H, d, J=6.8Hz), 1.98-2.05 (1H, m), 3.72 (2H, d, J=6.4Hz), 3.84 (3H, s), 6.84 (1H, d, J= 8.8Hz), 7.38(1H, dd, J=8.8, 2.4Hz), 7.6 (1H, d, J=2.4Hz).

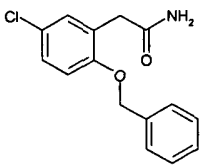
2-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-2,2-difluoroacetamide



Methyl {5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)acetate (1.53g, 5.96mmol) was treated with 7N ammonia in methanol (6ml) and stirred at room temperature for 1 hour; solvent was evaporated to give the title compound as a solid (1.45g).

^1H NMR ($CDCl_3$) δ: 1.0 (6H, d, J=6.8Hz), 2.0-2.1 (1H, m), 3.75 (2H, d, J=6.4Hz), 5.7-5.9(1H, bs), 6.4-6.6 (1H, bs), 6.85 (1H, d, J= 8.8Hz), 7.38(1H, dd, J=8.8, 2.4Hz), 7.63 (1H, d, J=2.8Hz).

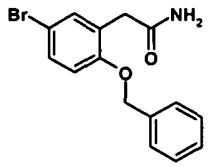
2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}acetamide



A stirred solution of {5-chloro-2-[(phenylmethyl)oxy]phenyl}acetic acid (6.86g, 24.79mmol) in dichloromethane (60ml) was treated with ammonium 1*H*-1,2,3-benzotriazol-1-olate (4.15g, 27.27mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (5.68g, 29.75mmol) and N-methylmorpholine (5.45ml, 49.58mmol). The mixture was stirred at room temperature for 2h. The solvent was evaporated and the residue dissolved in ethyl acetate which was washed with 5% sodium bicarbonate solution, 2M hydrochloric acid and water, dried ($MgSO_4$) and evaporated. The residue was triturated with iso-hexane and diethyl ether (1:1) and the beige solid filtered and dried *in vacuo* (4.28g).

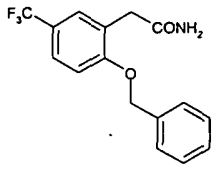
LC/MS Rt = 2.88 min, [MH^+] 276, 278.

2-{5-Bromo-2-[(phenylmethyl)oxy]phenyl}acetamide



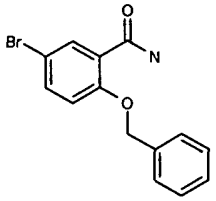
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}acetamide using {5-bromo-2-[(phenylmethyl)oxy]phenyl} acetic acid.
^{1}HNMR($CDCl_3$)δ: 3.56 (2H,s), 5.09 (2H,s), 5.2 (1H,bs), 5.6 (1H,bs), 6.85(1H,d), 7.34-7.40 (7H,m).

2-[2-[(Phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetamide



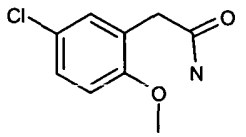
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}acetamide using [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetic acid. LC/MS Rt = 2.84 min, [MH^+] 310.

5-Bromo-2-[(phenylmethyl)oxy]benzamide



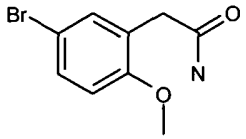
A solution of 5-bromo-2-[(phenylmethyl)oxy]benzoic acid (13.8g, 45 mmol) and 4-methylmorpholine (4.77g, 47.2mmol) in dry tetrahydrofuran (100ml) was cooled to -12°C and treated with isobutyl chloroformate (6.44g, 47.2mmol) . The reaction mixture was stirred at -12°C for 4 minutes, then .880 ammonia (50ml) was added and the mixture allowed to warm to room temperature. The mixture was diluted with ethyl acetate (50ml). The organic phase was separated, washed with water and brine, dried and evaporated. The residue was triturated with iso-hexane to give the title compound as a colourless solid 11.1g, 81%. LC/MS Rt = 2.99 min, [MH^+] 306, 308.

2-[5-Chloro-2-(methyloxy)phenyl]acetamide.



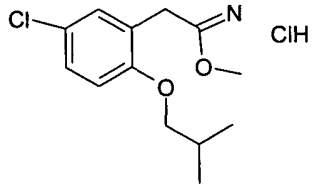
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}acetamide using [5-chloro-2-(methyloxy)phenyl]acetic acid. LC/MS Rt = 1.89 min, [MH^+] 200 .

2-[5-Bromo-2-(methyloxy)phenyl]acetamide.



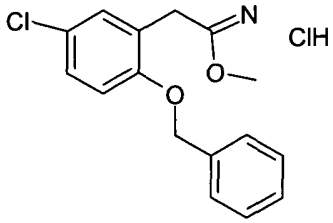
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}acetamide using [5-bromo-2-(methyloxy)phenyl]acetic acid. ^1H NMR ($CDCl_3$) δ: 3.36(2H, s), 3.75(3H, s), 6.85(1H, d, J = 8Hz), 7.25-7.50(2H, m).

Methyl 2-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}ethanimidoate hydrochloride



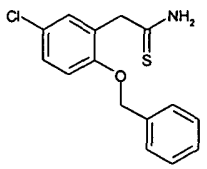
HCL was bubbled through an ice cold solution of {5-chloro-2-[(2-methylpropyl)oxy] phenyl}acetonitrile(13g, 58.2mmol) in 80 ml of methanol for 1/2h until saturated. The solution was allowed to reach room temperature and left stirring for 2 h. The solvent was evaporated to give a solid which was triturated with Et_2O and filtered off to give 10.4g of a light pink solid. LC/MS Rt = 1.9, [MH^+] 256.2, 258.2, 259.1.

Methyl 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanimidoate hydrochloride



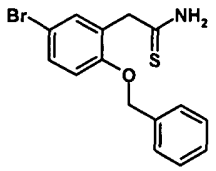
HCL was bubbled through a ice cold solution of {5-chloro-2-[(phenylmethyl) oxy]phenyl}acetonitrile (12.9g, 50mmol) in methanol (80ml) for 1/2h until saturated. The solution was allowed to reach room temperature and left stirring for 3 h. LCMS analysis showed the presence of some starting material, the mixture was left in the fridge over the weekend. The solvent was evaporated and the residue was triturated with Et_2O to give the title compound as a white solid. LC/MS Rt = 1.97, [MH^+] 290.1, 292.1.

2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide



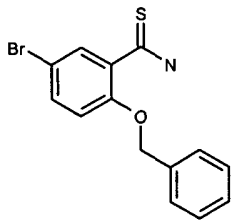
A solution of 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}acetamide (4.28g, 15.52mmol) in 1,2-dimethoxyethane (40ml) was treated with Lawesson's Reagent (3.14g, 7.76mmol). The mixture was stirred at room temperature for 2h. The solvent was evaporated and the residue dissolved in dichloromethane and washed with 1% sodium hydroxide solution (x2) and brine, dried ($MgSO_4$) and evaporated. The solid was triturated with diethyl ether, filtered and dried in vacuo (3.43g). LC/MS Rt = 3.32 min, [MH^+] 292, 294.

2-{5-Bromo-2-[(phenylmethyl)oxy]phenyl}ethanethioamide



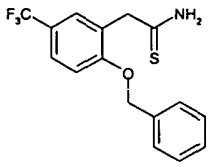
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide using 2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}acetamide.
^{1}HNMR($CDCl_3$)δ: 4.05 (2H,s), 5.10 (2H,s), 6.88 (1H,d), 7.36-7.47 (7H,m).

5-Bromo-2-[(phenylmethyl)oxy]benzenecarbothioamide



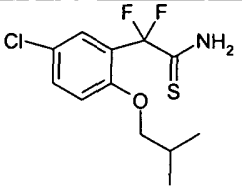
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide using 5-bromo-2-[(phenylmethyl)oxy]benzamide.
^{1}H NMR ($CDCl_3$) δ: 5.16(2H, s), 6.92(1H, d), 7.39-7.44(5H, m), 7.53(1H, d), 7.88-7.90(1H, br s), 8.75(1H, s), 8.85-8.90(1H, br s).

2-[2-[(Phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]ethanethioamide



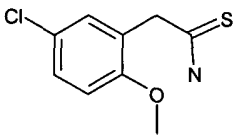
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide using 2-[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]acetamide. LC/MS Rt = 3.20 min, [MH$^+$] 326.

2-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-2,2-difluoroethanethioamide



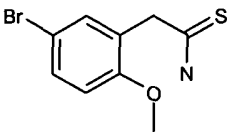
Phosphorus pentasulfide (1.28g, 2.89mmol) was added to a solution of 2-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}-2,2-difluoroacetamide (1.6, 5.78mmol) in 1,2-dimethoxyethane (10ml), the mixture was stirred at room temperature for 6 h. Diluted with ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water. The organic phase was dried ($MgSO_4$) and evaporated to give a yellow solid (1.54g).
LC/MS Rt = 3.21 min, [MH$^+$] 294.1, [MH$^-$] 292.1, 294.1

2-[5-Chloro-2-(methyloxy)phenyl]ethanethioamide



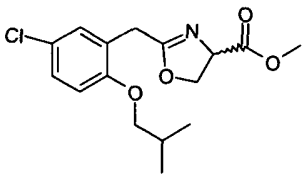
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide using 2-[5-chloro-2-(methyloxy)phenyl]acetamide.
^{1}H NMR ($CDCl_3$) δ: 3.85(3H, s), 4.03(2H, s), 6.85(1H, d), 7.23-7.29(2H, m).

2-[5-Bromo-2-(methyloxy)phenyl]ethanethioamide



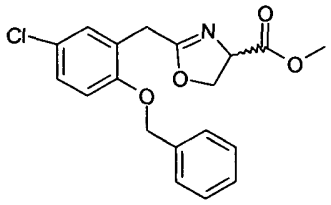
The title compound was prepared in a similar manner to 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide using 2-[5-bromo-2-(methyloxy)phenyl]acetamide.
^{1}H NMR ($CDCl_3$) δ: 3.85(3H,s), 4.03(2H, s), 6.80(1H, d), 7.38-7-43(2H, m).

Methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate



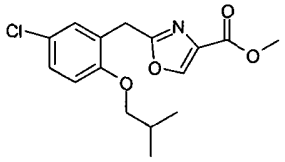
Methyl 2-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}ethanimidoate hydrochloride (10.4g, 35.6mmol), diisopropylethylamine(6.2ml, 35.6mmol) and DL-serine hydrochloride (5.5g, 35.6mmol) in 100ml of DCM was stirred at room temperature overnight. Washed with water, dried and evaporated; the residue was purified on a Biotage using 30% of ethyl acetate in hexane to give a yellow oil (8.32g).
LC/MS Rt = 3.29, [MH^+] 326.2, 328.4, 329.2

Methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate



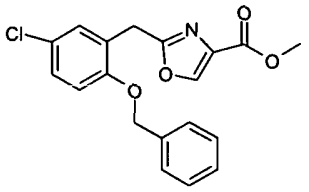
The title compound was prepared in a similar manner to methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate.
LC/MS Rt = 3.11, [MH^+] 360, 361, 362, 363

Methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate



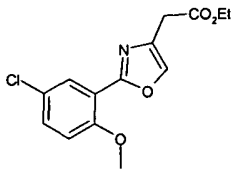
1,8-Diazabicyclo(5.4.0)undec-7-ene (15.3ml, 102.1mmol) was added to an ice cold solution of $CuBr_2$ (22.77g, 102.1 mmol) and hexamethylene tetramine (14.3g, 102.1mmol) in DCM (250ml); to this mixture methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (8.32g, 25.5mmol) was slowly added. The reaction mixture was stirred at room temperature overnight, diluted with diethyl ether and washed (x3) with a 1:1 mixture of aqueous ammonia (0.88) and saturated ammonium chloride solution, followed by H_2O and 2M HCl. The organic phase was dried, evaporated and the residue purified on a Biotage using 20% of ethyl acetate in hexane to give the title compound as a white solid (4.8g). LC/MS Rt = 3.46, [MH^+] 324.1, 326.1.

Methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate



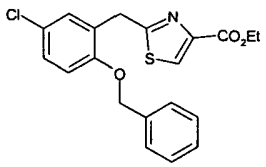
The title compound was prepared in a similar manner to methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate.
LC/MS Rt = 3.32, [MH^+] 358.1, 360

Ethyl {2-[5-chloro-2-(methyloxy)phenyl]-1,3-oxazol-4-yl}acetate



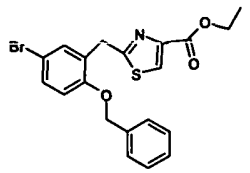
A mixture of ethyl 4-chloroacetoacetate (2.82g, 17.1mmol), 5-chloro-2-methoxybenzamide (3.5g, 18.9mmol) and pyridine (1.49g, 18.9mmol) was heated at 120°C for 3 hours. After cooling to room temperature the mixture was partitioned between ethyl acetate (25ml) and water (25ml). The organic phase was separated, washed with brine, dried and evaporated. Purification of the residue by flash chromatography eluting with 20-50% ethyl acetate in hexane gave the title compound as a yellow solid 1.62g, 30%.
LC/MS Rt = 3.10 min, [MH^+] 296.

Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate



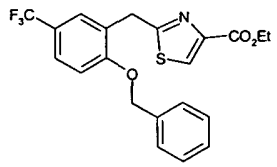
2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}ethanethioamide (3.43g, 11.76mmol) and potassium hydrogen carbonate (9.43g, 94.3mmol) were stirred in 1,2-dimethoxyethane (40ml) under nitrogen for 5 minutes. Ethyl bromopyruvate (4.44ml, 35.28mmol) was added and the resulting mixture stirred for 1 minute, then the suspension cooled to 0°C. Trifluoroacetic anhydride (6.64ml, 47.04mmol) and pyridine (7.6ml, 94.3mmol) were dissolved in 1,2-dimethoxyethane (50ml) and cooled to 0°C. The solution was added carefully to the original mixture at 0°C. The resulting slurry was stirred and allowed to reach room temperature over 1.5h. The solvent was evaporated and the residue dissolved in dichloromethane and washed with water (x2), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 20% ethyl acetate in iso-hexane to leave orange oil (3.93g). LC/MS Rt = 3.79 min, [MH^+] 388, 390.

Ethyl 2-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate



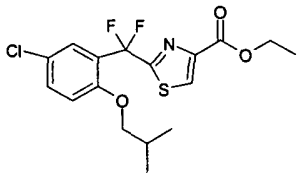
The title compound was prepared in a similar manner to ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate using 2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}ethanethioamide. LC/MS Rt = 3.84, [MH^+] 434,435.

Ethyl 2-{[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate



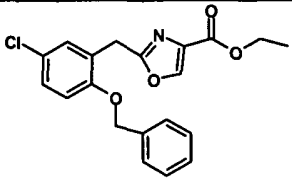
The title compound was prepared in a similar manner to ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate using 2-[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]ethanethioamide.
LC/MS Rt = 3.43 min, [MH^+] 422.

Ethyl 2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazole-4-carboxylate



The title compound was prepared in a similar manner to ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate using 2-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}-2,2-difluoroethanethioamide.
LC/MS Rt = 3.77 min, [MH^+] 390.1, 392.1

Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate

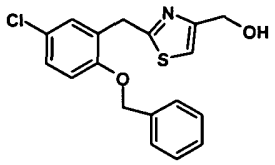


2-(Bromomethyl)-4-chlorophenyl phenylmethyl ether (600mg, 1.92 mmol) was added dropwise to a suspension of activated zinc dust* (500mg, 7.7 mmol) in dry THF under a nitrogen atmosphere. As soon as the flask reached room temperature, the solution was filtered under an inert atmosphere and added to a mixture of ethyl 2-bromo-1,3-oxazole-4-carboxylate (333mg, 1.5mmol) and $Pd(PPh_3)_4$ (catalytic) in dry THF under nitrogen. The

mixture was stirred at room temperature for 26h then evaporated and purified using 20% of ethyl acetate in iso-hexane to give the title compound as white solid (240mg).
LC/MS Rt =3.34,[MH^+] 372, 374

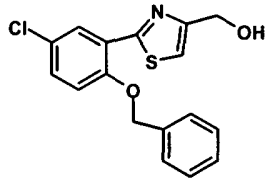
*Activation of Zinc dust.
A Suspension of 500mg of zinc in 2ml of THF containing 1, 2-dibromoethane (26µl, 0.30mmol) was heated at 65°C for 1 minute. Cooled to 25°C and 29µl of chlorotrimethylsilane (0.23mmol) was added. The mixture was stirred at 20°C for 15 minutes before being used.

[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]methanol



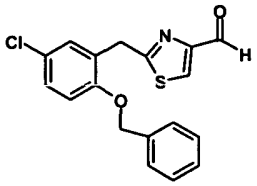
1.0M Lithium aluminium hydride in tetrahydrofuran (0.56ml, 0.56mmol) was added, under nitrogen, to a solution of ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate (0.2g, 0.51mmol) in tetrahydrofuran (4ml) at -78°C . The reaction mixture was stirred at -78°C for 1 hour then warmed to room temperature before adding water. The solution was then extracted with dichloromethane, the solvent was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography eluting with 20% of ethyl acetate in iso-hexane to yield the title compound.
^1H NMR ($CDCl_3$)δ: 2.09 (1H,bs), 4.32 (2H,s), 4.72 (2H,s), 5.07 (2H,s), 6.86 (1H,d), 7.03 (1H,s), 7.18-7.37 (7H,m).

(2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)methanol



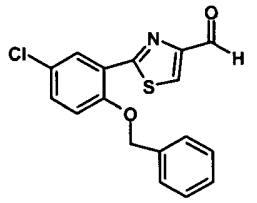
The title compound was prepared in a similar manner to [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]methanol using ethyl 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazole-4-carboxylate.
^1H NMR ($CDCl_3$)δ: 2.28 (1H,t), 4.83 (2H,d), 5.28 (2H,s), 6.99 (1H,d), 7.21 (1H,s), 7.27-7.49 (6H,m), 8.40 (1H, d).

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbaldehyde



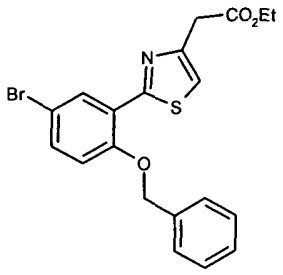
Chromium (VI) oxide (344mg, 3.47mmol) was added to a stirred solution of pyridine (0.56ml, 6.9mmol) in dichloromethane (5ml). The mixture was stirred for 15 minutes, then [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]methanol (200mg, 0.58mmol) in dichloromethane (5ml) was slowly added. When there was no starting material left the solvent was decanted and the residue washed several times with diethyl ether. The combined organic solutions were washed with 5% sodium hydroxide solution, 5% hydrochloric acid solution, 5% sodium hydrogen carbonate solution and saturated sodium chloride solution. The organic solvent was then dried ($MgSO_4$) and evaporated to dryness to give the title compound as colourless oil 130mg.
^{1}H NMR ($CDCl_3$)δ: 4.3 (2H,s), 4.99 (2H,s), 6.81 (1H,d), 7.12-7.29 (7H,m), 7.94 (1H,s), 9.9 (1H,s).

2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazole-4-carbaldehyde



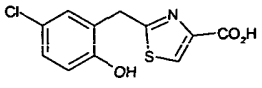
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbaldehyde using (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)methanol.
^{1}H NMR ($CDCl_3$)δ: 5.29(2H,s), 7.04 (1H,d), 7.34-7.48 (6H,m), 8.18 (1H, s), 8.50 (1H,d), 10.1 (1H,s).

Ethyl (2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate



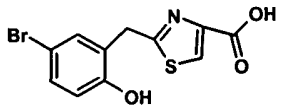
The title compound was prepared in a manner similar to ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate using 5-bromo-2-[(phenylmethyl)oxy]benzenecarbothioamide.
LC/MS Rt = 4.11 min, [MH+] 432, 434.

2-[(5-Chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid



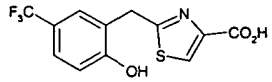
Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate (2.7g, 6.96mmol) was dissolved in dimethylformamide (20ml) and sodium methanethiolate (2.44g, 34.81mmol) added. The mixture was heated at 100°C for 2h. After cooling, water (100ml) was added and the mixture extracted with diethyl ether (x2). The aqueous layer was acidified with glacial acetic acid and extracted with ethyl acetate (x2) which was washed with water (x3), dried ($MgSO_4$) and evaporated to an orange oil 2.01g.
LC/MS Rt = 3.01 min, [MH^+] 270, 272.

2-[(5-Bromo-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid



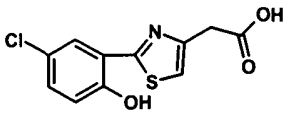
The title compound was prepared in a similar manner to 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid using ethyl 2-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate.
LC/MS Rt = 3.09, [MH^+] 316,317.

2-{[2-Hydroxy-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylic acid



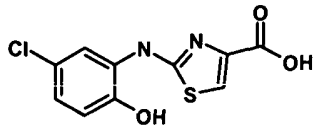
The title compound was prepared in a similar manner to 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid using ethyl 2-{[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate.

[2-(5-Chloro-2-hydroxyphenyl)-1,3-thiazol-4-yl]acetic acid



The title compound was prepared in a similar manner to 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid using ethyl (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate. LC/MS Rt = 3.14, [MH^+] 270,272.

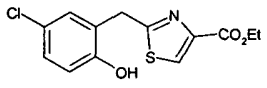
2-[(5-Chloro-2-hydroxyphenyl)amino]-1,3-thiazole-4-carboxylic acid



A) The title compound was prepared in a similar manner to 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid using ethyl 2-{[5-chloro-2-(methyloxy)phenyl]amino}-1,3-thiazole-4-carboxylate and heating the reaction mixture at 60°C for one day. LC/MS Rt = 3.0 min., [MH^+] 271.

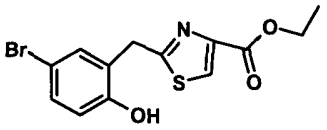
B) Boron tribromide (39.75g; 15ml; 158.4mmol) was added carefully dropwise to a water-bath cooled solution of ethyl 2-{[5-chloro-2-(methyloxy)phenyl]amino}-1,3-thiazole-4-carboxylate (10.0g, 31.97mmol) in dichloromethane (250ml). The resulting mixture was stirred at room temperature for 1 hour, then poured onto ice (~500g) and ethyl acetate and water added. The organic layer was dried ($MgSO_4$) and evaporated to a buff solid 8.65g. LC/MS Rt = 3.0 min., [MH^+] 271.

Ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate



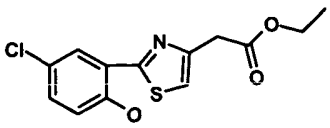
2-[(5-Chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid (2.0g, 7.42mmol) was dissolved in ethanol (20ml) and concentrated sulphuric acid (0.2ml) added. The solution was heated at reflux for 2h. The solvent was evaporated and the residue dissolved in diethyl ether and washed with 5% sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 30-50% ethyl acetate in iso-hexane to give an orange oil, 983mg.
LC/MS Rt = 3.03 min, [MH^+] 298, 300.

Ethyl 2-[(5-bromo-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate



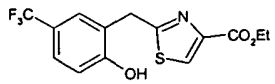
The title compound was prepared in a similar manner to ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate using 2-[(5-bromo-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylic acid.
LC/MS Rt = 3.15, [MH^+] 344,345.

Ethyl [2-(5-chloro-2-hydroxyphenyl)-1,3-thiazol-4-yl]acetate



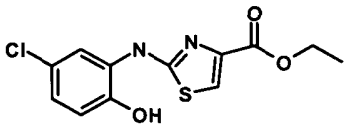
The title compound was prepared in a similar manner to ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate using [2-(5-chloro-2-hydroxyphenyl)-1,3-thiazol-4-yl]acetic acid. LC/MS Rt = 3.5, [MH^+] 298,301, [MH^-] 296.

Ethyl 2-{[2-hydroxy-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate



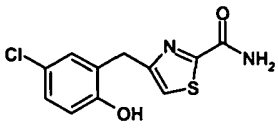
The title compound was prepared in a similar manner to ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate using 2-{[2-hydroxy-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylic acid.
LC/MS Rt = 2.97 min, [MH^+] 332.

Ethyl 2-[(5-chloro-2-hydroxyphenyl)amino]-1,3-thiazole-4-carboxylate



A)The title compound was prepared in a similar manner to ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate using 2-[(5-chloro-2-hydroxyphenyl)amino]-1,3-thiazole-4-carboxylic acid.
LC/MS Rt = 3.33 min., [MH^+] 299,301.
B) 2-[(5-chloro-2-hydroxyphenyl)amino]-1,3-thiazole-4-carboxylic acid (8.65g, 31.97mmol) was dissolved in ethanol (100ml) and concentrated sulphuric acid (10ml) added carefully. The solution was heated at 80°C for 6 hours and left at room temperature overnight. The solvent was evaporated and ethyl acetate and water added. Potassium carbonate was added until the mixture was basic and the organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether and the solid filtered and dried 6.3g. LC/MS Rt = 2.93min [MH^+] 299, 301.

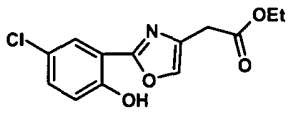
4-[(5-Chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-2-carboxamide



Ethyl 4-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-2-carboxylate (1g, 2.57mmol) in 3.15 ml of hydrogen bromide in acetic acid (48%) was heated at 50°C for 3 hours. The mixture was then cooled, diluted with water, basified with potassium carbonate and extracted with diethyl ether (3 x 20ml). The combined organic phases were dried and

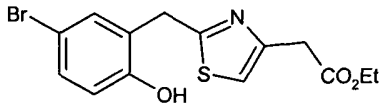
evaporated to dryness. The residue was dissolved with ethanol, 3 ml of ammonia were added and the resulting solution was stirred at room temperature overnight. The mixture was then acidified with 2M hydrochloric acid solution and extracted with ethyl acetate (x3). The combined organic phases were dried, filtered and concentrated to yield the title compound (0.6g, 87%). LC/MS Rt = 2.66, [MH^+] 269,271.

Ethyl [2-(5-chloro-2-hydroxyphenyl)-1,3-oxazol-4-yl]acetate



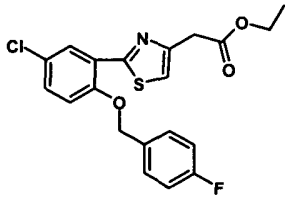
The title compound was prepared from ethyl {2-[5-chloro-2-(methyloxy)phenyl]-1,3-oxazol-4-yl}acetate in a manner similar to that used to prepare ethyl {2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazol-4-yl}acetate. LC/MS Rt = 3.63 min, [MH^+] 282.

Ethyl {2-[(5-bromo-2-hydroxyphenyl)methyl]-1,3-thiazol-4-yl}acetate



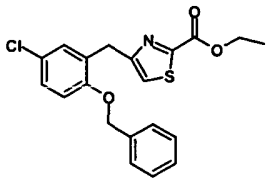
The title compound was prepared from ethyl (2-{[5-bromo-2-(methyloxy)-phenyl]methyl}-1,3-thiazol-4-yl)acetate in a manner similar to that used to prepare ethyl {2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazol-4-yl}acetate. LC/MS Rt = 3.16 min, [MH^+] 356,358.

Ethyl [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate



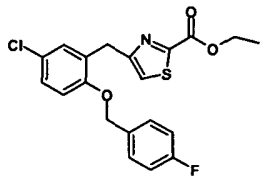
(5-Chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)boronic acid (2.96g, 10.5mmol), ethyl (2-bromo-1,3-thiazol-4-yl)acetate (2.2g, 8.8mmol), potassium carbonate (9.7g, 70mmol), and tetrakis(triphenylphosphine)palladium(0) (576mg, 0.5mmol) in 1:1 toluene/ethanol (40ml) were stirred and heated at 90°C under nitrogen for two hours. After cooling the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 x 30ml), the combined organic phases were dried and evaporated to dryness. The residue was purified by flash chromatography eluting with 15% of ethyl acetate in iso-hexane to yield the title compound as a white solid (2.9g, 81%). LC/MS Rt = 3.77 min, [MH^+] 406,409.

Ethyl 4-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-2-carboxylate



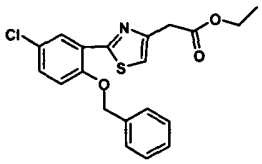
The title compound was prepared in a similar manner to ethyl [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate using {5-chloro-2-[(phenylmethyl)oxy]phenyl}boronic acid and ethyl 4-(bromomethyl)-1,3-thiazole-2-carboxylate. LC/MS Rt = 3.95 min, [MH^+] 388.

Ethyl 4-[(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate



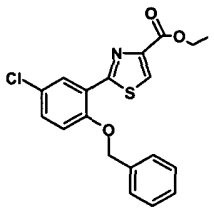
The title compound was prepared in a similar manner to ethyl [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate using (5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)boronic acid and ethyl 4-(bromomethyl)-1,3-thiazole-2-carboxylate. LC/MS Rt = 3.95 min, [MH^+] 406.

Ethyl (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate



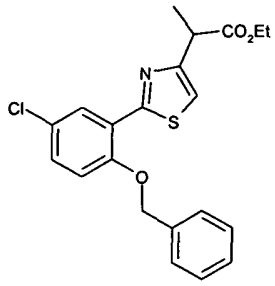
The title compound was prepared in a similar manner to ethyl [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate using {5-chloro-2-[(phenylmethyl)oxy]phenyl}boronic acid. LC/MS Rt = 4.03 min, [MH^+] 388.

Ethyl 2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazole-4-carboxylate



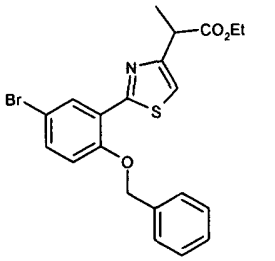
The title compound was prepared in a similar manner to ethyl [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate using {5-chloro-2-[(phenylmethyl)oxy]phenyl}boronic acid and ethyl 2-bromo-1,3-thiazole-4-carboxylate. LC/MS Rt = 3.94, [MH^+] 374,376.

Ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate



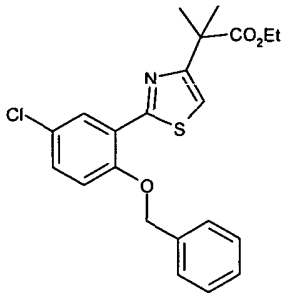
A solution of ethyl (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate (400mg, 1.03mmol) in dry tetrahydrofuran (5ml) was cooled to -78°C, under N_2 and treated with 2.0M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (0.5ml, 1mmol). The mixture was stirred at -78°C for 15 mins. Then treated with methyl iodide (142mg, 1mmol). After stirring at room temperature for 30mins. the mixture was cooled to -78°C and treated with a further portion of 2.0M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (0.5ml, 1mmol) and methyl iodide (142mg, 1mmol). The mixture was stirred at room temperature for 1 hour then quenched with water (10ml). The mixture was extracted with diethyl ether (2x10ml). The combined extracts were dried and evaporated. The residue was purified by flash chromatography, eluting with 8% ethyl actetate in hexane to give the title compound as a colourless oil. 170mg 42%.
LC/MS Rt = 4.16 min, [MH^+] 416.

Ethyl 2-(2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate



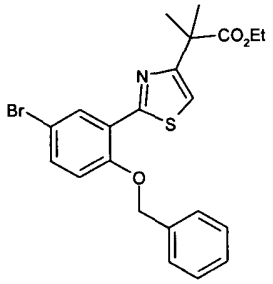
The title compound was prepared from ethyl (2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate in a similar manner to that used to prepare ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate. LC/MS Rt = 4.30 min, [MH^+] 446, 448.

Ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)-2-methylpropanoate



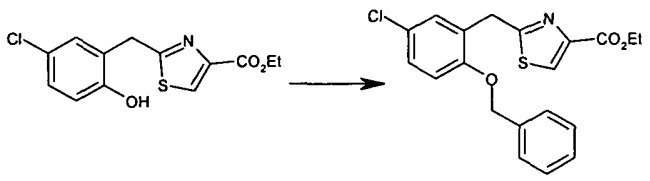
The title compound was prepared in a similar manner to ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate using ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate as the starting material.
LC/MS Rt = 4.42 min, [MH^+] 416.

Ethyl 2-(2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)-2-methylpropanoate



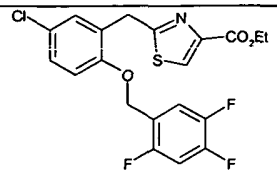
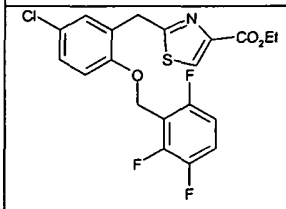
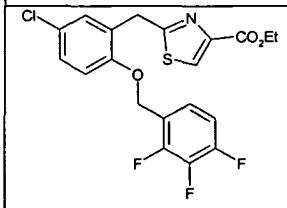
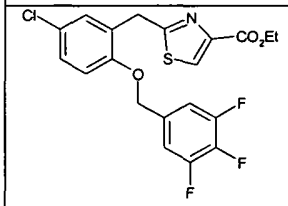
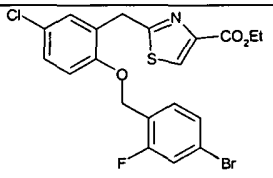
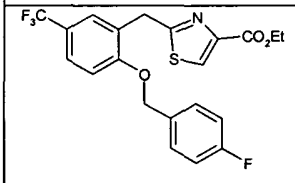
The title compound was prepared in a similar manner to ethyl 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate using ethyl 2-(2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate as the starting material.
LC/MS Rt = 4.31 min, [MH^+] 460, 462.

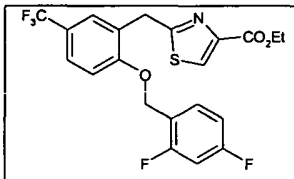
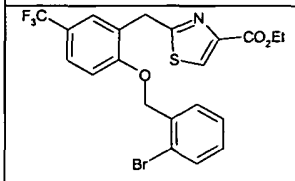
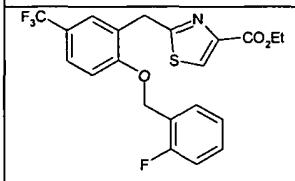
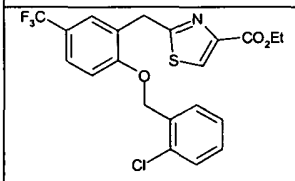
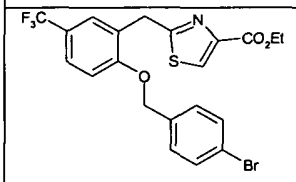
General Procedure 1

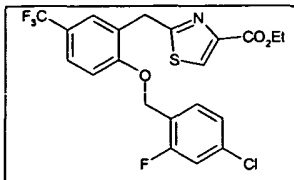
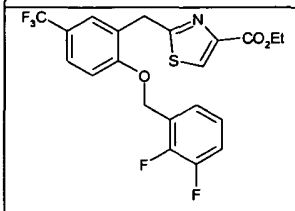
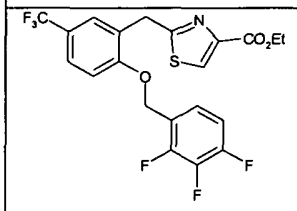
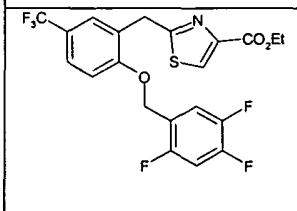
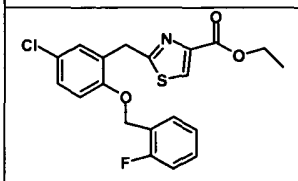
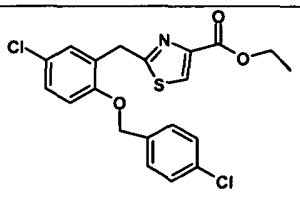


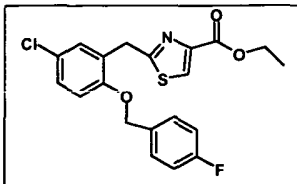
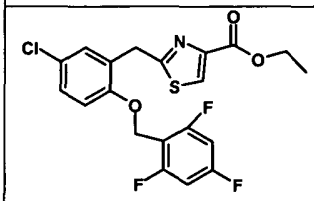
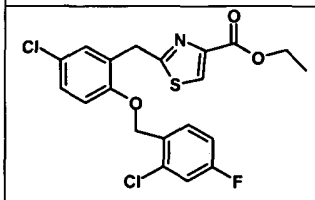
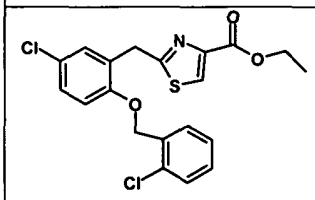
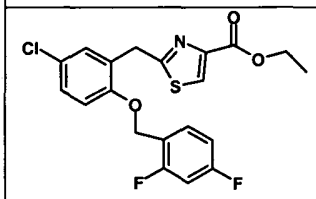
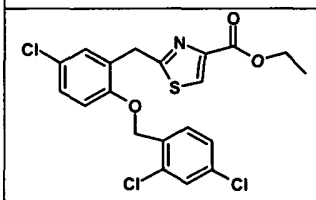
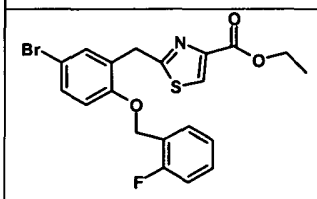
The ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate was dissolved in acetone and potassium carbonate (2.5 to 5 equivalents) was added, followed by the appropriate benzyl bromide (1.1 to 2 equivalents). The reaction was stirred at reflux for between 1 and 18h. The mixture was filtered and the filtrate evaporated.
The residue was purified by flash chromatography on silica.

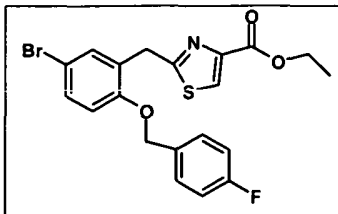
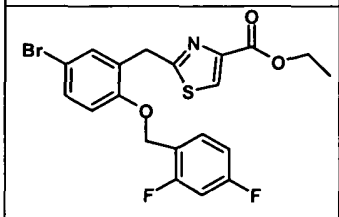
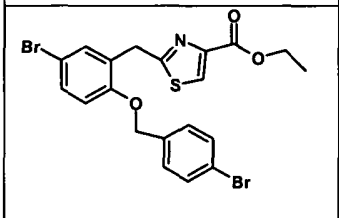
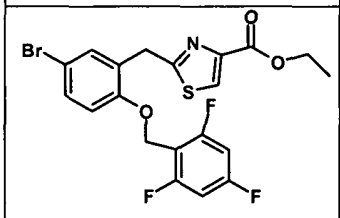
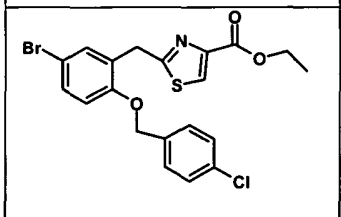
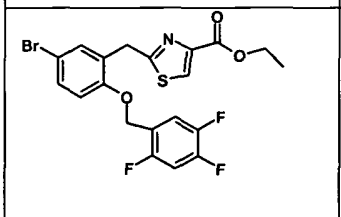
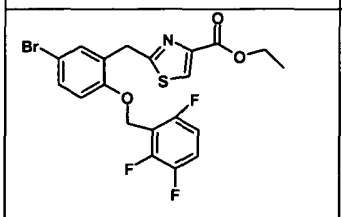
The following intermediates were prepared by general procedure 1 from the appropriate starting materials.

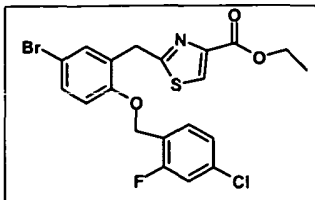
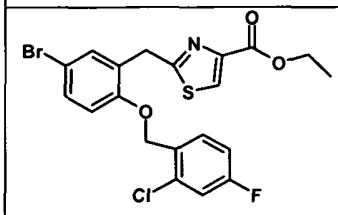
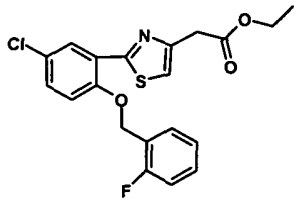
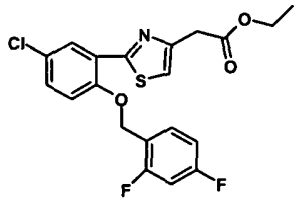
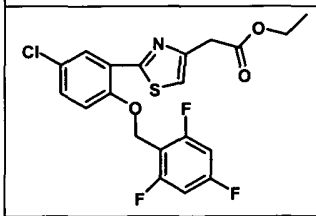
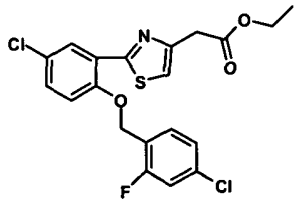
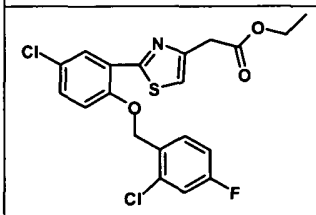
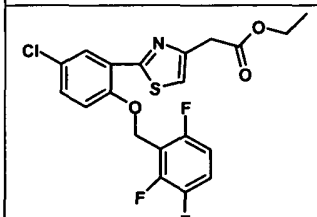
	Name	Data
	ethyl 2-[(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.46 min, [MH$^+$] 442, 444.
	Ethyl 2-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.41 min, [MH$^+$] 442, 444.
	Ethyl 2-[(5-chloro-2-{[(2,3,4-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.47 min, [MH$^+$] 442, 444.
	Ethyl 2-[(5-chloro-2-{[(3,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.45 min, [MH$^+$] 442, 444.
	Ethyl 2-[(2-{[(4-bromo-2-fluorophenyl)methyl]oxy}-5-chlorophenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.66 min, [MH$^+$] 486, 488.
	Ethyl 2-{[2-{[(4-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.56 min, [MH$^+$] 440.

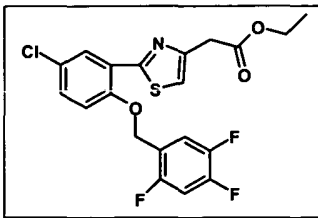
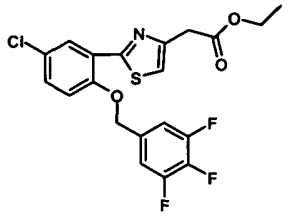
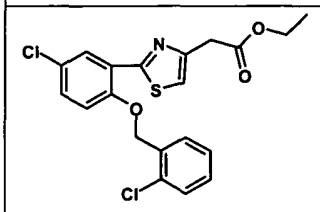
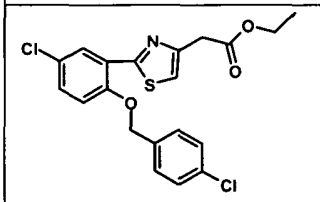
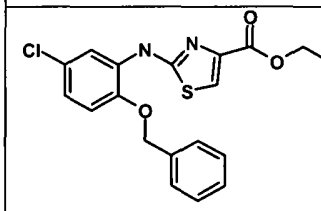
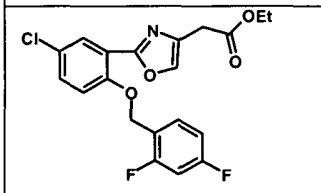
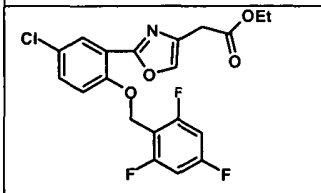
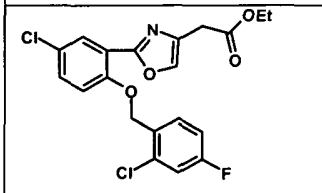
	Ethyl 2-{[2-{[(2,4-difluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.58 min, [MH^+] 458.
	Ethyl 2-{[2-{[(2-bromophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.11 min, [MH^+] 500, 502.
	Ethyl 2-{[2-{[(2-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.90 min, [MH^+] 440.
	Ethyl 2-{[2-{[(2-chlorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.05 min, [MH^+] 456, 458.
	Ethyl 2-{[2-{[(4-bromophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.10 min, [MH^+] 500, 502.

	Ethyl 2-{[2-{[(4-chloro-2-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.09 min, [MH$^+$] 474, 476.
	Ethyl 2-{[2-{[(2,3-difluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.92 min, [MH$^+$] 458.
	Ethyl 2-[(5-(trifluoromethyl)-2-{[(2,3,4-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.97 min, [MH$^+$] 476.
	Ethyl 2-[(5-(trifluoromethyl)-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.94 min, [MH$^+$] 476.
	Ethyl 2-[(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.62 min [MH$^+$] 406,408
	Ethyl 2-[(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.80min [MH$^+$] 422,425

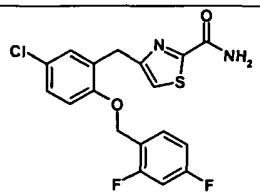
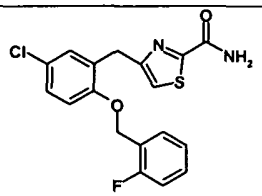
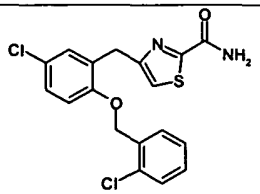
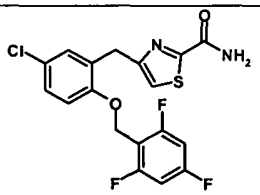
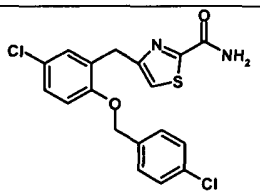
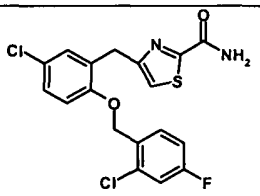
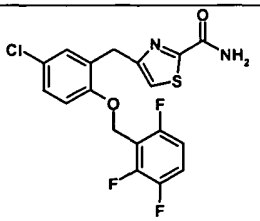
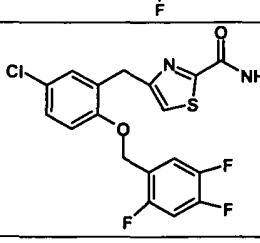
	Ethyl 2-[(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.63 min [MH$^+$] 406
	Ethyl 2-[(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.64 min, [MH+] 442,445
	Ethyl 2-[(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.88 min [MH+] 440,444
	Ethyl 2-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.86 min. [MH+] 422,426
	Ethyl 2-[(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.77 min. [MH+] 424,427
	Ethyl 2-[(5-chloro-2-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 4.16 min. [MH+] 458,460
	Ethyl 2-[(5-bromo-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.9 min. [MH+] 452,453

	Ethyl 2-[(5-bromo-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.9 min. [MH+] 452,453
	Ethyl 2-[(5-bromo-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.89 min.[MH+] 470,471
	Ethyl 2-[(5-bromo-2-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 4.07 min [MH+] 510,512,514, 515
	Ethyl 2-[(5-bromo-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.83 min [MH+] 488,489
	Ethyl 2-[(5-bromo-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.88 min [MH+] 468,470
	Ethyl 2-[(5-bromo-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.89 min. [MH+] 488,489
	Ethyl 2-[(5-bromo-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.83 min [MH+] 488,489

	Ethyl 2-[(5-bromo-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 4.05 min [MH+] 486,488
	Ethyl 2-[(5-bromo-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 4.07 min [MH+] 486,488
	Ethyl [2-(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.92 min [MH+] 406,408
	Ethyl [2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.99 min [MH+] 424,426
	Ethyl [2-(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.99 min [MH+] 442,444
	Ethyl [2-(5-chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 4.0 min. [MH+] 440,444
	Ethyl [2-(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 4.22 min [MH+] 440,443
	Ethyl [2-(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.9 min [MH+] 442,444

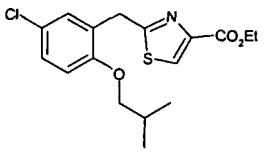
	Ethyl [2-(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.4 min [MH+] 442,444
	Ethyl [2-(5-chloro-2-{[(3,4,5-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 4.11 min [MH+] 442,444
	Ethyl [2-(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 4.0 min [MH+] 422,425
	Ethyl [2-(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.6 min [MH+] 422,426
	Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylate	Rt = 3.83 min [MH+] 389,391
	Ethyl [2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.71 min [MH+] 408.
	Ethyl [2-(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.61 min [MH+] 426.
	Ethyl [2-(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.92 min [MH+] 424.

The following examples were prepared by general procedure 1 from the appropriate intermediates.

Example		Name	Data
1		4-[(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.60 min [MH+] 395,397
2		4-[(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.57 min [MH+] 377,379
3		4-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.77 min[MH+] 393,397
4		4-[(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.57 min [MH+] 413,415
5		4-[(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.73 min [MH+] 393
6		4-[(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.78 min [MH+] 411,415
7		4-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.56 min[MH+] 413,415
8		4-[(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide	Rt = 3.63 min [MH+] 413,415

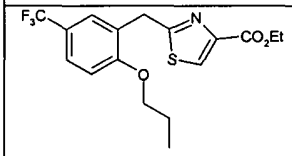
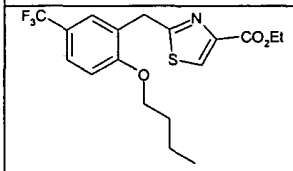
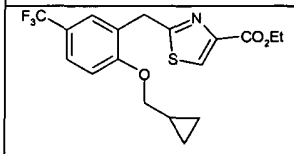
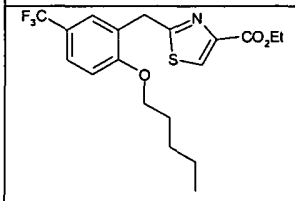
General Procedure 2:

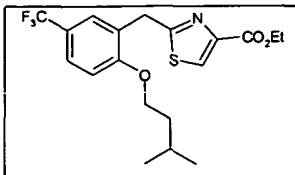
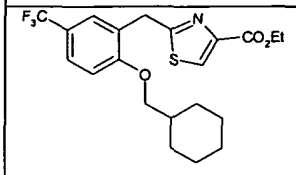
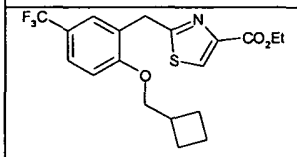
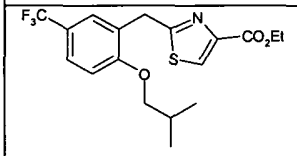
Ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate



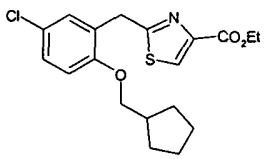
Ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate (98mg, 0.329mmol) was dissolved in dimethylformamide (2ml) and potassium carbonate (227mg, 1.65mmol) added, followed by 1-iodo-2-methylpropane (89mg, 0.395mmol). The reaction was stirred at 90°C for 6h. The mixture was filtered and the filtrate evaporated. The residue was purified by flash chromatography, eluting with 20% ethyl acetate in iso-hexane (53mg). LC/MS Rt = 3.44 min, [MH^+] 354, 356.

The following intermediates were prepared by general procedure 2 from the appropriate starting materials.

	Name	Data
	Ethyl 2-{[2-(propyloxy)-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.77 min, [MH^+] 374.
	Ethyl 2-{[2-(butyloxy)-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.93 min, [MH^+] 388.
	Ethyl 2-{[2-[(cyclopropylmethyl)oxy]-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.77 min, [MH^+] 386.
	Ethyl 2-{[2-(pentyloxy)-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.09 min, [MH^+] 402.

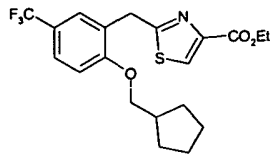
	Ethyl 2-{[2-[(3-methylbutyl)oxy]-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.05 min, $[MH^+]$ 402.
	Ethyl 2-{[2-[(cyclohexylmethyl)oxy] -5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.26 min, $[MH^+]$ 428.
	Ethyl 2-{[2-[(cyclobutylmethyl)oxy]-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.99 min, $[MH^+]$ 400.
	Ethyl 2-{[2-[(2-methylpropyl)oxy]-5-(trifluoromethyl)phenyl] methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.92 min, $[MH^+]$ 388.

Ethyl 2-({5-chloro-2-[(cyclopentylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate



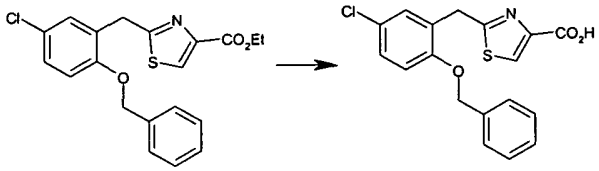
Ethyl 2-[(5-chloro-2-hydroxyphenyl)methyl]-1,3-thiazole-4-carboxylate (130mg, 0.437mmol) was dissolved in tetrahydrofuran (2ml) under nitrogen. Triphenylphosphine (115mg, 0.478mmol), diethyl azodicarboxylate (91µl, 0.478mmol) and cyclopentanemethanol (47µl, 0.437mmol) were added and the mixture stirred at room temperature for 16h. The reaction was incomplete, so powdered 4A sieve (50mg) was added, followed by triphenylphosphine (115mg, 0.478mmol), diethyl azodicarboxylate (91µl, 0.478mmol) and cyclopentanemethanol (47µl, 0.437mmol). The reaction was stirred for a further 3h. The solvent was evaporated and the residue purified by flash chromatography, eluting with 10% ethyl acetate in iso-hexane (62mg). LC/MS Rt = 4.00 min, $[MH^+]$ 326, 328.

Ethyl 2-{[2-[(cyclopentylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate



The title compound was prepared in a similar manner to ethyl 2-({5-chloro-2-[(cyclopentylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate using ethyl 2-{[2-hydroxy-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate and cyclopentanemethanol. LC/MS Rt = 4.15 min, [MH^+] 414.

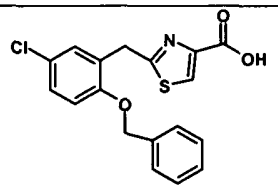
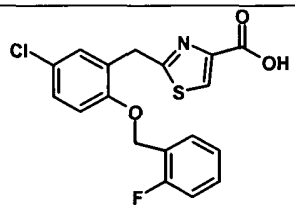
General Procedure 3

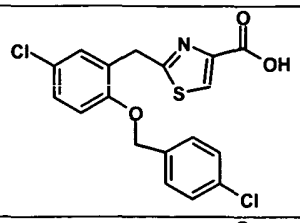
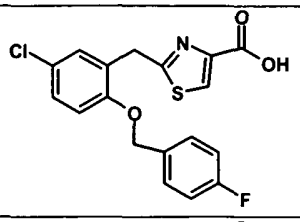
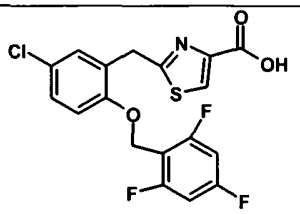
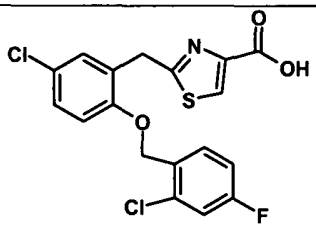
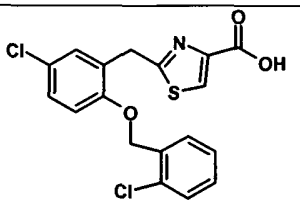
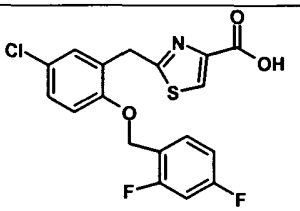
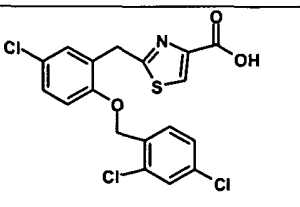


Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate was dissolved in ethanol and an excess of sodium hydroxide added [either 2M sodium hydroxide solution or solid NaOH followed by H_2O]. The solution was stirred at room temperature or warmed to 60°C overnight.

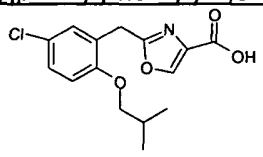
The solvent was evaporated and the residue diluted with water, extracted with 1:1 diethyl ether and iso-hexane and the aqueous layer acidified with 1M hydrochloric acid or acetic acid. The mixture was extracted with either dichloromethane, diethyl ether or ethyl acetate; the organic phases were washed with water, dried and evaporated.

The following examples were prepared by general procedure 3 from the appropriate intermediates

Example		Name	Data
9		2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid	Rt = 3.68 min [MH+] 360,362
10		2-[(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 3.71 min [MH+] 378,380

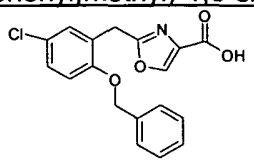
11		2-[(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 3.93 min [MH+] 394
12		2-[(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 3.6 min [MH+] 378
13		2-[(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 3.64 min [MH+] 414,416
14		2-[(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 4.02 min [MH+] 412,416
15		2-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 4.05 min [MH+] 394,398
16		2-[(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 3.74 min [MH+] 396,398
17		2-[(5-chloro-2-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylic acid	Rt = 4.34 min [MH+] 430,432

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid



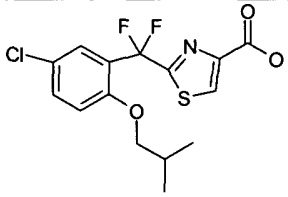
Methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate (6.54g, 20.2mmol) was dissolved in methanol (35ml) and 2M sodium hydroxide solution (10ml) added. The solution was stirred at 50°C for 1h. The solvent was evaporated and the residue diluted with water, extracted with diethyl ether and the aqueous layer acidified with 2M hydrochloric acid. The aqueous layer was extracted with ethyl acetate (x3), dried and evaporated to give a white solid (5.94g). LC/MS Rt = 3.08, [MH+] 310.2, 312.2.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid



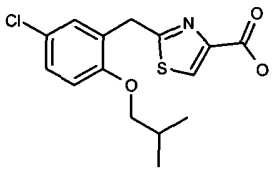
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid.
LC/MS Rt = 2.89, [MH+] 344, 346.

2-[{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazole-4-carboxylic acid



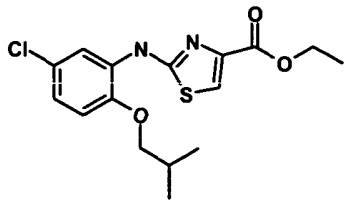
Ethyl 2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazole-4-carboxylate (275mg, 0.7mmol) was dissolved in EtOH (6ml) and 2M NaOH (2ml) added, the solution was stirred at 50°C for 2 h. Cooled, solvent evaporated, diluted with water, extracted with diethyl ether, the aqueous layer acidified with CH_3COOH. The mixture was extracted with ethyl acetate(x3), dried ($MgSO_4$) and evaporated to give a pale yellow solid.
LC/MS Rt = 3.26 min, [MH^+] 362.1, 364, [MH] 360.1, 362.1

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid



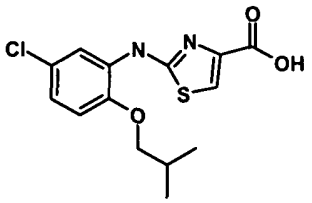
The title compound was prepared from ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}-methyl)-1,3-thiazole-4-carboxylate using a method analogous to General Procedure 3.
LC/MS Rt = 3.02 min, [MH^+] 326.

Ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylate



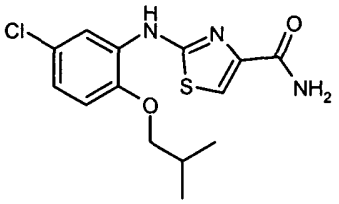
Ethyl 2-[(5-chloro-2-hydroxyphenyl)amino]-1,3-thiazole-4-carboxylate (3.0g; 10mmol), 1-bromo-2-methylbutane (2.74g; 2.18ml; 20mmol) and potassium carbonate (5.52g; 40mmol) in DMF (50ml) were stirred under argon and heated at 90°C for 16 hours. Diethyl ether and water were added and the organic layer washed with water (x3), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 10-30% ethyl acetate in hexane 1.69g. LC/MS Rt = 3.84min [MH^+] 355, 357.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylic acid



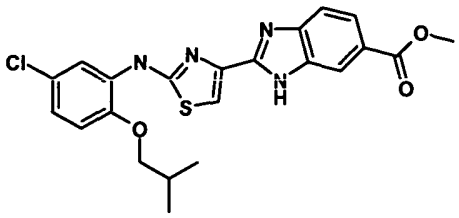
Ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylate (1.69g, 4.76mmol) was dissolved in ethanol (20ml) and 2M sodium hydroxide solution (10ml) added. The mixture was stirred at 80°C for 30minutes, cooled, then ethyl acetate and water added. The mixture was acidified with concentrated hydrochloric acid and the organic layer washed with water, dried ($MgSO_4$) and evaporated to a yellow foam 1.69g. LC/MS Rt = 3.17min [MH^+] 327, 329.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxamide



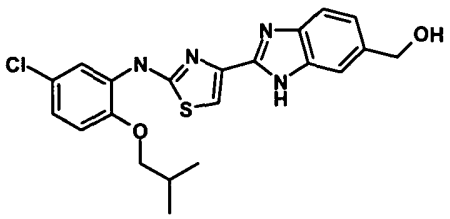
A mixture of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylic acid (810mg, 2.48mmol), EDAC (570mg, 2.98mmol), triethylamine (606mg, 6mmol) and hydroxybenzotriazole ammonium salt (417mg, 2.73mmol) in dichloromethane (20ml) was stirred at room temperature for 18 hours then washed with saturated sodium bicarbonate, dried (magnesium sulphate), evaporated and purified by flash chromatography on silica eluting with ethyl acetate/hexane (1:1) to give the title compound as an off-white solid (760mg). LC/MS: Rt=3.11, [MH^+] 326.11, 328.11

Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazole-5-carboxylate



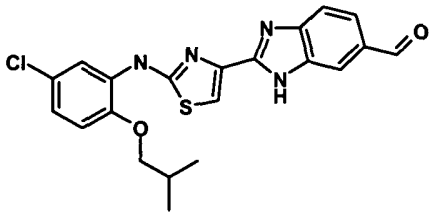
2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylic acid (1.7g. 5.2mmol), HOBT (773mg, 5.8mmol), EDAC (1.1g, 5.8mmol), N-methylmorpholine (1.15ml, 10.4mmol) and methyl 3,4-diaminobenzoate (950mg, 5.8mmol) were dissolved in dichloromethane (25ml) and the mixture stirred at room temperature for 3 hours. The mixture was washed with 5% sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated. The residue was dissolved in glacial acetic acid (5ml) and heated at 110°C for 2 hours. The solvent was evaporated and the residue re-evaporated from toluene, then purified by flash chromatography, eluting with 10-50% ethyl acetate in hexane. The product was triturated with diethyl ether and the solid filtered and dried 980mg. LC/MS Rt = 3.56min [MH^+] 457, 459.

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methanol



Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazole-5-carboxylate (980mg, 2.15mmol) was dissolved in THF (10ml) and stirred under argon. 1M Lithium aluminium hydride in diethyl ether (2.25ml, 2.25mmol) was added carefully at room temperature over 5 minutes. The reaction was stirred at room temperature for 1 hour then a few drops of water carefully added. After effervescence had subsided, ethyl acetate and water were added. The mixture was filtered through Hyflo to remove insoluble material and the organic layer washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 10-50% ethyl acetate in hexane to give a yellow oil 850mg. LC/MS Rt = 2.49min [MH^+] 429, 431.

2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazole-5-carbaldehyde

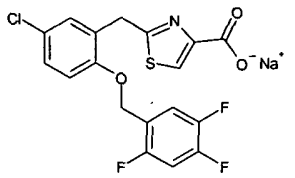


{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methanol (850mg, 1.98mmol) was dissolved in dichloromethane (15ml) and Dess-Martin

periodinane (899mg, 2.17mmol) added. The reaction was stirred at room temperature for 1 hour. The mixture was diluted with dichloromethane and washed with 5% sodium thiosulfate solution and water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 5-30% ethyl acetate in hexane 470mg.
LC/MS Rt = 3.51min [MH^+] 427, 429.

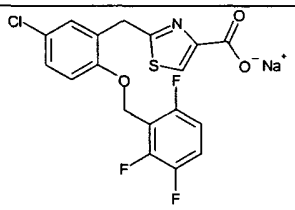
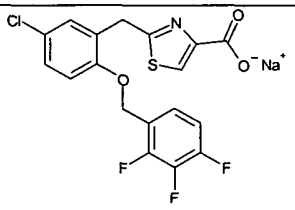
General Procedure 4:

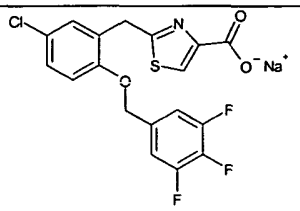
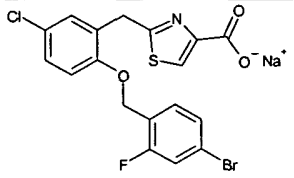
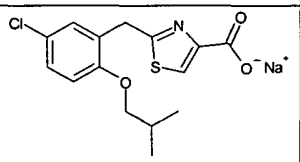
Example 18: Sodium 2-[(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate



Ethyl 2-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate (86mg, 0.195mmol) was dissolved in ethanol (1ml) and 2M sodium hydroxide solution (0.5ml) was added. The mixture was heated at 120°C for 10 minutes in a Smithcreator ®microwave. After cooling, the reaction was diluted with water and extracted with ethyl acetate (x2). The combined organics were washed with water, dried ($MgSO_4$) and evaporated. The residue was triturated with iso-hexane and diethyl ether and the product filtered and dried in vacuo (18mg). LC/MS Rt = 3.69 min, [MH^+] 414, 416.

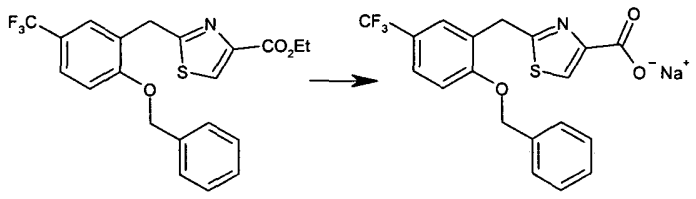
The following examples were prepared by general procedure 4 from the appropriate intermediates.

Example		Name	Data
19		Sodium 2-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.63 min, [MH^+] 414, 416.
20		Sodium 2-[(5-chloro-2-{[(2,3,4-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.78 min, [MH^+] 414, 416.

21		Sodium 2-[(5-chloro-2-{[(3,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.71 min, [MH^+] 414, 416.
22		Sodium 2-[(2-{[(4-bromo-2-fluorophenyl)methyl]oxy}-5-chlorophenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.04 min, [MH^+] 458, 460.
23		Sodium 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.58 min, [MH^+] 458, 460.

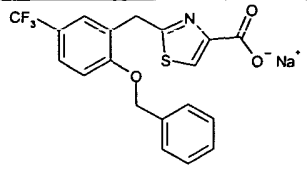
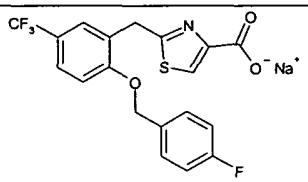
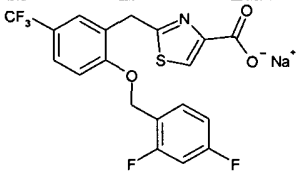
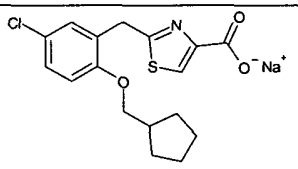
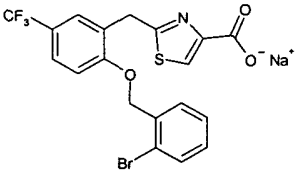
General Procedure 5

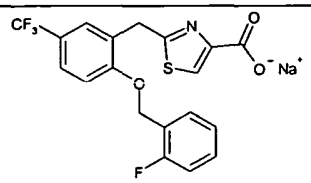
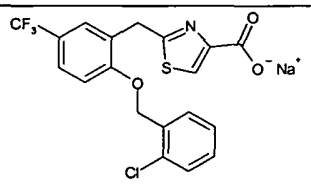
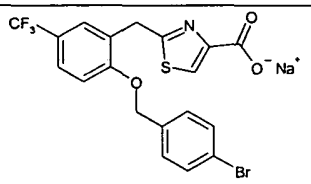
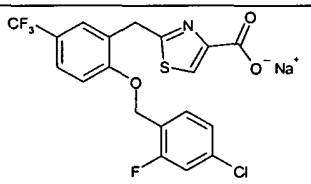
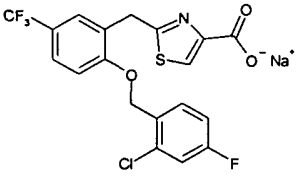
Example 24: Sodium 2-{[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate

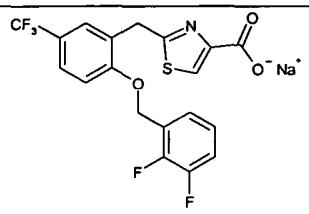
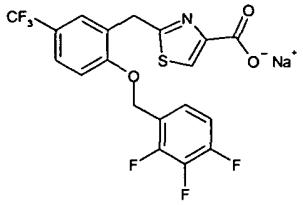
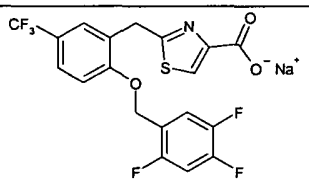
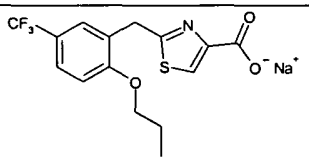
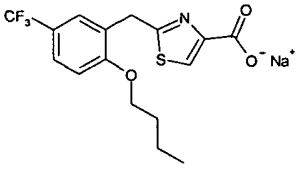
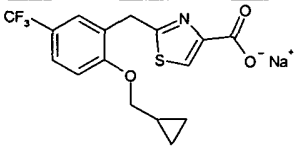


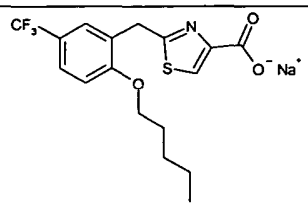
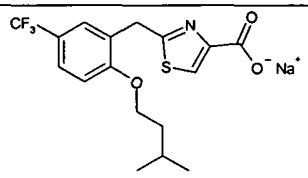
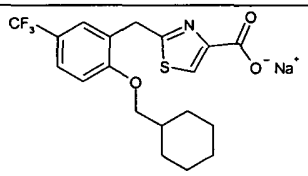
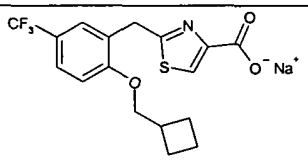
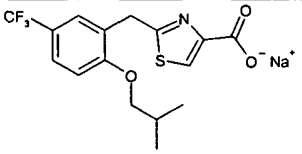
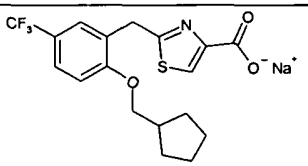
Ethyl 2-{[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate was dissolved in ethanol and excess sodium hydroxide added (either 2M sodium hydroxide solution or solid NaOH followed by H_2O). The solution was stirred from 50°C to 80°C from 1h to 3h. In some cases solid precipitated and this was filtered off and dried. When solid did not precipitate, the solvent was evaporated and the residue partitioned between ethyl acetate and water or just diluted with ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated.

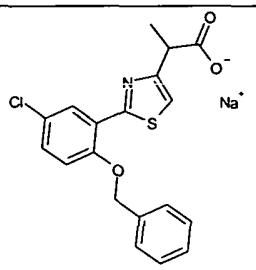
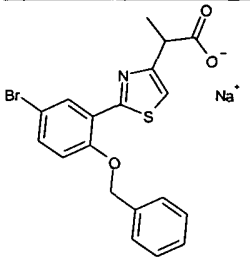
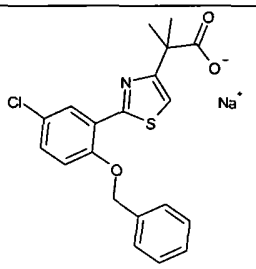
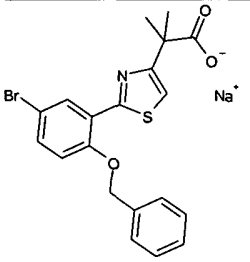
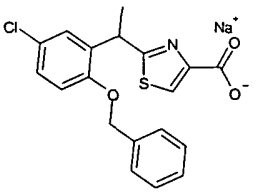
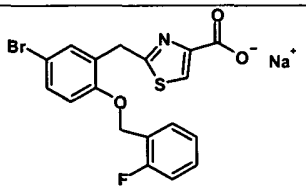
The following examples were prepared by general procedure 5 from the appropriate intermediates.

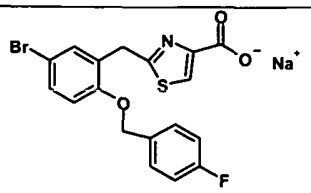
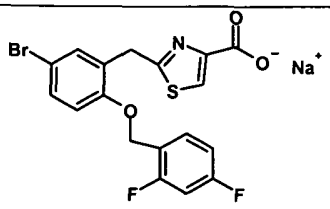
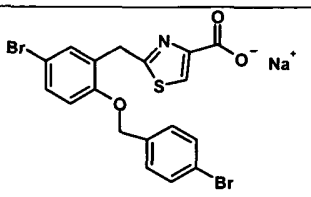
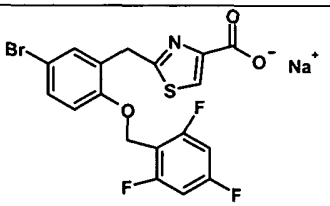
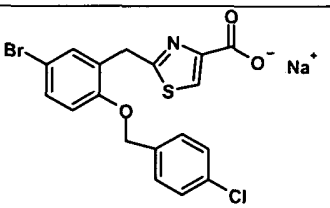
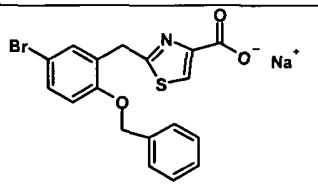
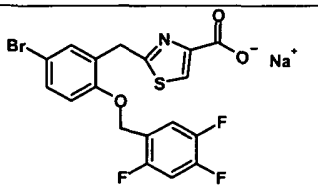
Example		Name	Data
24		Sodium 2-{[2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.27 min, [MH+] 394
25		Sodium 2-{[2-{[(4-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.14 min, [MH+] 412.
26		Sodium 2-{[2-{[(2,4-difluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.28 min, [MH+] 430.
27		Sodium 2-({5-chloro-2-[(cyclopentylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.08 min, [MH+] 352, 354.
28		Sodium 2-{[2-{[(2-bromophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.95 min, [MH+] 472, 474.

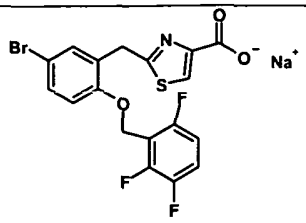
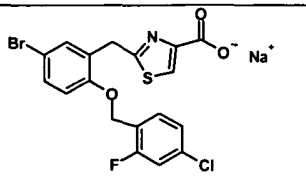
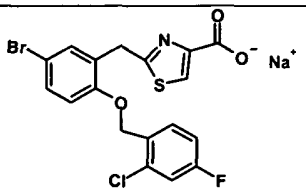
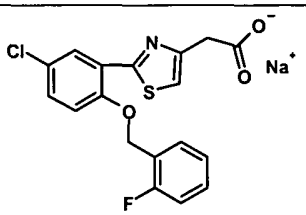
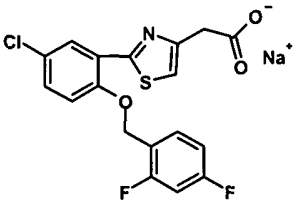
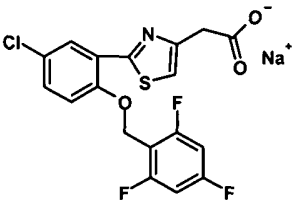
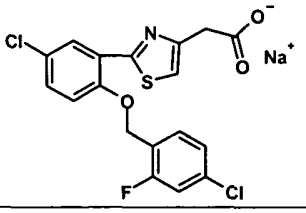
29		Sodium 2-{[2-{[(2-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.65 min, [MH^+] 412.
30		Sodium 2-{[2-{[(2-chlorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.83 min, [MH^+] 428, 430.
31		Sodium 2-{[2-{[(4-bromophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.91 min, [MH^+] 472, 474.
32		Sodium 2-{[2-{[(4-chloro-2-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.90 min, [MH^+] 446, 448.
33		Sodium 2-{[2-{[(2-chloro-4-fluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.91 min, [MH^+] 446, 448.

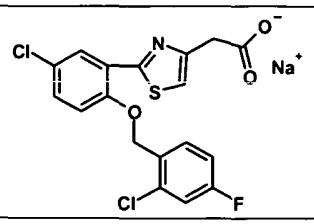
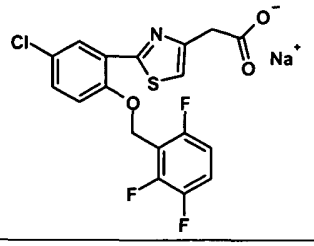
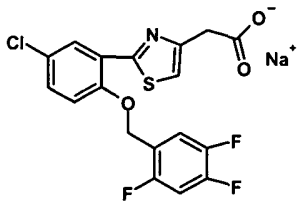
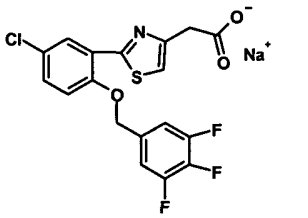
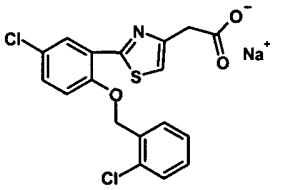
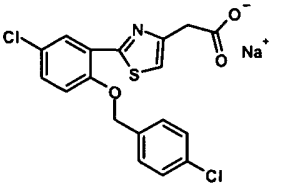
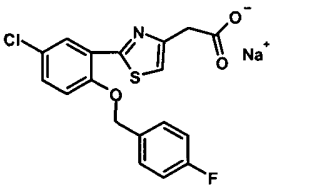
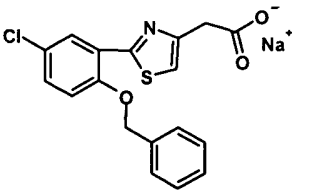
34		Sodium 2-{[2-{[(2,3-difluorophenyl)methyl]oxy}-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.69 min, [MH^+] 430.
35		Sodium 2-[(5-(trifluoromethyl)-2-{[(2,3,4-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.74 min, [MH^+] 448.
36		Sodium 2-[(5-(trifluoromethyl)-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.67 min, [MH^+] 448.
37		Sodium 2-{[2-(propyloxy)-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.51 min, [MH^+] 346.
38		Sodium 2-{[2-(butyloxy)-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.70 min, [MH^+] 360.
39		Sodium 2-{[2-[(cyclopropylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.50 min, [MH^+] 358.

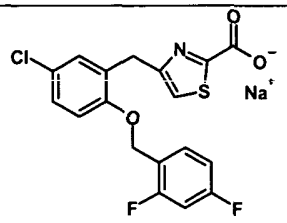
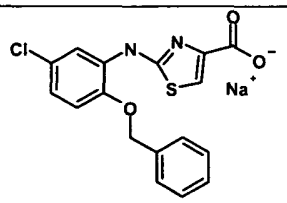
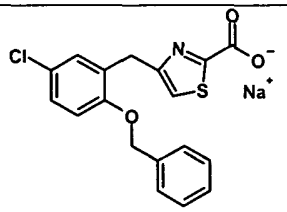
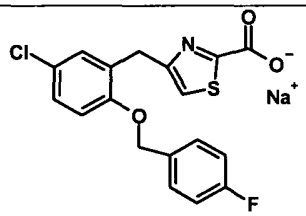
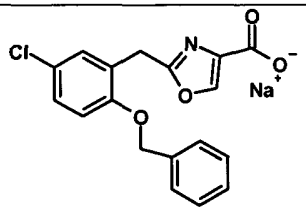
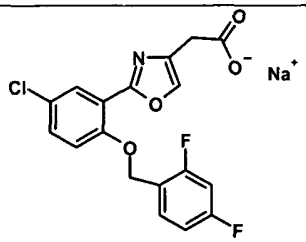
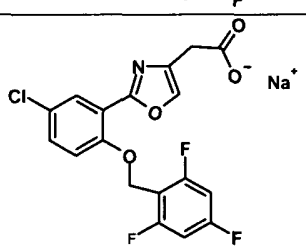
40		Sodium 2-{[2-(pentyloxy)-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.89 min, [MH^+] 374.
41		Sodium 2-{[2-[(3-methylbutyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.85 min, [MH^+] 374.
42		Sodium 2-{[2-[(cyclohexylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.13 min, [MH^+] 400.
43		Sodium 2-{[2-[(cyclobutylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.79 min, [MH^+] 372.
44		Sodium 2-{[2-[(2-methylpropyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.67 min, [MH^+] 360.
45		Sodium 2-{[2-[(cyclopentylmethyl)oxy]-5-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxylate	LC/MS Rt = 4.02 min, [MH^+] 386.

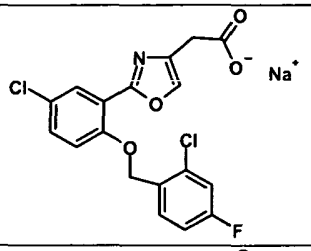
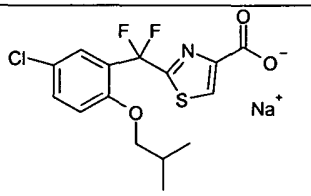
46		Sodium 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate	LC/MS Rt = 3.88 min, [MH^+] 374
47		Sodium 2-(2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)propanoate	LC/MS Rt = 3.82 min, [MH^+] 418, 420.
48		Sodium 2-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)-2-methylpropanoate	LC/MS Rt = 4.04 min, [MH^+] 388.
49		Sodium 2-(2-{5-bromo-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)-2-methylpropanoate	LC/MS Rt = 4.10 min, [MH^+] 432,434.
50		Sodium 2-(1-{5-chloro-2-[(phenylmethyl)oxy]phenyl}ethyl)-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.77 min, [MH^+] 374.
51		Sodium 2-[(5-bromo-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.4 min [MH+] 424,425

52		Sodium 2-[(5-bromo-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.52 min [MH+] 424
53		Sodium 2-[(5-bromo-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.58 min[MH+] 442,443
54		Sodium 2-[(5-bromo-2-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.71 min [MH+] 484,486
55		Sodium 2-[(5-bromo-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.46 min [MH+] 460,461
56		Sodium 2-[(5-bromo-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.7 min [MH+] 440,442
57		Sodium 2-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylate	Rt = 3.77 min [MH+] 406,407
58		Sodium 2-[(5-bromo-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.49 min [MH+] 460,461

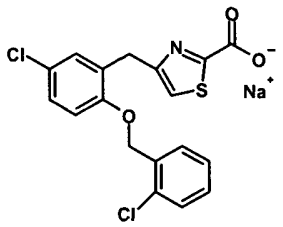
59		Sodium 2-[(5-bromo-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.3 min [MH+] 460,461
60		Sodium 2-[(5-bromo-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.83 min [MH+] 458,460
61		Sodium 2-[(5-bromo-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-4-carboxylate	Rt = 3.9 min [MH+] 458,460
62		Sodium [2-(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.51 min [MH+] 378,380
63		Sodium [2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.58 min[MH+] 396,398
64		Sodium [2-(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.5 min [MH+] 414,416
65		Sodium [2-(5-chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.75 min [MH+] 412,415

66		Sodium [2-(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.75 min [MH+] 412,416
67		Sodium [2-(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.5 min [MH+] 414,416
68		Sodium [2-(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.59 min [MH+] 414,416
69		Sodium [2-(5-chloro-2-{[(3,4,5-trifluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.62 min [MH+] 414,416
70		Sodium [2-(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.73 min [MH+] 394,398
71		Sodium [2-(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.5 min [MH+] 394
72		Sodium [2-(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)-1,3-thiazol-4-yl]acetate	Rt = 3.38 min [MH+] 378
73		Sodium (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1,3-thiazol-4-yl)acetate	Rt = 3.65 min [MH+] 360,362

74		Sodium 4-[(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.29 min [MH+] 396,398
75		Sodium 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxylate	Rt =3.77 min [MH+] 361,363
76		Sodium 4-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-2-carboxylate	Rt = 3.85 min, [MH+] 360,362.
77		Sodium 4-[(5-chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt = 4.1min, [MH+] 378.
78		Sodium 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate	Rt = 3.40 min [MH+] 344.
79		Sodium [2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.51 min [MH^+] 380.
80		Sodium [2-(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.35 min [MH^+] 398.

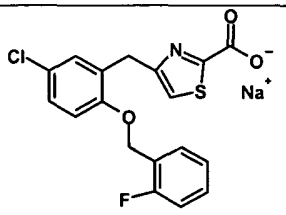
81		Sodium [2-(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)-1,3-oxazol-4-yl]acetate	Rt = 3.83 min [MH$^+$] 396.
82		Sodium 2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazole-4-carboxylate	LC/MS Rt = 3.26 min, [MH$^+$] 362, 364, [MH$^-$] 360.1, 362.1

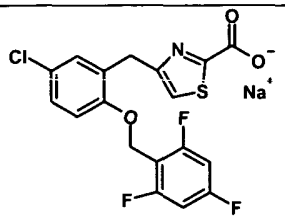
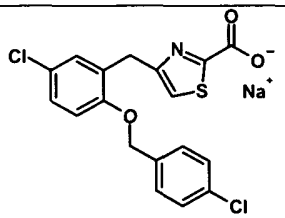
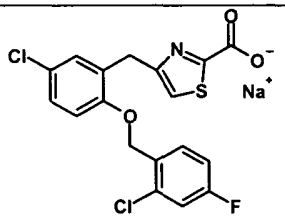
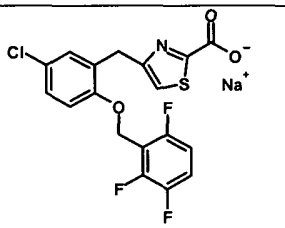
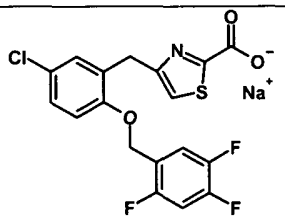
Example 83: Sodium 4-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate



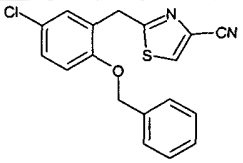
4-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxamide (54mg, 0.137mmol) was dissolved in ethanol (3ml) and water (1ml), sodium hydroxide (22mg, 0.55mmol) was added and the solution heated at 60°C for 8 hours, then at 90°C for another 10 hours. The mixture was cooled, evaporated, diluted with water and extracted with ethyl acetate (x3). The organic phase was dried, filtered and concentrated to yield the title compound. LC/MS Rt = 4.76, [MH+] 394.

The following compounds were prepared in a similar manner to sodium 4-[(5-chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate from the appropriate intermediates

Example		Name	Data
84		Sodium 4-[(5-chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.12 min [MH+] 378

85		Sodium 4-[(5-chloro-2-{[(2,4,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.0 min [MH+] 414,416
86		Sodium 4-[(5-chloro-2-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.3 min [MH+] 394
87		Sodium 4-[(5-chloro-2-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.52 min [MH+] 412
88		Sodium 4-[(5-chloro-2-{[(2,3,6-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.02 min [MH+] 414,416
89		Sodium 4-[(5-chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1,3-thiazole-2-carboxylate	Rt =4.07 min [MH+] 414,416

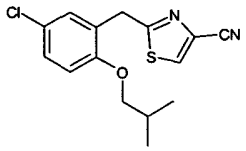
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile



2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide (632mg, 1.76mmol) was dissolved in phosphorus(III)oxychloride (6ml) and the solution heated at 90°C for 1h.

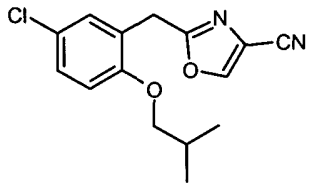
The solution was evaporated and the residue dissolved in diethyl ether and washed with water and 5% sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The orange oil was triturated with diethyl ether and iso-hexane and the cream solid filtered and dried in vacuo (600mg). LC/MS Rt = 3.78 min, [MH] 341, 343.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile



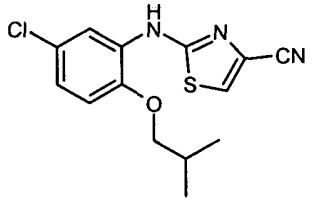
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide.
LC/MS Rt = 3.57 min, [MH^+] 307.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carbonitrile



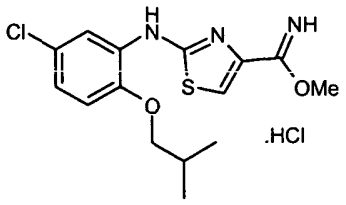
A solution of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxamide (1.16g, 3.76mmol) in phosphorus oxychloride (5ml) was stirred and heated at 75°C for one hour then poured onto ice, extracted with ether and the organic phase washed with water and saturated sodium bicarbonate solution then dried with magnesium sulphate and evaporated to dryness. The residue was purified by chromatography on a Biotage eluting with (1:9) ethyl acetate/hexane to give the title compound as a colourless gum (990mg). LC/MS Rt = 3.56, [MH^+] 291.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carbonitrile



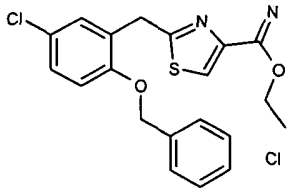
A mixture of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboxamide (690mg, 2.12mmol) and phosphorus oxychloride (5ml) was stirred and heated to reflux for one minute then cooled to room temperature. The solution was poured onto ice, extracted with ether and the organic phase washed with 2M sodium hydroxide, dried ($MgSO_4$), evaporated and purified by flash chromatography on silica eluting with ethyl acetate/hexane (15:85) to give the title compound as a white solid (510mg).
LC/MS: Rt=3.74, [MH^+] 308.17, 310.17

Methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carboximidoate hydrochloride



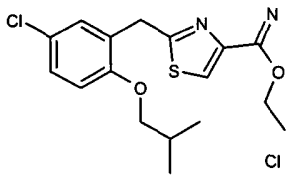
60% Sodium hydride (10mg, 0.25mmol) was added to a solution of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazole-4-carbonitrile (500mg, 1.62mmol) in methanol (20ml) and left at room temperature for 20 hours then evaporated, dissolved in ether/water and the organic phase dried ($MgSO_4$), and filtered. The resulting solution was treated with 1M hydrogen chloride in ether producing a gummy yellow precipitate. The solvent was decanted and the residue dissolved in dichloromethane/ether and evaporated to give the title compound as a yellow foam (580mg). LC/MS: Rt=2.49, [MH^+] 340.19, 342.22.

Ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride



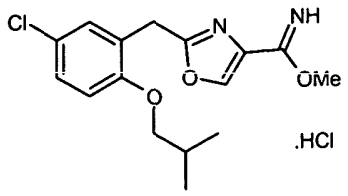
A solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile (250mg, 0.73mmol) and ethanol (40mg, 0.9mmol) in dry diethyl ether (10ml) was saturated with hydrogen chloride gas and allowed to stand for four days at 4°C. The solvent was evaporated and the residue triturated with dry diethyl ether to give the title compound as a colourless solid 200mg, 67%.

Ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride



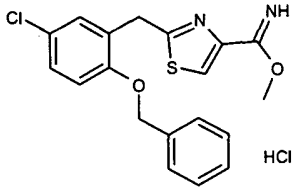
The title compound was prepared in a similar manner to ethyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile.

Methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboximidoate hydrochloride



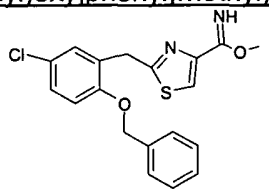
60% Sodium hydride (20mg, 0.5mmol) was added to a solution of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carbonitrile (990mg, 3.4mmol) in methanol (15ml) and left at room temperature for 16 hours then evaporated to dryness. The residue was dissolved in ether, washed with water, dried ($MgSO_4$), evaporated and treated with 1M hydrogen chloride in ether (6ml). The gum which separated crystallised on scratching and was filtered off to give the title compound as a white solid (1.05g).
LC/MS Rt = 2.89, [MH^+] 323, 325

Methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride



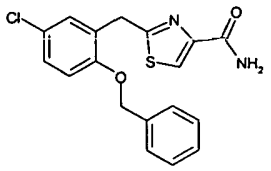
Sodium hydride, 60% in oil (100mg, 2.5mmol) was added portionwise to a solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile (1.30g, 3.82mmol) in methanol (25ml). The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue dissolved in diethyl ether (25ml). The solution was washed with water (2x10ml). The organic phase was dried, then treated with 1.0M hydrogen chloride in diethyl ether (10ml) to give the title compound as colourless solid 900mg. LC/MS Rt = 2.69 min, [MH^+] 373.

Methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate



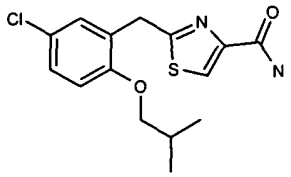
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile (1.32g, 3.87mmol) was dissolved in methanol (20ml) and NaOMe(90mg) was added, the mixture was stirred at room temperature overnight. The solvent was evaporated, redissolved with methanol and more NaOMe added, stirred for another 4 hours. The solvent was evaporated and the residue triturated with diethyl ether/hexane mixture to give the title compound as a brown solid. LC/MS Rt = 2.68min, [MH^+] 373.1, 375.2

Example 90: 2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide



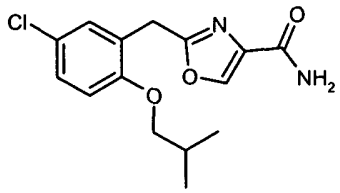
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (108mg, 0.3mmol) was dissolved in dichloromethane (5ml) and ammonium 1*H*-1,2,3-benzotriazol-1-olate (50mg, 0.33mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (60mg, 0.33mmol) and N-methylmorpholine (66µl, 0.33mmol) were added. The mixture was stirred at room temperature for 2h. The solvent was evaporated and the residue dissolved in ethyl acetate which was washed with 5% sodium bicarbonate solution (x2) and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 20 -50% ethyl acetate in iso-hexane to leave a white solid (57mg).
LC/MS Rt = 3.17 min, [MH^+] 359, 361.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide



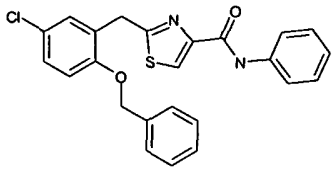
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid.
LC/MS Rt = 2.99 min, [MH^+] 325.

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxamide



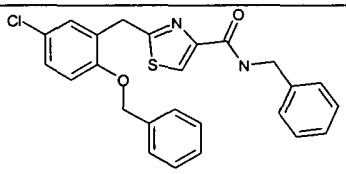
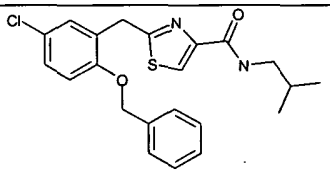
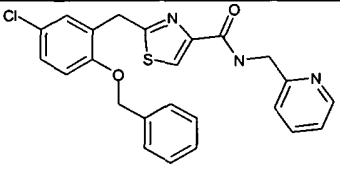
Oxalyl chloride (1ml) was added to a solution of 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid (1.21g, 3.91mmol) and DMF (1 drop) in dichloromethane (15ml) and left at room temperature for one hour. The resulting solution was evaporated to dryness and azeotroped with toluene then dissolved in dichloromethane (20ml) and aqueous ammonia (6ml) added with vigorous stirring. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to dryness to give the title compound as a white solid (1.16g). LC/MS Rt = 3.00, [MH^+] 309.

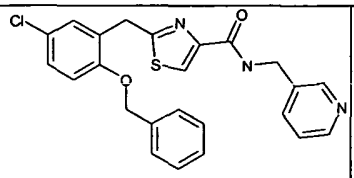
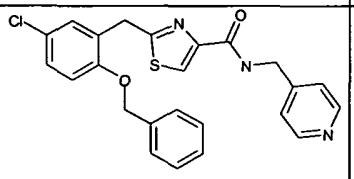
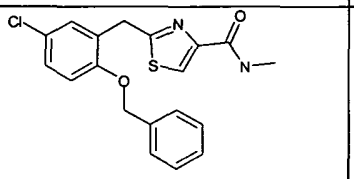
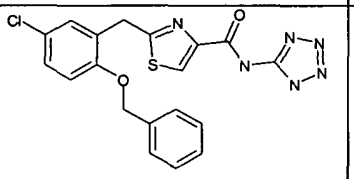
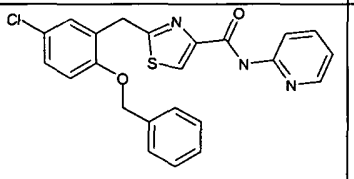
Example 91: 2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-*N*-phenyl-1,3-thiazole-4-carboxamide



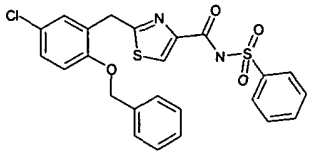
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (72mg, 0.2mmol) was dissolved in tetrahdrofuran (2ml). Aniline (20µl, 0.22mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (44mg, 0.24mmol) and N,N-dimethyl-4-pyridinamine (2mg) were added. The mixture was stirred at room temperature for 2h. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with 5% sodium bicarbonate solution, 1M hydrochloric acid and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 2% methanol in dichloromethane. The product was triturated with iso-hexane and diethyl ether to leave a cream solid (16mg). LC/MS Rt = 4.11 min, [MH$^+$] 435, 437.

The following examples were prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-*N*-phenyl-1,3-thiazole-4-carboxamide from the appropriate intermediates.

Example		Name	Data
92		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(phenylmethyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.95 min, [MH$^+$] 449, 451.
93		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(2-methylpropyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.89 min, [MH$^+$] 415, 417.
94		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(2-pyridinylmethyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.59 min, [MH$^+$] 450, 452.

95		2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-N-(3-pyridinylmethyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.43 min, [MH$^+$] 450, 452.
96		2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-N-(4-pyridinylmethyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.39 min, [MH$^+$] 450, 452.
97		2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-N-methyl-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.47 min, [MH$^+$] 373, 375.
98		2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-N-1H-tetrazol-5-yl-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.66 min, [MH$^+$] 427, 429.
99		2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-N-2-pyridinyl-1,3-thiazole-4-carboxamide	LC/MS Rt = 4.08 min, [MH$^+$] 436, 438.

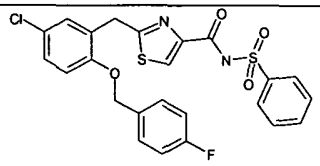
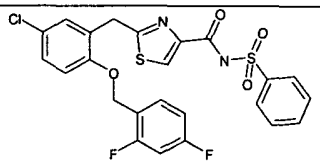
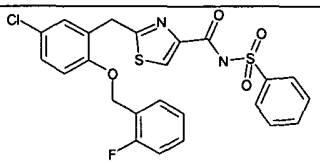
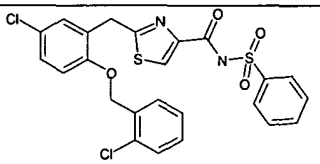
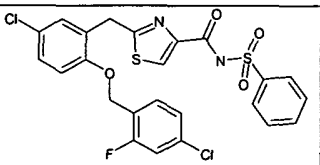
Example 100: 2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-*N*-(phenylsulfonyl)-1,3-thiazole-4-carboxamide

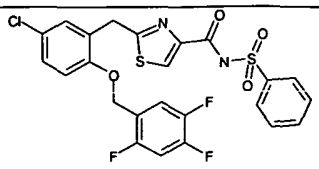
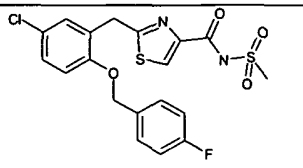
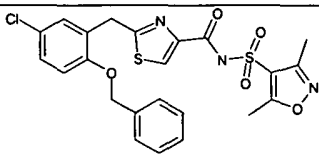


2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (130mg, 0.361mmol) was dissolved in tetrahydrofuran (1ml) and dichloromethane (1ml). Benzenesulphonamide (85mg, 0.542mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (79mg, 0.434mmol) and *N,N*-dimethyl-4-pyridinamine (5mg) were added. The mixture was stirred at room temperature for 3h. The mixture was diluted with dichloromethane and washed with 5% sodium bicarbonate solution (x2), 1M hydrochloric acid and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash

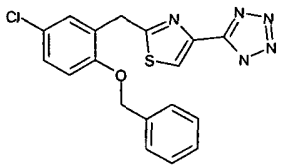
chromatography, eluting with 2% methanol in dichloromethane. The product was triturated with iso-hexane and diethyl ether and the cream solid dried *in vacuo* (102mg).
LC/MS Rt = 3.92 min, [MH^+] 499, 501.

The following examples were prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-*N*-(phenylsulfonyl)-1,3-thiazole-4-carboxamide from the appropriate intermediates.

Example		Name	Data
101		2-[(5-Chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.89 min, [MH^+] 517, 519.
102		2-[(5-Chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.95 min, [MH^+] 535, 537.
103		2-[(5-Chloro-2-{[(2-fluorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.92 min, [MH^+] 517, 519.
104		2-[(5-Chloro-2-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 4.11 min, [MH^+] 533, 535.
105		2-[(5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 4.14 min, [MH^+] 551, 553.

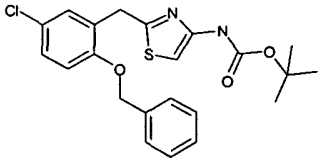
106		2-[(5-Chloro-2-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-N-(phenylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.93 min, [MH$^+$] 553, 555.
107		2-[(5-Chloro-2-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-N-(methylsulfonyl)-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.42 min, [MH$^-$] 453, 455.
108		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]-1,3-thiazole-4-carboxamide	LC/MS Rt = 3.71 min, [MH$^-$] 518, 520.

Example 109: 5-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-tetrazole



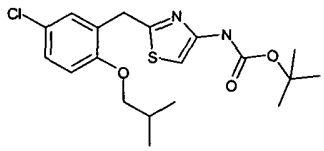
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carbonitrile (170mg, 0.5mmol) was dissolved in dimethylformamide (3ml) and sodium azide (98mg, 1.5mmol) and ammonium chloride (80mg, 1.5mmol) added. The mixture was heated at 100°C for 64h. The cooled mixture was diluted with ethyl acetate and washed with water (x4). The organic layer was dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether and the cream powder filtered and dried *in vacuo* (127mg).
LC/MS Rt = 3.84 min, [MH$^-$] 384, 386.

Example 110: 1,1-Dimethylethyl [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]carbamate



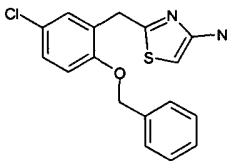
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (10.79g, 30mmol) was stirred in 2-methyl-2-propanol (100ml) under nitrogen. Triethylamine (4.62g, 33mmol) and diphenylphosphoryl azide (7.12ml, 33mmol) were added and the mixture was heated to reflux for 6h. The solvent was evaporated and the residue purified by flash chromatography, eluting with 15% ethyl acetate in iso-hexane to give the title compound as a cream solid (8.94g). LC/MS Rt = 4.18 min, [MH] 431, 433.
A second crop was obtained from slightly impure chromatography fractions which were evaporated and triturated with diethyl ether filtered and dried (1.1g)

Example 111: 1,1-Dimethylethyl [2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]carbamate



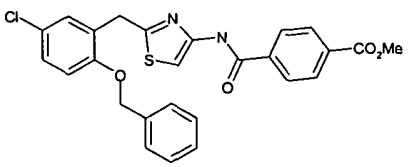
The title compound was prepared in a manner similar to 1,1-dimethylethyl [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]carbamate. LC/MS Rt = 4.04 min, [MH^+] 397.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-amine



1,1-Dimethylethyl [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]carbamate (8.94g, 20.75mmol) was dissolved in acetonitrile (50ml) and 4-toluenesulphonic acid (11.83g, 62.26mmol) added. The mixture was stirred and heated to reflux for 30 minutes, cooled and evaporated. The residue was dissolved in ethyl acetate and washed with 5% sodium bicarbonate solution (x2) and water, dried ($MgSO_4$) and evaporated. The brown residue was purified by flash chromatography, eluting with 1-2% methanol in dichloromethane to give the title compound as an orange oil which crystallised on standing (3.48g). LC/MS Rt = 3.40 min, [MH] 331, 333.

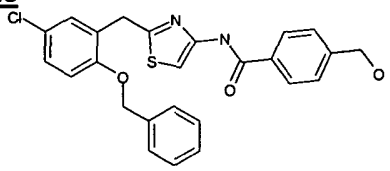
Methyl 4-({[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]amino}carbonyl)benzoate



A solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-amine (600mg, 2mmol), methyl 4-(chlorocarbonyl)benzoate (436mg, 2.2mmol) and triethylamine

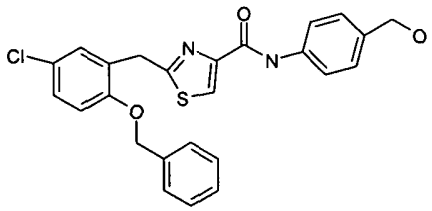
(255mg, 2.5mmol) in dichloromethane (10ml) was stirred at room temperature for 1 hour. The solvent was evaporated and the residue purified by flash chromatography eluting with 25% ethyl acetate in hexane to give the title compound as an off white solid.
LC/MS Rt = 3.76 min, [MH^+] 493.

Example 112: *N*-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-(hydroxymethyl)benzamide



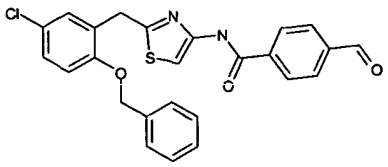
A solution of methyl 4-({[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]amino}carbonyl)benzoate (299mg, 0.4mmol) in dry tetrahydrofuran (2ml) was cooled to 0°C under argon and treated with 1.0M lithium aluminium hydride in diethyl ether (0.40ml, 0.4mmol). The reaction mixture was stirred at 0°C for 30 mins., then quenched with water (10ml). The mixture was extracted with ethyl acetate (2x10ml). The combined extracts were dried and evaporated. The residue was triturated with ethyl acetate/hexane to give the title compound as a colourless solid 160mg, 86%. LC/MS Rt = 3.33 min, [MH^+] 465.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[4-(hydroxymethyl)phenyl]-1,3-thiazole-4-carboxamide



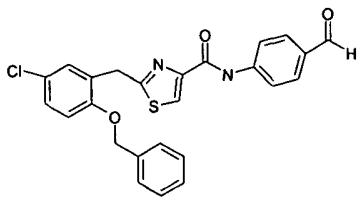
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (600mg, 1.67mmol) was dissolved in DCM, 4-methylmorpholine (0.36ml, 3.3mmol), EDAC (383mg, 2mmol), HOBt (270mg, 2mmol) and (4-aminophenyl)methanol (406mg, 3.3mmol) were added and the solution was stirred under argon overnight. The solvent was evaporated; the residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution, 0.5N HCl, brine and water. The organic phase was dried ($MgSO_4$) and evaporated to give a brown oil that was purified on a Biotage using 1-3% methanol in dichloromethane; the residue was triturated with diethyl ether and purified on a Flash Master II using 20-60% ethyl acetate in hexane. Trituration with Et_2O gave the title compound as a white solid.
LC/MS Rt = 3.36 min, [MH^+] 465,467 [MH] 463.1, 465.2

N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-formylbenzamide



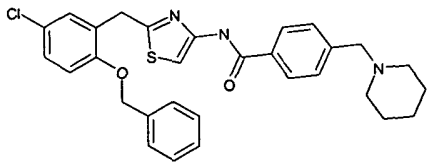
Dess-Martin periodinane (146mg, 0.34mmol) was added to a stirred solution of N-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-(hydroxymethyl)benzamide (160mg, 0.34mmol) in dry dichloromethane (2ml) and stirred at room temperature for 1 hour. 10% aqueous sodium thiosulphate (10ml) and saturated sodium hydrogen carbonate (10ml) were added. The mixture was extracted with dichloromethane (2x10ml). The combined extracts were dried and evaporated to give the title compound as a yellow oil.
LC/MS Rt = 3.61 min, [MH^+] 463.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(4-formylphenyl)-1,3-thiazole-4-carboxamide



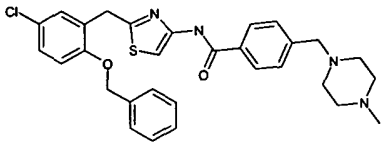
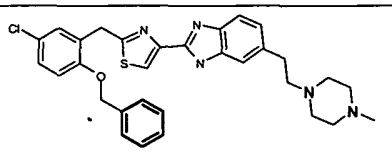
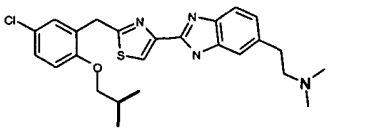
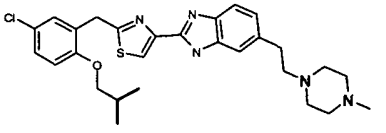
Dess-Martin periodinane (433mg, 1.02mmol) was added to a stirred solution 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[4-(hydroxymethyl)phenyl]-1,3-thiazole-4-carboxamide (473mg, 1.02mmol) in dichloromethane (20ml) and a drop of water and stirred at room temperature for 1 hour. The reaction was quenched with10% aqueous sodium thiosulphate, washed with saturated sodium hydrogen carbonate, and the organic phase dried ($MgSO_4$) and evaporated to give the title compound as solid (520mg).
LC/MS Rt = 3.7 min, [MH^+] 463.1, 465 [MH^-] 461.1, 463.1

Example 113: N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-(1-piperidinylmethyl)benzamide

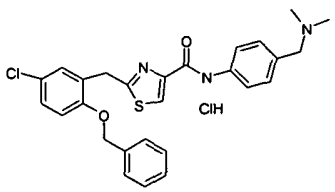


A mixture of N-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-formylbenzamide (157mg, 0.34mmol), piperidine (29mg, 0.34mmol), acetic acid (20mg,0.34mmol) and sodium triacetoxyborohydride (71mg, 0.34mmol) in dry dichloromethane (2ml) was stirred at room temperature overnight. The solvent was evaporated and the residue purified by flash chromatography eluting with 3% methanol in dichloromethane to give the title compound as a yellow oil.
LC/MS Rt = 2.53 min, [MH^+] 532.

The following examples were prepared in a similar manner to N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-(1-piperidinylmethyl)benzamide *from the appropriate intermediates*

Example		Name	LC/MS
114		*N*-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-4-[(4-methyl-1-piperazinyl)methyl]benzamide	Rt = 2.46min., [MH$^+$] 546.
115		2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-benzimidazole	Rt = 2.17 min., [MH$^+$] 558
116		(2-{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazol-5-yl}ethyl)dimethylamine	Rt = 2.33 min., [MH$^+$] 469
117		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-benzimidazole	Rt = 2.27 min., [MH$^+$] 524

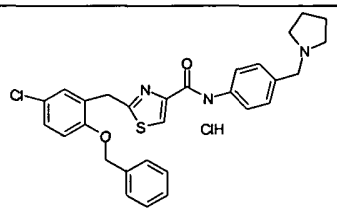
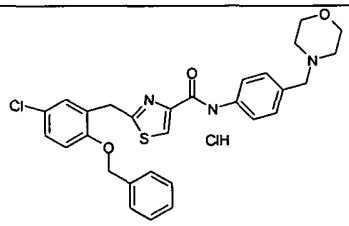
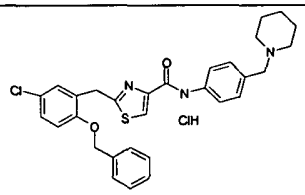
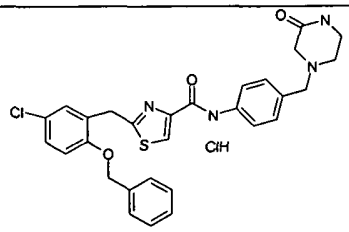
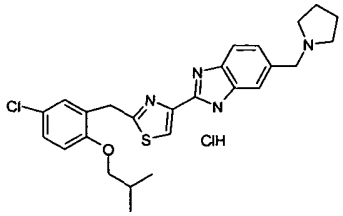
Example 118: 2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-{4-[(dimethylamino)methyl]phenyl}-1,3-thiazole-4-carboxamide hydrochloride

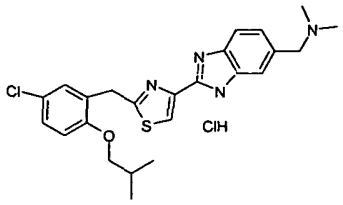
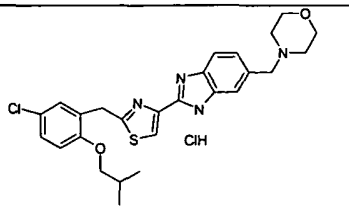
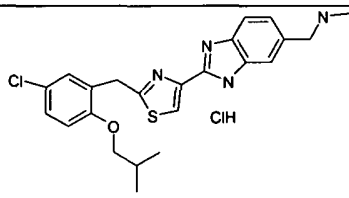


Sodium triacetoxyborohydride (69mg, 0.32mmol) was added to a stirred solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(4-formylphenyl)-1,3-thiazole-4-carboxamide (75mg, 0.16mmol) and dimethylamine (18 µl, 0.32mmol) in THF (4ml). The mixture was stirred at room temperature over the weekend. More sodium triacetoxyborohydride was added and the mixture stirred for another 20h. Diluted with H_2O and extracted with ethyl

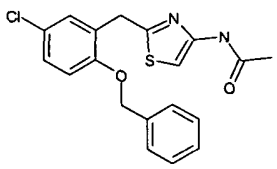
acetate (x3), combined organics dried and evaporated. The residue was first purified on a Flash Master II (8% of methanol in dichloromethane), followed by purification on a MDAP. The oil obtained was treated with 1M HCl in Et_2O to give a white solid.
LC/MS Rt = 2.44 min, [MH] 490.2, 492.1

The following compounds were prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-{4-[(dimethylamino)methyl]phenyl}-1,3-thiazole-4-carboxamide hydrochloride from the appropriate intermediates

Example		Name	LC/MS
119		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[4-(1-pyrrolidinylmethyl)phenyl]-1,3-thiazole-4-carboxamide hydrochloride	LC/MS Rt = 2.55 min, [MH^+] 518.3 [MH] 516.1, 518.1
120		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[4-(4-morpholinylmethyl)phenyl]-1,3-thiazole-4-carboxamide hydrochloride	LC/MS Rt = 2.5 min, [MH^+] 534.3 [MH] 532.2, 534.2
121		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[4-(1-piperidinylmethyl)phenyl]-1,3-thiazole-4-carboxamide hydrochloride	LC/MS Rt = 2.56 min, [MH^+] 532.3 [MH] 530.2
122		2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-{4-[(3-oxo-1-piperazinyl)methyl]phenyl}-1,3-thiazole-4-carboxamide hydrochloride	LC/MS Rt = 2.55 min, [MH^+] 547.1 [MH] 545.2
123		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(1-pyrrolidinylmethyl)-1H-benzimidazole hydrochloride	LC/MS Rt = 2.34min, [MH^+] 481.1 [MH] 479.1, 481.2

124		({2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methyl)dimethylamine hydrochloride	LC/MS Rt = 2.34min, [MH]⁺ 453.1, 455.2
125		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-morpholinylmethyl)-1H-benzimidazole hydrochloride	LC/MS Rt = 2.23min, [MH⁺] 497.1 [MH]⁺ 495.2, 497.2
126		({2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methyl)methylamine hydrochloride	LC/MS Rt = 2.25min, [MH⁺] 441.2 [MH]⁺ 439.2, 441.2

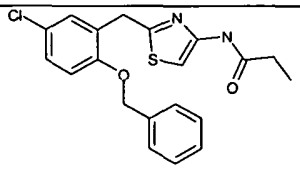
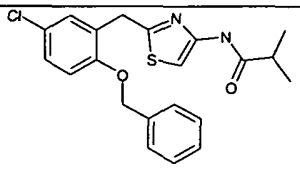
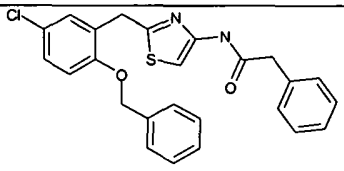
Example 127: *N*-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]acetamide



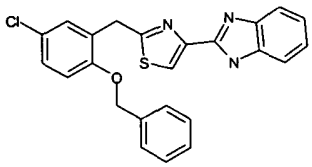
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-amine (100mg, 0.3mmol) was dissolved in dichloromethane (2ml) and triethylamine (50µl, 0.36mmol) added, followed by acetyl chloride (24µl, 0.33mmol). The reaction was stirred at room temperature for 2h. The mixture was diluted with diethyl ether and washed with 1M hydrochloric acid, 5% sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 10-20% ethyl acetate in iso-hexane. The product was triturated with iso-hexane and diethyl ether to give the title compound (26mg). LC/MS Rt = 3.52 min, [MH]⁺ 373, 375.

The following examples were prepared in a similar manner to *N*-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]acetamide from the appropriate intermediates.

Example		Name	Data

128		N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]propanamide	LC/MS Rt = 3.68 min, [MH⁺] 387, 389.
129		N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-2-methylpropanamide	LC/MS Rt = 3.84 min, [MH⁺] 401, 403.
130		N-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-2-phenylacetamide	LC/MS Rt = 3.98 min, [MH⁺] 449, 451.

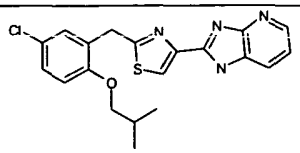
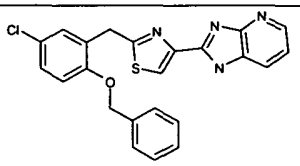
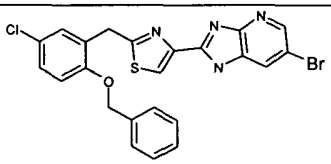
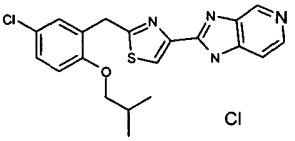
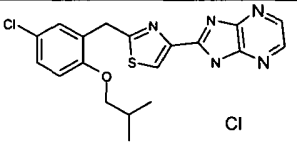
Example 131: 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole

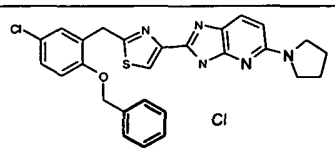
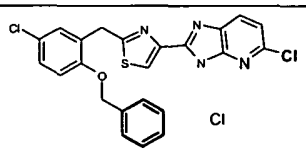
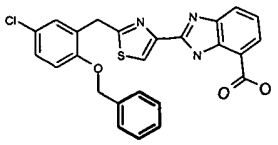
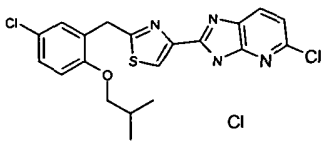


A mixture of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (200mg, 0.55mmol) and1,2-phenylenediamine (60mg, 0.55mmol) in phosphorus oxychloride (1ml) was heated at 100°C for 30 mins. The reaction mixture was cooled, and poured onto ice (50ml). The mixture was neutralized with saturated sodium hydrogen carbonate and extracted with ethyl acetate (2x20ml). The combined extracts were dried and evaporated, the residue was purified by chromatography, eluting with 2% methanol in dichloromethane to give the title compound as a brown solid 50mg 20%.
LC/MS Rt = 2.81 min, [MH⁺] 432.

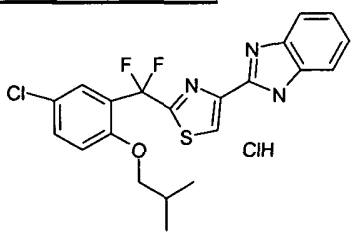
The following compounds were made in a manner similar to 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole using the appropriate intermediates.

Hydrochloride salts were prepared by stirring a solution of benzimidazole product in 1.0M hydrogen chloride in diethyl ether (2ml) for 15mins. The solvent was evaporated and the products were obtained by trituration of the solid with diethyl ether/hexane.

Example		Name	Data
132		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine	LC/MS Rt = 3.11 min, [MH$^+$] 399.
133		2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine	LC/MS Rt = 2.95 min, [MH$^+$] 433.
134		6-Bromo-2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine	LC/MS Rt = 3.48 min, [MH$^+$] 510, 512.
135		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-c]pyridine hydrochloride	LC/MS Rt = 2.29 min, [MH$^+$] 399.
136		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyrazine hydrochloride	LC/MS Rt = 3.17 min, [MH$^+$] 400.

137		2-[2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-1,3-thiazol-4-yl]-5-(1-pyrrolidinyl)-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt = 2.72 min, [MH$^+$] 502.
138		5-Chloro-2-[2-({5-chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt = 3.47 min, [MH$^+$] 467.
139		2-[2-({5-Chloro-2-[(phenylmethyl)oxy] phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole-4-carboxylic acid	LC/MS Rt = 3.24 min, [MH$^+$] 476.
140		5-Chloro-2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt = 3.52 min, [MH$^+$] 432.

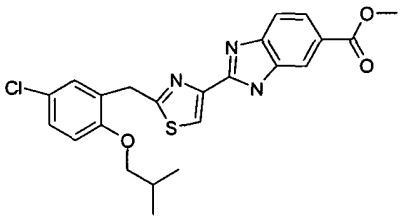
Example 141: 2-{2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazol-4-yl}-1H-benzimidazole hydrochloride



2-[{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazole-4-carboxylic acid (125mg, 0.345mmol) and 1,2-phenylenediamine (37mg, 0.345mmol) in phosphorus oxychloride (1.5ml) was heated at 100°C for 4h. The reaction mixture was cooled, and poured onto ice neutralized with potassium carbonate and extracted with ethyl acetate

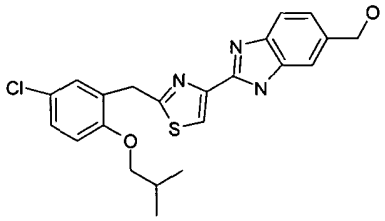
(x3). The combined extracts were dried and evaporated; the residue was purified using a FLEX. The residue was redissolved in methanol and 3ml of 1M HCl in Et_2O added, stirred for 15 minutes, evaporated and triturated with Et_2O to give the title compound as a white solid. LC/MS Rt = 3.44 min, [MH^+] 434.2, 436.2, [MH^-] 432.06, 434.05.

Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole-5-carboxylate



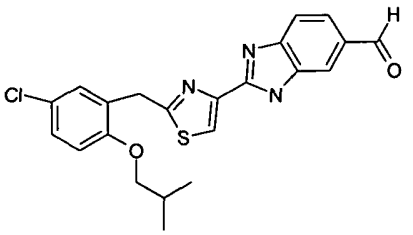
The title compound was prepared in a similar manner to 2-{2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazol-4-yl}-1H-benzimidazole hydrochloride using 1.2 equivalent of the methyl 3,4-diaminobenzoate.
LC/MS Rt = 3.58min, [MH^+] 456.1, 458, [MH^-] 454.1, 456.1

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methanol



Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole-5-carboxylate (0.35mmol) was dissolved in THF, cooled at -10°C under argon, 1M $LiAlH_4$ in THF (0.35ml) was added, allowed to warm to room temperature. More $LiAlH_4$ (0.35ml) was added, the mixture stirred for other 2 h, then quenched with water and extracted with diethyl ether(x4). The combined organic phases were dried ($MgSO_4$), evaporated and purified on a Biotage using 2-4% of methanol in dichloromethane.
LC/MS Rt = 2.62min, [MH^+] 428.2, 430.2, [MH^-] 426.1, 428.

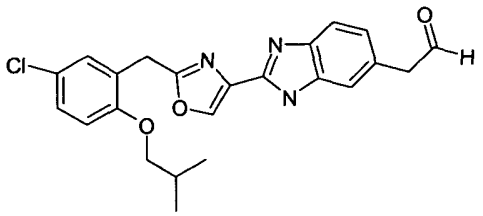
2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole-5-carbaldehyde



The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-(4-formylphenyl)-1,3-thiazole-4-carboxamide.

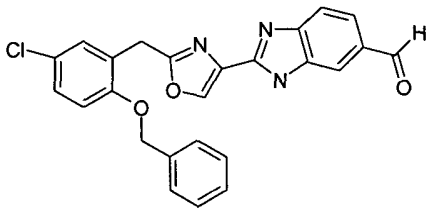
LC/MS Rt = 3.47 min, [MH^+] 426.2, 428.1 [MH] 424

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}acetaldehyde



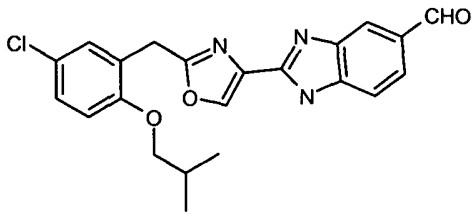
2-{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}ethanol (353mg, 0.829mmol) was dissolved in THF(6ml). Dess Martin periodinane (352mg, 0.829mmol) was added and the mixture was stirred at room temperature for 1 hour. Diluted with DCM and washed with 10% aqueous sodium thiosulphate followed by saturated sodium hydrogen carbonate. The organic phase was dried and evaporated to give the title compound as a yellow solid (345mg). LC/MS Rt = 3.0, [MH^+] 424.1, 426.1.

2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carbaldehyde



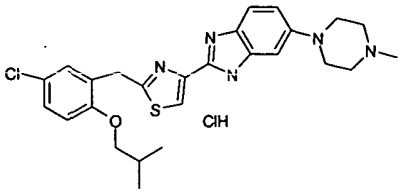
The title compound was prepared in a similar manner to {2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}acetaldehyde. LC/MS Rt =3.28, [MH^+] 444.1, 446.1

2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carbaldehyde



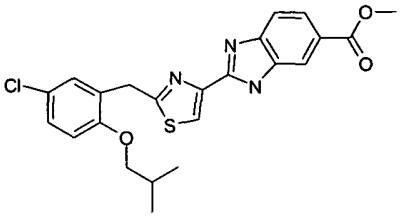
Prepared in a similar manner to {2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}acetaldehyde using {2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methanol. LC/MS Rt =3.32, [MH^+] 410.1, 412.1

Example 142: 2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole hydrochloride



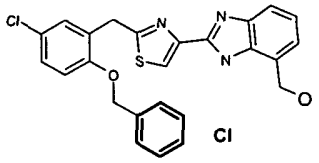
The title compound was prepared in a similar manner to 2-{2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazol-4-yl}-1H-benzimidazole hydrochloride. LC/MS Rt = 2.14 min, [MH^+] 496.1 [MH^-] 494.2, 496.3, 497.3.

Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole-5-carboxylate



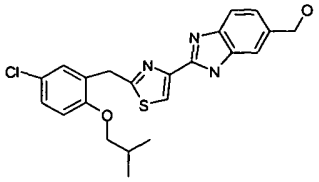
The title compound was prepared in a similar manner to 2-{2-[{5-chloro-2-[(2-methylpropyl)oxy]phenyl}(difluoro)methyl]-1,3-thiazol-4-yl}-1H-benzimidazole hydrochloride using 1.2 equivalent of the methyl 3,4-diaminobenzoate.
LC/MS Rt = 3.58min, [MH^+] 456.1, 458, [MH^-] 454.1, 456.1

Example 143: {2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-4-yl}methanol hydrochloride



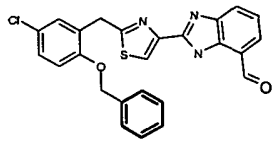
A solution of methyl 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole-4-carboxylate hydrochloride (200mg, 0.41mmol) in dry tetrahydrofuran (5ml) was treated with 1.0M lithium aluminium hydride in THF (0.45ml, 0.45mmol) and stirred at room temperature for 1 hour. The reaction was quenched by the careful addition of 2M sodium hydroxide solution. The mixture was extracted with ethyl acetate (3x5ml). The combined extracts were washed with water, dried and evaporated. Trituration of the residue with diethyl ether gave the title compound as an off-white solid 160mg 84%.
LC/MS Rt = 2.60min., [MH^+] 462.

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}methanol



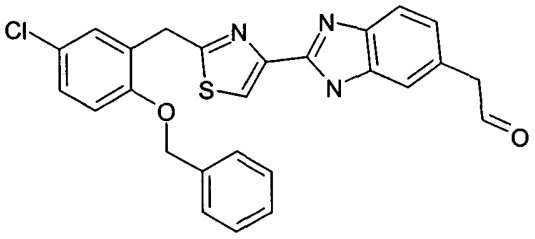
Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1*H*-benzimidazole-5-carboxylate(0.35mmol) was dissolved in THF, cooled at -10°C under argon, 1M $LiAlH_4$ in THF (0.35ml) was added, allowed to warm to room temperature. More $LiAlH_4$ (0.35ml) was added, the mixture stirred for another 2 h, then quenched with water and extracted with diethyl ether (x4). The combined organic phases were dried ($MgSO_4$), evaporated and purified on a Biotage using 2-4% of methanol in dichloromethane.
LC/MS Rt = 2.62min, [MH^+] 428.2, 430.2, [MH] 426.1, 428

2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole-4-carbaldehyde



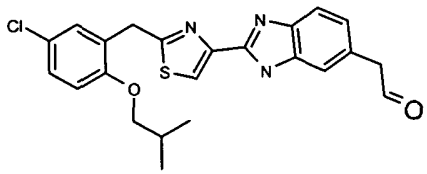
Dess-Martin periodinane (148mg, 0.35mmol) was added, under argon, to a stirred solution of {2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-4-yl}methanol (160mg, 0.35mmol) in dry dichloromethane (10ml). The reaction mixture was stirred at room temperature for 2 hours. Saturated aqueous sodium hydrogen carbonate (5ml) and 10% aq. sodium thiosulphate (5ml) were added. The organic phase was separated dried and evaporated to give the title compound as a brown gum.
LC/MS Rt = 3.51min., [MH^+] 460.

{2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}acetaldehyde



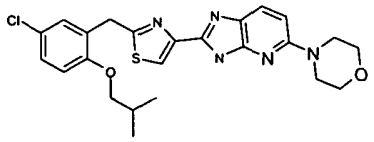
The title compound was prepared in a similar manner to 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole-4-carbaldehyde using 2-{2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}ethanol. Crude product used without purification.

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}acetaldehyde



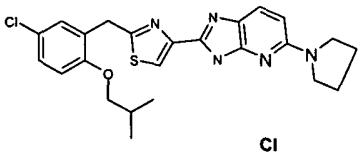
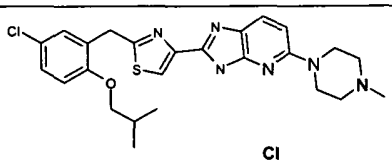
The title compound was prepared in a similar manner to 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazole-4-carbaldehyde using 2-{2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}ethanol. Crude product used without purification.

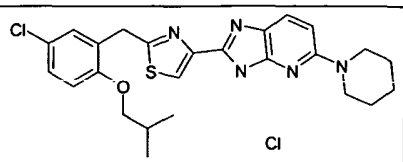
Example 144: 2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-morpholinyl)-1H-imidazo[4,5-b]pyridine



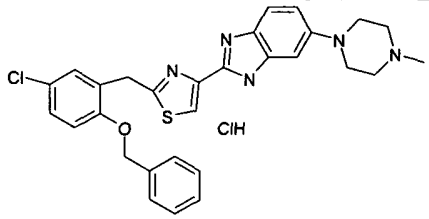
A solution of 5-chloro-2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine (50mg, 0.1mmol), morpholine (34mg, 0.4mmol), and methanesuphonic acid (38mg, 0.4mmol) in 1,4-dioxane (1ml) was heated, in a microwave, to 180°C for 11 hours. The reaction mixture was cooled to room temperature and diluted with methanol (5ml). The solvent was evaporated and the residue dissolved in ethyl acetate (10ml). The solution was washed with saturated sodium hydrogen carbonate, water and brine. The organic phase was dried and evaporated and the residue purified by MDAP to give the title compound as a colourless solid.
LC/MS Rt = 3.07 min, [MH^+] 484.

The following compounds were prepared in a similar manner to 2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-morpholinyl)-1H-imidazo[4,5-b]pyridine using the appropriate amine.

Example		Name	Data
145		2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-thiazol-4-yl]-5-(1-pyrrolidinyl)-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt= 2.69 min, [MH^+] 468.
146		2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt= 2.21 min, [MH] 495.

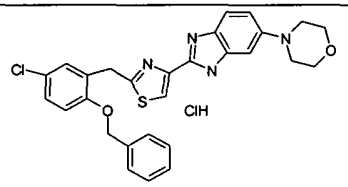
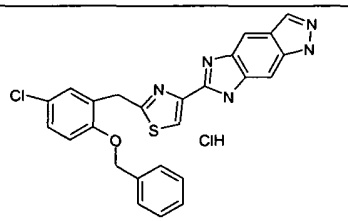
147		[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-thiazol-4-yl]-5-(1-piperidinyl)-1H-imidazo[4,5-b]pyridine hydrochloride	LC/MS Rt= 3.24 min, [MH$^+$] 482.

Example 148: 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1H-benzimidazole hydrochloride

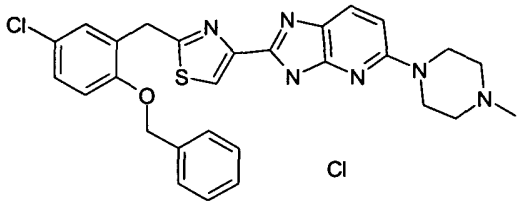


Methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride (200mg, 0.49mmol) was dissolved in EtOH (4ml) and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (59mg, 0.54mmol) was added and the mixture heated at 90°C for 3h.The solvent was evaporated and the residue was diluted with water, basified with 2M NaOH and extracted with ethyl acetate (x5). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified on a Biotage using DCM/MeOH gradient mixture to give a solid. The solid was treated with 1M HCl in Et_2O to give the title compound. LC/MS Rt = 2.06 min, [MH$^+$] 530.1, 533.2 [MH$^-$] 528.2, 530.2.

The following compounds were prepared in a manner similar to 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1H-benzimidazole hydrochloride

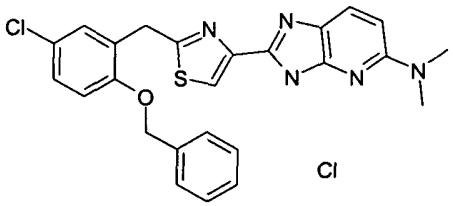
Example		Name	Data
149		2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl) -1,3-thiazol-4-yl]-5-(4-morpholinyl)-1H-benzimidazole hydrochloride	LC/MS Rt = 2.65 min, [MH$^+$] 517.1, 519.1, 521.1 [MH$^-$] 515.2, 517.1
150		6-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl) -1,3-thiazol-4-yl]-1,5-dihydroimidazo[4,5-f]indazole hydrochloride	LC/MS Rt = 2.64 min, [MH$^+$] 472, 474 [MH$^-$] 470.1, 472.1

Example 151: 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1H-imidazo[4,5-b]pyridine hydrochloride



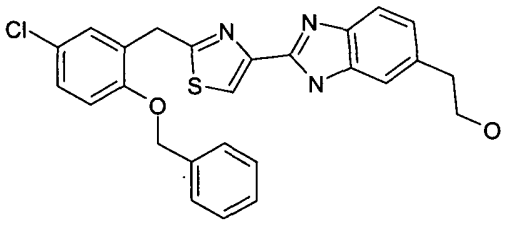
A solution of 5-chloro-2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine hydrochloride (100mg, 0.21mmol) in 1-methyl-2-pyrrolidinone (2ml) was treated with 1-methylpiperazine (0.5ml, large excess) and water (a few drops). The mixture was heated in a microwave at 200°C for 6 hours. The mixture was partitioned between ethyl acetate (25ml) and water (25ml). The aqueous phase was extracted with ethyl acetate (20ml). The combined organics were washed with water (3x10ml), dried and evaporated. Purification of the residue by flash chromatography eluting with 5% methanol in dichloromethane followed by conversion to the hydrochloride salt by treatment with hydrogen chloride in diethyl ether gave the title compound as a pale yellow solid 20mg LC/MS Rt = 2.29min., [MH^+] 531.

Example 152: 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-N,N-dimethyl-1H-imidazo[4,5-b]pyridin-5-amine hydrochloride



The title compound was prepared in a similar manner to 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-(4-methyl-1-piperazinyl)-1H-imidazo[4,5-b]pyridine hydrochloride using 5-chloro-2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-imidazo[4,5-b]pyridine and 40% aqueous dimethylamine. LC/MS Rt = 2.70 min., [MH^+] 476.

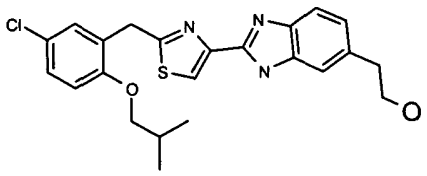
Example 153: 2-{2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}ethanol



A mixture of methyl 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride (450mg, 1.1mmol) and 2-(3,4-diaminophenyl)ethanol

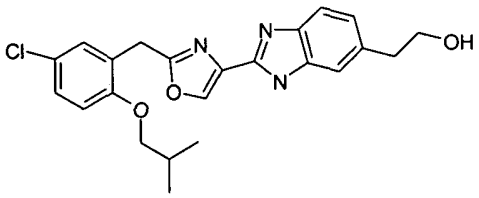
(182mg, 1.2 mmol) in ethanol (10ml) was refluxed for 1 hour.The mixture was cooled to room temperature and the solvent evaporated. Purification of the residue by flash chromatography eluting with 30-60% ethyl acetate in hexane followed by 5% methanol in dichloromethane gave the title compound as a pale yellow solid 180mg 34%. LC/MS Rt = 2.51min., [MH^+] 476.

Example 154: 2-{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-benzimidazol-5-yl}ethanol



A solution of N-[2-amino-5-(2-hydroxyethyl)phenyl]-2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide (660mg, 1.44mmol) in glacial acetic acid (5ml) was refluxed for 2hours. The mixture was cooled, diluted with water (20ml) and extracted with ethyl acetate (2x10ml). The combined extracts were washed with saturated sodium hydrogen carbonate, water and brine. The organic phase was dried and evaporated. Purification of the residue by flash chromatography eluting with 30-60% ethyl acetate in hexane followed by 5% methanol in dichloromethane gave the title compound as a pale yellow solid 100mg. LC/MS Rt = 2.53 min., [MH^+] 442.

2-{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}ethanol



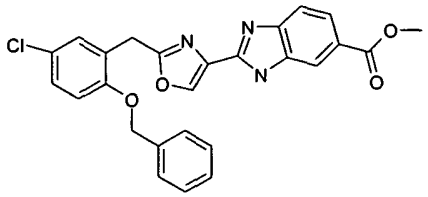
2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid (900mg, 2.9mmol), EDAC (666mg, 3.49mmol), HOBt (471mg, 3.49mmol), 4-methylmorpholine(5.8mmol, 638 µl) and 2-(3,4-diaminophenyl)ethanol (530mg, 3.49mmol) were stirred at room temperature in dichloromethane (30ml) for 3 hours. Diluted with more DCM and washed with a saturated solution of sodium bicarbonate and water. The organic phase was dried and evaporated to give a dark oil that was purified on a 50g SPE Si column with 5% of methanol in ethyl acetate to give a yellow oil (530 mg).

The yellow oil (530mg) was dissolved in 5ml of acetic acid and heated at 110°C for 30 minutes. The mixture was then diluted with water, extracted with EtOAc (x3), the combined organics were washed with saturated sodium bicarbonate solution (x3), dried ($MgSO_4$) and evaporated.

The residue was chromatographed using a mixture of hexane/ethyl acetate to give the title compound as a yellow solid (157mg).

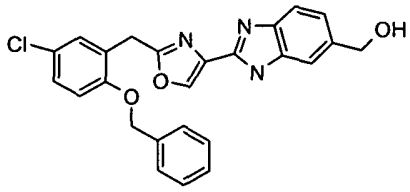
LC/MS Rt = 2.61, [MH^+] 426.2, 428.2, [MH-] 424.2, 426.2

Methyl 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carboxylate



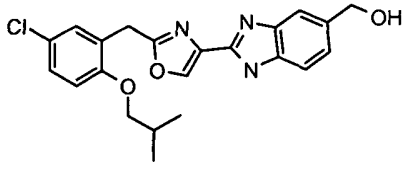
The title compound was prepared in a similar manner to 2-{2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1H-benzimidazol-5-yl}ethanol. LC/MS Rt = 3.41, [MH$^+$] 474.2, 476.2

{2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methanol



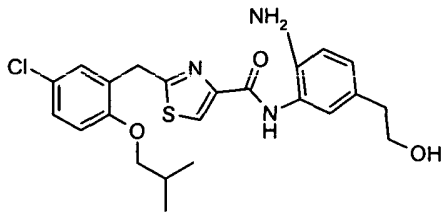
Methyl 2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carboxylate (648mg, 1.36mmol in THF (8ml) under argon was cooled to -10°C, 1.0M lithium aluminium hydride in THF (1.5ml) was added. The reaction mixture was warmed to room temperature, more $LiAlH_4$ (0.35ml) was added and solution stirred for another 40 minutes. The mixture was quenched with water, diluted with diethyl ether, filtered off insoluble solid on celite, aqueous extracted with ethyl ether (x3), dried and evaporated. The residue was purified on an SPE column using hexane/ethyl acetate gradient to give the title compound as an orange solid(400mg).
LC/MS Rt = 2.57, [MH$^+$] 446.1, 448.1

{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methanol



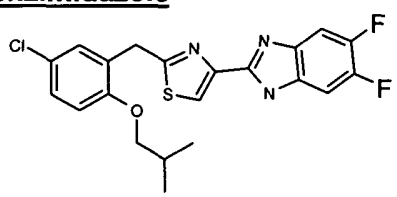
Was prepared in a similar manner to {2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methanol using methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carboxylate as starting material. LC/MS Rt = 2.61, [MH+] 412.2, 414.3

N-[2-Amino-5-(2-hydroxyethyl)phenyl]-2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide



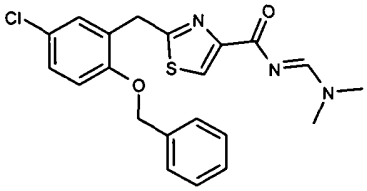
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-phenyl-1,3-thiazole-4-carboxamide using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid and 2-(3,4-diaminophenyl)ethanol. LC/MS Rt = 3.23 min., [MH^+] 460.

Example 155: 2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5,6-difluoro-1H-benzimidazole



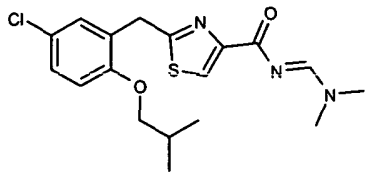
A mixture of ethyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboximidoate hydrochloride (100mg, 0.26mmol) and 4,5-difluoro-1,2-phenylenediamine (45mg, 0.3mmol) in ethanol (5ml) was heated at 80°C for 2 hours. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was separated, dried and evaporated. Purification by column chromatography gave the title compound. LC/MS Rt = 3.62 min, [MH^+] 434.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide



A solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide (500mg, 1.4mmol) in dimethylformamide dimethyl acetal (2ml) was heated at 120°C for two hours. The reaction mixture was allowed to cool to room temperature. The title compound crystallised and was collected by filtration 400mg, 70%.
^{1}H NMR ($CDCl_3$) δ: 3.18(3H, s), 3.19(3H, s), 4.43(2H, s) 5.09(2H, s), 6.86(1H, d), 7.12-7.76(7H, m), 8.15(1H,s), 8.67(1H, s).

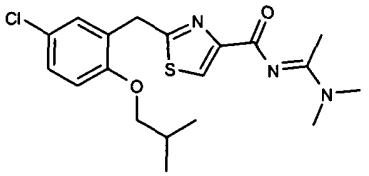
2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-*N*-[(1*E*)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide



The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide.

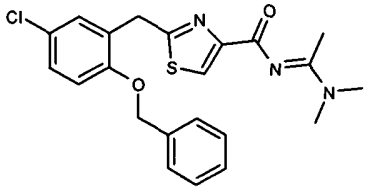
^{1}H NMR (CDCl3) δ: 0.96(6H, d), 2.03-2.09(1H, m), 3.18(3H, s), 3.20(3H,s), 3.71(2H,d), 4.39(2H, s), 6.79(1H, s), 7.18-7.24(2H, m), 8.15(1H, s), 8.67(1H,s).

2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-N-[(1E)-1-(dimethylamino)ethylidene]-1,3-thiazole-4-carboxamide



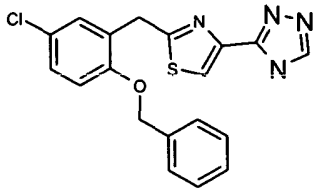
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide using 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxamide and dimethylacetamide dimethylacetal. The product was used directly without purification.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-1-(dimethylamino)ethylidene]-1,3-thiazole-4-carboxamide



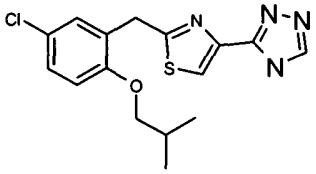
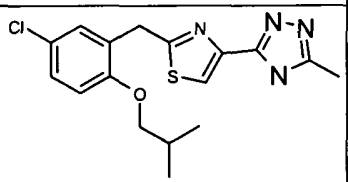
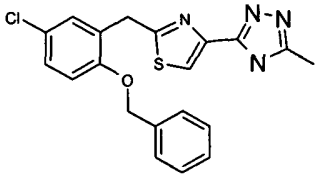
The title compound was prepared in a similar manner to 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide using dimethylacetamide dimethylacetal. The product was used directly without purification.

Example 156: 3-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-1,2,4-triazole

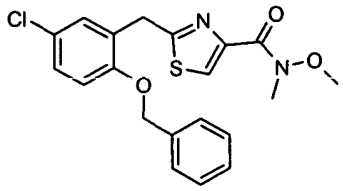


A mixture of hydrazine hydrate (18mg, 0.35mmol) and 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-[(1E)-(dimethylamino)methylidene]-1,3-thiazole-4-carboxamide (133mg, 0.32mmol) in glacial acetic acid (1ml) was refluxed for 1 hour. The reaction mixture was cooled to room temperature, the solvent was evaporated and the residue triturated with ethyl acetate/hexane to give the title compound as a pale yellow solid 70mg, 57%. LC/MS Rt = 2.90 min, [MH^+] 383.

The following examples were prepared in a similar manner to 3-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-1,2,4-triazole from the appropriate intermediates.

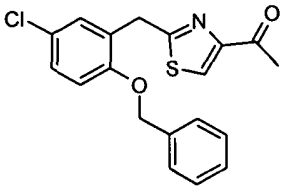
Example		Name	Data
157		3-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-1H-1,2,4-triazole	LC/MS Rt = 2.96 min, [MH^+] 349.
158		3-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-methyl-1H-1,2,4-triazole	LC/MS Rt = 2.95 min, [MH^+] 363.
159		3-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]-5-methyl-1H-1,2,4-triazole	LC/MS Rt = 2.89 min, [MH^+] 397.

2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-methyl-N-(methyloxy)-1,3-thiazole-4-carboxamide



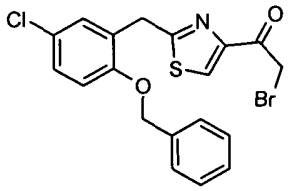
2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazole-4-carboxylic acid (360mg, 1.0mmol) was dissolved in dichloromethane (5ml) and N-methylmorpholine (202mg, 2mmol), N-hydroxybenzotriazole hydrate (184mg, 1.2mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (230mg, 1.2mmol) and O,N-dimethylhydroxylamine hydrochloride (116mg, 1.2mmol) were added. The reaction mixture was stirred at room temperature overnight. Then the mixture was diluted with ethyl acetate (20ml) and washed with saturated sodium hydrogen carbonate, 2M hydrochloric acid, water and brine. The organic phase was dried and evaporated. Purification of the residue by chromatography eluting with 20% ethyl acetate in hexane gave the title compound as a colourless solid 340mg, 80%. LC/MS Rt = 3.22 min, [MH^+] 403.

1-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]ethanone



A solution of 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-N-methyl-N-(methyloxy)-1,3-thiazole-4-carboxamide (340mg, 0.84mmol) in dry tetrahydrofuran(5ml) was cooled to 0°C and treated with 3.0M methylmagnesium bromide in diethyl ether (0.330ml, 0.9 mmol). The mixture was stirred at 0°C for 30 minutes, then diluted with diethyl ether(10ml). The solution was washed with 2M hydrochloric, and water. The organic phase was dried and evaporated to give the title compound as an off-white solid 250mg 83%.
LC/MS Rt = 3.37 min, [MH^+] 358.

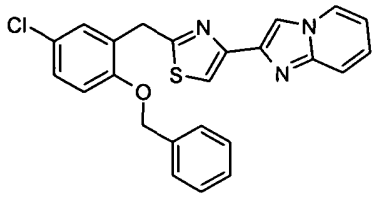
2-Bromo-1-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]ethanone



Bromine (112mg, 0.7mmol) was added to a solution of 1-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]ethanone (250mg, 0.7mmol) in chloroform (5ml). The mixture was refluxed for 1hour, a further portion of bromine (112mg, 0.7mmol) was added and reflux continued for another hour. The reaction mixture was cooled to room temperature, the solvent was evaporated and the residue

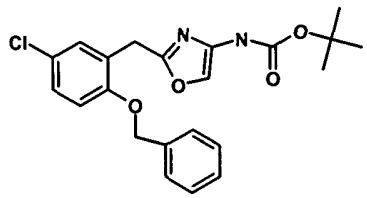
chromatographed eluting with 5% ethyl acetate in hexane to give the title compound as a colourless oil 130mg 43%. LC/MS Rt = 3.61 min, [MH^+] 436, 438.

Example 160: 2-[2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]imidazo[1,2-a]pyridine



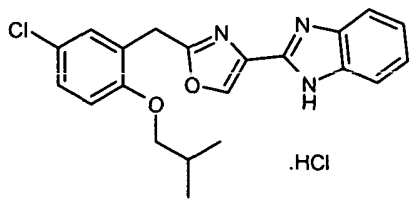
A mixture of 2-bromo-1-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-thiazol-4-yl]ethanone (130mg, 0.3mmol) and 2-aminopyridine (56mg, 0.6mmol) in ethanol (5ml) was refluxed for 1 hour. The mixture was cooled and the solvent evaporated. The residue was partitioned between ethyl acetate and water. The organic phase was separated dried and evaporated. Trituration of the residue with diethyl ether gave the title compound as an off-white soild 70mg 54%. LC/MS Rt = 2.65 min, [MH^+] 432.

Example 161: 1,1-Dimethylethyl [2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]carbamate



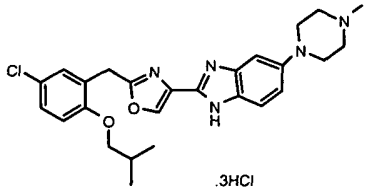
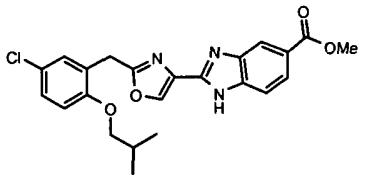
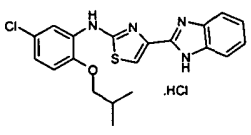
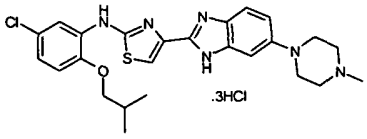
Sodium 2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylate was suspended in water and acidified with 2M hydrochloric acid and extracted with ethyl acetate (x3), the combined organic phases were dried, filtered and evaporated to give the free acid, 150mg. 2-({5-Chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboxylic acid (150mg, 0.43mmol) was dissolved in t-butanol (5ml), triethylamine (73 µl, 0.52mmol) and diphenyl phosphorylazide (104µl,0.48mmol) were added and the resulting solution was refluxed for 5 hours. After cooling the mixture was evaporated and the residue was purified by flash chromatography with 10% of ethyl acetate in iso-hexane to yield the title compound as a white solid.
^{1}H NMR ($CDCl_3$)δ:1.49 (9H,s), 4.04 (2H,s), 5.05(2H,s), 6.69(1H,bs), 6.84(1H,d), 7.17-7.23(2H,m), 7.30-7.40(5H,m), 7.67(1H,bs).

Example 162: 2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole hydrochloride

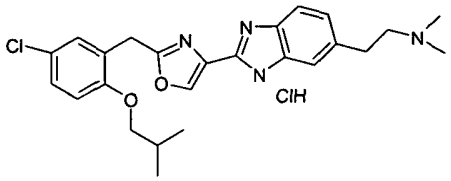


A mixture of methyl 2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazole-4-carboximidoate hydrochloride (72mg, 0.2mmol) and 1,2-phenylenediamine (27mg, 0.25mmol) in methanol (4ml) was stirred and refluxed for 4 hours. The resulting solution was cooled, diluted with ether/water and basified with 2M sodium hydroxide. The organic phase was dried with magnesium sulphate, evaporated and purified by chromatography on a Biotage eluting with (1:3) ethyl acetate/hexane. The product was dissolved in dichloromethane and 1M hydrogen chloride in ether (1ml) was added. The solution was evaporated to dryness to give the title compound as a solid (70mg).
LC/MS Rt = 3.00, [MH^+] 382, 384

The following compounds were prepared in a similar manner to 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole hydrochloride.

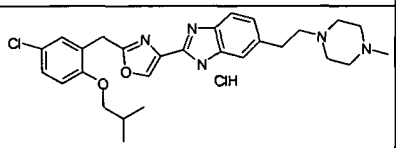
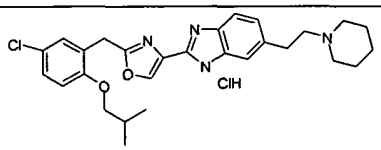
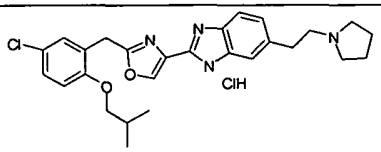
Example		Name	Data
163	 .3HCl	2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole trihydrochloride	LC/MS Rt = 2.06, [MH-] 478.2, 480.2
		Methyl 2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazole-5-carboxylate	LC/MS Rt = 3.44, [MH+] 440.1, 442.1
164	 .HCl	4-(1*H*-Benzimidazol-2-yl)-*N*-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}-1,3-thiazol-2-amine hydrochloride	LC/MS Rt=2.81 $[MH]^+$ 399.19, 401.19
165	 .3HCl	*N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1,3-thiazol-2-amine trihydrochloride	LC/MS Rt=2.03 $[MH]^-$ 495.21, 497.19

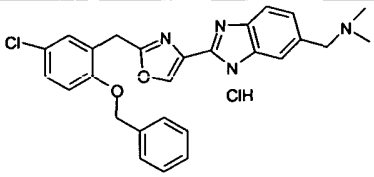
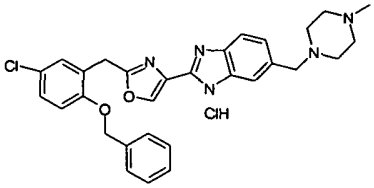
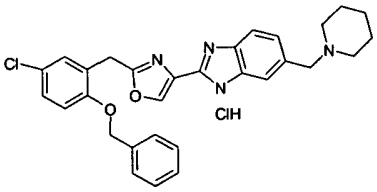
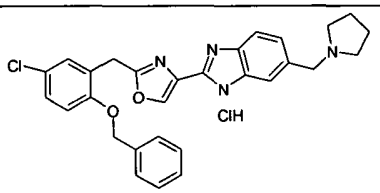
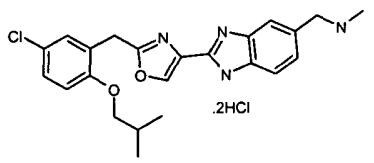
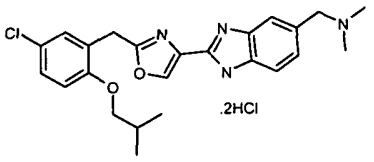
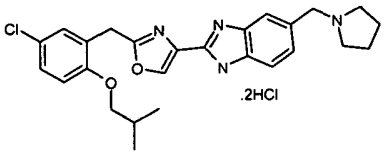
Example 166: (2-{2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}ethyl)dimethylamine hydrochloride

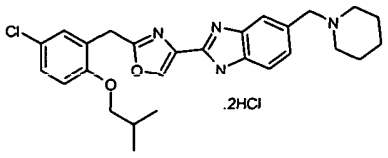
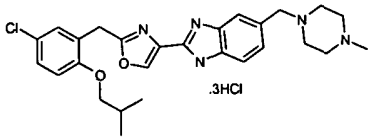


A mixture of {2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}acetaldehyde (86mg, 0.2mmol), sodium triacetoxyborohydride (129mg, 0.6mmol) and dimethylamine (108 µl, 0.6mmol, 5.6M in EtOH) in THF (4ml) was stirred at room temperature over the weekend. Diluted with H_2O and extracted with ethyl acetate (x3), combined organics dried and evaporated. The residue was purified on MDAP, solvent was evaporated, redissolved in methanol, treated with 1M HCl in Et_2O and evaporated to give the title compound. LC/MS Rt = 2.24, [MH$^+$] 451.2, 453.2

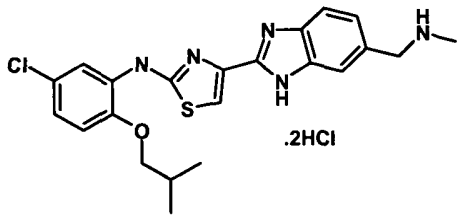
The following examples were prepared in a similar manner to (2-{2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}ethyl)dimethylamine hydrochloride:

Example		Name	Data
167		2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.1, [MH$^+$] 506.3, 508.2
168		2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.19, [MH$^+$] 493.2, 496.2 [MH$^+$] 491.3, 493.2
169		2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.19, [MH$^+$] 479.2, 481.2, 482.2 [MH$^+$] 477.3, 479.2

170		({2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methyl)dimethylamine hydrochloride	LC/MS Rt = 2.2, [MH]⁺ 471.3, 473.2
171		2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-5-[(4-methyl-1-piperazinyl)methyl]-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.1, [MH]⁺ 526.2, 528.2
172		2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-5-(1-piperidinylmethyl)-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.22, [MH]⁺ 511.3, 513.2
173		2-[2-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-5-(1-pyrrolidinylmethyl)-1*H*-benzimidazole hydrochloride	LC/MS Rt = 2.25, [MH]⁺ 497.2, 499.2
174		({2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methyl)methylamine dihydrochloride	LC/MS Rt = 2.23, [MH]⁺ 423.15, 425.11
175		({2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-1*H*-benzimidazol-5-yl}methyl)dimethylamine dihydrochloride	LC/MS Rt = 2.24, [MH]⁺ 437.17, 439.15
176		2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3-oxazol-4-yl]-5-(1-pyrrolidinylmethyl)-1*H*-benzimidazole dihydrochloride	LC/MS Rt = 2.24, [MH]⁺ 463.2, 465.2

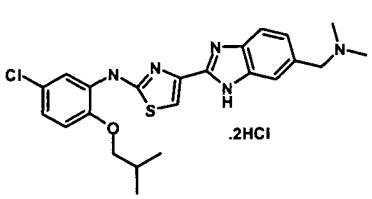
177	 .2HCl	2-[2-({5-chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-(1-piperidinylmethyl)-1*H*-benzimidazole dihydrochloride	LC/MS Rt = 2.32, [MH$^+$] 477.18, 479.16
178	 .3HCl	2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl} methyl)-1,3-oxazol-4-yl]-5-[(4-methyl-1-piperazinyl)methyl]-1*H*-benzimidazole trihydrochloride	LC/MS Rt = 2.08, [MH$^+$] 492.2, 494.3

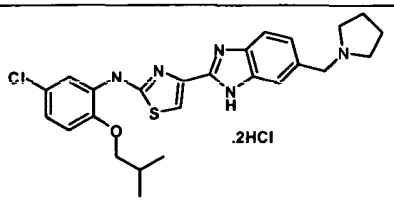
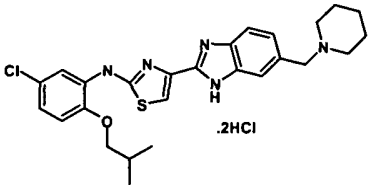
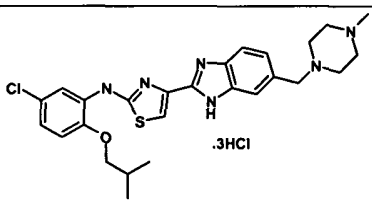
Example 179: *N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-{5-[(methylamino)methyl]-1*H*-benzimidazol-2-yl}-1,3-thiazol-2-amine hydrochloride


.2HCl

2-[2-({5-Chloro-2-[(2-methylpropyl)oxy]phenyl}amino)-1,3-thiazol-4-yl]-1H-benzimidazole-5-carbaldehyde (90.5mg, 0.21mmol) was dissolved in THF (2ml) and 40 wt% methylamine in water (33ul, 0.42mmol) and sodium triacetoxyborohydride (137mg, 0.63mmom) added. The reaction was stirred under argon at room temperature for 2 hours. Ethyl acetate and water were added and the organic layer dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 2-20% methanol in dichloromethane. The product was dissolved in dichloromethane (1ml) and 1M HCl in diethyl ether (1ml) added. The solid was isolated by decantation and dried 32mg. LC/MS Rt = 2.21, [MH$^+$] 442, 444.

The following examples were prepared in a similar manner to *N*-{5-chloro-2-[(2-methylpropyl)oxy]phenyl}-4-{5-[(methylamino)methyl]-1*H*-benzimidazol-2-yl}-1,3-thiazol-2-amine hydrochloride:

Example		Name	Data
180	 .2HCl	*N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-{5-[(dimethylamino)methyl]-1*H*-benzimidazol-2-yl}-1,3-thiazol-2-amine hydrochloride	LC/MS Rt = 2.27, [MH+] 456, 458

181	 .2HCl	*N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-[5-(1-pyrrolidinylmethyl)-1*H*-benzimidazol-2-yl]-1,3-thiazol-2-amine	LC/MS Rt = 2.34, [MH+] 482, 484
182	 .2HCl	*N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-[5-(1-piperidinylmethyl)-1*H*-benzimidazol-2-yl]-1,3-thiazol-2-amine	LC/MS Rt = 2.41, [MH+] 496, 498
183	 .3HCl	*N*-{5-Chloro-2-[(2-methylpropyl)oxy]phenyl}-4-{5-[(4-methyl-1-piperazinyl)methyl]-1*H*-benzimidazol-2-yl}-1,3-thiazol-2-amine	LC/MS Rt = 2.16, [MH+] 511, 513

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. Prostaglandin receptors that may be investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

Biological Activity at EP_1 and EP_3 Receptors

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-4, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected

using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable (pCIN; BioTechniques 20(1996): 102-110) vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 100μM flurbiprofen and 10μg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing Fluo-4 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

Binding Assay for the Human Prostanoid EP_1 Receptor

Competition assay using [^{3}H]-PGE2.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E_2 ([^{3}H]-PGE_2) for binding to the human EP_1 receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP_1 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10μg/ml puromycin and 10μM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na_2EDTA) and 10μM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na_2EDTA, 140mM NaCl, 10μM indomethacin (pH 7.4). The cells are homogenised using a Polytron

tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed (optional) three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na_2EDTA, 10mM $MgCl_2$ (pH 6). Aliquots are frozen at –80°C until required.

For the binding assay the cell membranes, competing compounds and [^{3}H]-PGE_2 (3nM final assay concentration) are incubated in a final volume of 100µl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques to determine the concentration of compound producing 50% inhibition of specific binding (IC_{50}).

Biological Activity at TP Receptor

To determine if a compound has agonist or antagonist activity at the TP receptor a functional calcium mobilisation assay may be performed. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of TP receptors by the stable TXA_2 mimetic U46619 (9,11-dideoxy-11α,9α-epoxy-methanoprostaglandin F2 α; commercially available from e.g Sigma-Aldrich). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of U46619 can mobilise. The net effect is to displace the U46619 concentration-effect curve. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-4, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software. The agonist activity of the compounds are determined by their ability to cause an increase in intracellular mobilisation in the absence of U46619.

The human TP calcium mobilisation assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable (pCIN; BioTechniques 20(1996): 102-110) vector containing TP cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 100µM flurbiprofen and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for

introduction into a 96-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing Fluo-4 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of U46619 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by U46619 (pIC_{50}) may then be estimated, and the percentage activation caused by the compounds directly can be used to determine if there is any agonism present.

Results

The compounds of examples 1-183 were tested in the binding assay for the human prostanoid EP_1 receptor. The results are expressed as pIC_{50} values. A pIC_{50} is the negative $logarithm_{10}$ of the IC_{50}. The results given are averages of a number of experiments. The compounds of examples 1-6, 8-160 and 162-183 had a pIC_{50} value ≥6. More particularly, the compounds of examples 9-18, 22-24, 26, 27, 29-34, 36, 37, 39, 41, 43-45, 51-54, 56-61, 65, 71, 73, 74, 76-78, 83-87, 89, 100-109, 115-117, 122-126, 132, 135, 136, 138, 140, 142, 146, 148-154, 162-169, 174-180 and 183 exhibited a pIC_{50} value ≥7.5. The compounds of examples 7 and 161 exhibited pIC_{50} values of <6.

The compounds of examples 46-49, 50, 79-81, 91-99, 101-108, 110-121, 124-37, 139, 140-155, 158-160, and 164-183 (free bases or sodium salts) were tested in the human EP_1 calcium mobilisation assay. The results are expressed as functional pK_i values. A functional pKi is the negative $logarithm_{10}$ of the antagonist dissociation constant as determined in the human EP_1 calcium mobilisation assay. The results given are averages of a number of experiments. The compounds of examples 46-49, 50, 94-96, 98, 101-108, 111, 113-117, 124-126, 129-137, 139, 140, 142, 144-155, 158-160, 164, 166-178, and 183 exhibited a functional pKi value >6. More particularly, the compounds of examples 98, 106, 108, 135, 136, 144 and 154 exhibited a functional pKi value of ≥ 7.5. The compounds of examples 79-81, 91-93, 97, 99, 110, 112, 118-121, 127, 128, 141, 143, 165, and 179-182 exhibited a functional pKi value <6.

The compounds of examples 46-50, 79-82, 90-99, 101-137, 139-160, and 166-183 (free bases or sodium salts) were tested in the human EP_3 calcium mobilisation assay. The results are expressed as functional pK_i values. A functional pKi is the negative $logarithm_{10}$ of the antagonist dissociation constant as determined in the human EP_3 calcium mobilisation assay. The results given are averages of a number of experiments. The compounds of examples 46, 47, 49, 50, 79-82, 90-93, 95-99, 101, 104-108, 110-137, 139-160, and 166-183 exhibited a functional pKi value of ≤6.5. The compounds of examples

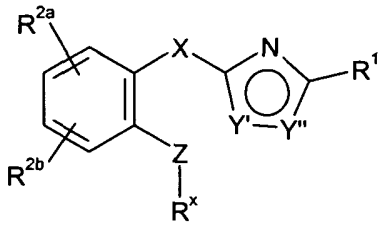
50, 79-82, 91-93, 95, 97, 99, 104, 107, 108, 110, 112-126, 129-131, 133, 136, 139-147, 149, 151-154, 156, 157, 159, 160, and 166-183 showed no activity in a functional assay.

No toxicological effects were observed in these tests.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compounds of formula (I):

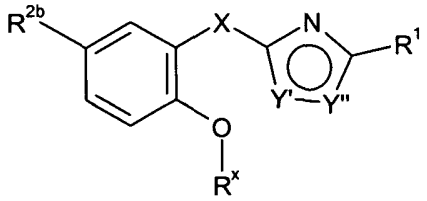


(I)

wherein:
either Y' is CH and Y" is O or S, or Y' is O or S and Y" is CH thus forming an oxazole or a thiazole ring;
X is CR^7R^8, O, NR^4, S, SO, or SO_2, or X is a bond;
Z is O, S, SO or SO_2;
R^x is optionally substituted C_{3-10}alkyl, optionally substituted C_{3-10}alkenyl, optionally substituted C_{3-10}alkynyl, optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl, or optionally substituted CQ^aQ^b-aryl;
R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, $NR^4CO_2R^6$, NR^4COR^6 or 1,2,4-triazol-3-yl optionally substituted on a ring carbon; or R^1 represents imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;
R^{2a} and R^{2b} independently represents hydrogen, halo, CN, SO_2alkyl, SR^4 or NO_2; or optionally substituted alkyl or optionally substituted alkoxy;
R^4 is hydrogen or optionally substituted alkyl;
R^5 is hydrogen or optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heterocyclyl, optionally substituted CQ^aQ^baryl, or optionally substituted CQ^aQ^bheterocyclyl; or
R^4 and R^5 together with the nitrogen to which they are attached form a heterocyclic or bicyclic heterocyclic ring;
R^6 is optionally substituted alkyl or optionally substituted aryl;
R^7 is hydrogen, fluorine or alkyl;
R^8 is hydrogen, hydroxy, fluorine or alkyl;
or R^7 and R^8 together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH and N-alkyl; or R^7 and R^8 together with the carbon to which they are attached form a carbonyl group; and
Q^a and Q^b are each independently selected from hydrogen, CH_3 and fluorine;
Q^c and Q^d are each independently selected from hydrogen and CH_3;
or a derivative thereof;
provided that:

when X is a bond, then R^1 is $CQ^cQ^dCO_2H$;
when X is CR^7R^8, then R^1 is not $CQ^cQ^dCO_2H$;
when R^1 is benzimidazolyl it is unsubstituted on the 1-position; and
when R^1 is benzimidazole optional substituents on the 4 or 7 position are selected from CH_2OH or CO_2H.

2. A compound according to claim 1 which is a compound of formula (IA):



(IA)

wherein:
either Y' is CH and Y" is O or S, or Y' is O or S and Y" is CH thus forming an oxazole or a thiazole ring;
X is CR^7R^8, or NR^4, or X is a bond;
R^x is optionally substituted C_{3-10}alkyl, optionally substituted C_{3-10}alkenyl, optionally substituted C_{3-10}alkynyl, optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl, or optionally substituted CQ^aQ^b-aryl;
R^1 is CO_2H, $CQ^cQ^dCO_2H$, tetrazolyl, CH_2tetrazolyl, $CONR^4R^5$, NR^4COR^6 or 1,2,4-triazol-3-yl optionally substituted on a ring carbon; or R^1 represents imidazolyl or pyrazolyl wherein optionally the imidazole or pyrazole ring is fused to give an optionally substituted bicyclic or tricyclic ring system;
R^{2b} is Cl, Br, or CF_3.
R^4 is hydrogen or optionally substituted alkyl;
R^5 is hydrogen or optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heterocyclyl, optionally substituted CQ^aQ^baryl, or optionally substituted CQ^aQ^bheterocyclyl; or
R^4 and R^5 together with the nitrogen to which they are attached form a heterocyclic or bicyclic heterocyclic ring;
R^6 is optionally substituted alkyl or optionally substituted aryl;
R^7 is hydrogen, fluorine or alkyl;
R^8 is hydrogen, hydroxy, fluorine or alkyl;
or R^7 and R^8 together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH and N-alkyl; or R^7 and R^8 together with the carbon to which they are attached form a carbonyl group; and
Q^a and Q^b are each independently selected from hydrogen, CH_3 and fluorine;
Q^c and Q^d are each independently selected from hydrogen and CH_3;
or a derivative thereof;

provided that:
when X is a bond, then R^1 is $CQ^cQ^dCO_2H$;
when X is CR^7R^8, then R^1 is *not* $CQ^cQ^dCO_2H$;
when Y' or Y" is O, then R^1 is not $CQ^cQ^dCO_2H$;
when R^1 is benzimidazolyl it is unsubstituted on the 1-position; and
when R^1 is benzimidazole optional substituents on the 4 or 7 position are selected from CH_2OH or CO_2H.

3. A compound according to claim 1 selected from the compounds of Examples 1 to 183 or a derivative thereof.

4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.

5. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance.

6. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

7. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof.

8. A method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof.

9. A method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof.

10. Use of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

11. Use of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or

prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

12. Use of a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/003810

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D413/04 C07D471/04 C07D263/32 C07D263/34
A61K31/422 A61K31/427 A61K31/426 A61K31/437 A61K31/4985
C07D417/04 C07D417/12 A61P25/04 C07D277/30 C07D277/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 811 459 A (BREAULT ET AL) 22 September 1998 (1998-09-22) claims 1-8,10,11 column 1, lines 5-24 column 81; example 72	1-12
Y	WO 96/11902 A (ZENECA LIMITED; BREAULT, GLORIA, ANN; OLDFIELD, JOHN; TUCKER, HOWARD;) 25 April 1996 (1996-04-25) page 95; examples 72,73 claims 1-7,10 page 1	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2006	04/09/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marzi, E

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 843 942 A (BREAULT ET AL) 1 December 1998 (1998-12-01) column 1, lines 6-25 claims 1,3-8,12,13 table 1a; compounds 4, 6, 13, 19 table 2b; compounds 3-10 table 3; compounds 1-5 table 4; compounds 12, 13 table 6b; compounds 2, 3 table 6c; compounds 2,4 table 7c; compounds 2, 6-8 table 8c; compounds 11, 12, 17	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/003810

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/003810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5811459 A	22-09-1998	AU 3616295 A	06-05-1996
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		DE 69514087 T2	27-04-2000
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		NZ 289905 A	25-11-1998
		PL 318283 A1	09-06-1997
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		SK 10197 A3	06-08-1997
		TW 411328 B	11-11-2000