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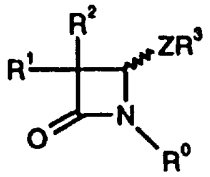
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(54) Title: AZETIDINONE COMPOUNDS FOR THE TREATMENT OF ATHEROSCLEROSIS

(57) Abstract

Azetidinone compounds of formula (I) in which *inter alia*: R^0 is $CR^4R^5\text{-}X^1\text{-}Y^1$ or $(CH_2)_pX^2(CH_2)_qY^2$; R^4 and R^5 which may be the same or different is each selected from hydrogen and $C_{(1\text{-}6)}$alkyl, or R^4 and R^5 may be linked together to form the residue of a $C_{(3\text{-}7)}$cycloalkyl ring; X^1 is a linker group and Y^1 is optionally substituted $C_{(1\text{-}12)}$alkyl $C_{(2\text{-}12)}$alkynyl, $C_{(2\text{-}12)}$alkynyl, $C_{(3\text{-}7)}$-cycloalkyl$C_{(1\text{-}8)}$ alkyl or an optionally substituted heteroaryl group; and X^2 is a heteroaryl group and Y^2 is an optionally substituted aryl group, p is an integer from 1 to 6, q is 0 or an integer from 1 to 6; are inhibitors of the phospholipase A2 enzyme Lp PLA2 and are of use in therapy, for instance in treating atherosclerosis.



(I)

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AZETIDINONE COMPOUNDS FOR THE TREATEMENT OF ATHEROSCLEROSIS.

The present invention relates to certain novel monocyclic β-lactam compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A2 enzyme Lipoprotein Associated Phospholipase A_2 (Lp-PLA_2), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996:16;591-9) wherein it is referred to as LDL-PLA_2. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA_2 and suggest that it may have potential as a therapuetic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA_2 is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA_2 action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA_2 enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA_2 could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA_2 inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

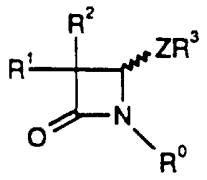
In addition, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA_2 activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

International patent applications WO 96/13484, WO 96/19451 and PCT EP96/02765 (SmithKline Beecham plc) describe a series of azetidinone derivatives which are inhibitors of Lp PLA2.

We have now identified a further series of azetidinone compounds which are distinguished over previous series by the substituent at the ring nitrogen and which act as inhibitors of Lp-PLA_2.

Accordingly, the present invention provides a compound of formula (I):



(I)

in which:

R^0 is $CR^4R^5\text{-}X^1\text{-}Y^1$, $CR^4R^5\text{-}X^2\text{-}Y^2$, or $(CH_2)_pX^3(CH_2)_qY^3$;

R^1 and R^2, which may be the same or different, is each selected from hydrogen, halogen or $C_{(1\text{-}8)}$alkyl;

R^4 and R^5 which may be the same or different is each selected from hydrogen and $C_{(1\text{-}6)}$alkyl, or R^4 and R^5 may be linked together to form the residue of a $C_{(3\text{-}7)}$ cycloalkyl ring;

X^1 is a linker group and Y^1 is optionally substituted $C_{(1\text{-}12)}$alkyl $C_{(2\text{-}12)}$alkenyl, $C_{(2\text{-}12)}$alkynyl, $C_{(3\text{-}7)}$-cycloalkyl$C_{(1\text{-}8)}$ alkyl;

X^2 is a linker group and Y^2 an optionally substituted heteroaryl group;

X^3 is a heteroaryl group and Y^3 is an optionally substituted aryl group, p is an integer from 1 to 6, q is 0 or an an integer from 1 to 6;

Z is O and R^3 is $C_{(1\text{-}8)}$alkyl, aryl$C_{(1\text{-}4)}$alkyl or aryl each of which may be optionally substituted, or

Z is S(O)n in which n is 0, 1 or 2 and R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl, $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl, aryl, aryl$C_{(1-4)}$alkyl or heteroaryl$C_{(1-4)}$alkyl each of which may be optionally substituted.

Compounds of formula (I) are inhibitors of Lp-PLA_2 and as such are expected to be of use in treating atherosclerosis and the other disease conditions noted elsewhere.

Representative examples of R^1 and R^2 include hydrogen, bromo, methyl and ethyl. Suitably, R^1 and R^2 is each hydrogen or one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is methyl (to give a *trans*-methyl). Preferably, R^1 and R^2 is each hydrogen.

Representative examples of $C_{(1-8)}$alkyl for R^3 include methyl, n-butyl, t-butyl and n-hexyl, cyclohexyl and cyclohexylmethyl, suitably methyl, n-butyl, t-butyl or n-hexyl. Suitable substituents for the alkyl or cycloalkyl group include halo, hydroxy and carboxy and esters thereof.

Representative examples of aryl$C_{(1-4)}$alkyl for R^3 include aryl$C_{(1-3)}$alkyl, preferably arylCH_2. Representative examples of the aryl group include phenyl and naphthyl, preferably phenyl. Suitable examples include benzyl, 2-phenylethyl and 3-phenylpropyl in each of which the phenyl ring may be optionally substituted by up to two substituents. Suitable substituents include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, aryl$C_{(1-6)}$alkoxy, carboxy and esters thereof, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, and (C_{1-6})alkylsulphonyl.

Representative examples of aryl for R^3 include phenyl and naphthyl. Preferably, the aryl group is optionally substitued phenyl. Suitable substituents for a phenyl or naphthyl ring include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, aryl$C_{(1-6)}$alkoxy, carboxy and esters thereof, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, and (C_{1-6})alkylsulphonyl.

Representative examples of heteroaryl group for incorporation into R^3- include include pyridyl, pyridyl N-oxide, furanyl, thienyl and thiazolyl. Suitably, the heteroarylalkyl group is heteroaryl$C_{(1-3)}$alkyl, more suitably heteroarylmethyl. Preferred values include optionally substitued pyridylmethyl, furanylmethyl, thienylmethyl or thiazolylmethyl. Suitable substituents for a heteroaryl ring include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, aryl$C_{(1-6)}$alkoxy, carboxy and esters thereof, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl and (C_{1-6})alkylsulphonyl.

Preferably, when Z is S(O)n, n is 1 or 2, more preferably 1.

Preferably Z is SO and R^3 is arylmethyl or heteroarylmethyl, in particular benzyl or furanylmethyl, especially benzyl.

Suitable esters for incorporation into R^3 include pharmaceutically acceptable esters of the formula CO_2R. Such esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically

acceptable *in vivo* hydrolysable ester groups for incorporation in R include those which break down readily in the human body to leave the parent acid or its salt.

Examples of suitable values for R include (C_{1-6})alkyl, for instance, methyl, ethyl and propyl, (C_{2-6})alkenyl, for instance allyl.

Further examples of suitable values for R include:

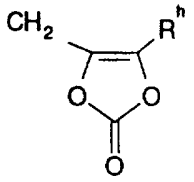
$-CH(R^a)O.CO.R^b$;

$-CH(R^a)O.CO.OR^c$;

$-CH(R^a)CO.NR^eR^f$

$-R^dNR^eR^f$;

$-CH_2OR^g$;



$CH(R^a)O.CO.C_6H_4Y^4COCH(R^i)NH_2$

in which:

R^a is hydrogen, (C_{1-6})alkyl, in particular methyl, (C_{3-7})cycloalkyl, or phenyl;

R^b is (C_{1-6})alkyl, (C_{1-6})alkoxy(C_{1-6})alkyl, phenyl, benzyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl(C_{3-7})cycloalkyl, 1-amino(C_{1-6})alkyl, or 1-(C_{1-6}alkyl)amino(C_{1-6})alkyl; or

R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^c is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl(C_{3-7})cycloalkyl;

R^d is (C_{1-6})alkylene optionally substituted with a methyl or ethyl group;

R^e and R^f which may be the same or different is each (C_{1-6})alkyl or aryl(C_{1-4}) alkyl, optionally substituted with e.g. hydroxy;

R^g is (C_{1-6})alkyl;

R^h is hydrogen, (C_{1-6})alkyl or phenyl;

R^i is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6})-alkyl, or (C_{1-6})alkoxy;

and

Y^4 is oxygen or NH;

for instance:

(a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl, and (1-aminoethyl)carbonyloxymethyl;

(b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl;

(c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;

(d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;

(e) lactone groups such as phthalidyl and dimethoxyphthalidyl; and

(f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.

It will be appreciated by those skilled in the art that the values in the further group of examples include those which have previously been proposed for use as pro-drug esters for various penicillin antibiotics such as ampicillin.

Representative examples of R^4 and R^5 when an alkyl group include methyl. Representative examples of a (C_{3-7})cycloalkyl ring include cyclopropyl. Suitably, R^4 and R^5 are both hydrogen or R^4 is hydrogen and R^5 methyl.

Suitably, X^1 is a direct bond or a group $(CH_2)_xX^4$ in which X^4 is CH_2O, CO, COO, $CONR^6$, $CONR^6CO$, or CONHO in which R^6 is hydrogen or $C_{(1-6)}$alkyl, x is 0 (for all except X^4 =COO) or an integer from 1 to 6. Suitably X^4 is CONH. Suitably x is 0. Preferably, X^1 is CONH.

Suitably, in Y^1, the alkyl chain is unbranched. Useful such values of Y^1 include $C_{(6-10)}$ alkyl, preferably $C_{(8-10)}$ alkyl or $C_{(3-7)}$cycloalkyl$C_{(5-7)}$ alkyl, preferably cyclohexyl$C_{(5-7)}$alkyl. Representative examples of Y^1 include nonyl and cyclohexylhexyl.

Suitably, X^2 is:

(a) a direct bond;

(b) a group $X^5(CH_2)_y$ in which X^5 is CO, $CONR^6$, COO, $CONR^6CO$, or CONHO in which R^6 is hydrogen or $C_{(1-6)}$alkyl and y is 0 or an integer from 1 to 12;

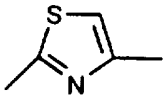
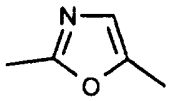
(c) a $C_{(1-12)}$alkylene chain optionally interupted by X^5;

(d) a group A-B in which A is a direct bond or X^5 and B is a $C_{(1-12)}$alkylene chain interupted and/or terminated at the end remote from A by one or more groups M selected from O, S(O)n, NR^6, alkene or alkyne in which R^6 is hydrogen or $C_{(1-6)}$alkyl and n is 0, 1 or 2.

Representative examples of X^2 include $CO(CH_2)_y$, $CONH(CH_2)_y$, $COO(CH_2)_y$, $CONHCO(CH_2)_y$, $CONHO(CH_2)_y$ and $C_{(1-12)}$alkylene. Preferably, X^3 is CO or $CONR^6$, more preferably CONH. Preferably, y is 1, 2, 5, 6, 7 or 9, preferably 6. Preferably, X^2 is $CONH(CH_2)_6$.

Representative examples of heteroaryl rings for incorporation into Y^2 include pyridyl and pyridyl N-oxide. Suitable substituents for a heteroaryl ring include halo, hydroxy, $C_{(1-8)}$alkyl and $C_{(1-8)}$alkoxy. Suitably, Y^2 is 2-pyridyl or 4-pyridyl, preferably in combination with X^1 being $CONH(CH_2)_6$.

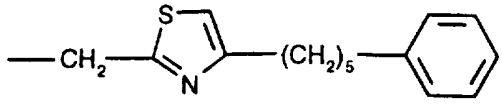
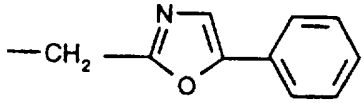
Representative examples of X^3 include thiazolyl and oxazolyl, in particular


and


Suitably, p is 1. Representative values of q include 0 and 5.

Representative examples of aryl rings for incorporation into Y^3 include phenyl and naphthyl. Suitable substituents for the aryl ring include halo, hydroxy, $C_{(1-8)}$alkyl and $C_{(1-8)}$alkoxy. Suitably, Y^3 is phenyl.

Representative examples of X^3-Y^3 include:


and


Suitably, R^0 is CH_2CONHY^1 in which Y^1 is $C_{(8-10)}$ alkyl or cyclohexyl$C_{(5-7)}$alkyl, in particular nonyl or cyclohexylhexyl.

It will be readily appreciated by the skilled person that C-4 of the β-lactam ring is a chiral centre which will give rise to the presence of stereoisomers. The present invention encompasses all such stereoisomers. An additional chiral centre will be introduced in compounds of formula (I) in which Z^1 is SO. The present invention encompasses all such stereoisomers. A further chiral centre will be introduced when R^4 and R^5 are not the same. This will give rise to the existence of extra stereoisomers. The present invention encompasses all such stereoisomers. In preferred compounds of formula (I), the absolute configurations at C-4 and the SO moiety are *R* and *S* respectively. In preferred compounds of formula (I) when R^4=H, R^5=Me, the absolute configuration at the α-carbon (to which R^5 is attached) is *S*.

When used herein, the term 'alkyl' and similar terms such as 'alkoxy' includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

Suitable substituents for an alkyl group include, for example, and unless otherwise defined, halogen, cyano, azido, nitro, carboxy, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6})alkylcarbamoyl, sulpho, sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, amino, mono- or di-(C_{1-6})alkylamino, acylamino, ureido, (C_{1-6})alkoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, aryl, heterocyclyl, hydroxy, (C_{1-6})alkoxy, acyloxy, oxo, acyl, 2-thienoyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, hydroxyimino, (C_{1-6})alkoxyimino, hydrazino, hydrazono, benzohydroximoyl, guanidino, amidino and iminoalkylamino.

When used herein, the term 'aryl' includes, unless otherwise defined, phenyl or naphthyl optionally substituted with up to five, preferably up to three substituents.

Suitable substituents for an aryl group include, for example, and unless otherwise defined, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkoxycarbonyl(C_{1-6})alkoxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})-alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, and heterocyclyl.

When used herein, the term 'heterocyclyl' includes aromatic and non-aromatic single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When substituted, a heteroaryl or a heterocyclyl group may have up to three substituents. Suitable such substituents include those previously mentioned for an aryl group as well as oxo.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

Preferred compounds of formula (I) include:
N-(6-Cyclohexylhexyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2);
N-(6-Cyclohexylhexyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide;
N-(Nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2); and
N-(Nonyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide.

Preferred compounds of formula (I) in which, in R^0, Y^2 is heteroaryl, include:
N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Diastereoisomer 2); and
N-(6-(2-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Diastereoisomer 2).

Preferred compounds of formula (I) in which R^0 is $(CH_2)_pX^3(CH_2)_qY^3$ include:
(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulphinyl-2-oxoazetidine.

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although

the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A_2 (Lp-PLA_2) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.
The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA_2 and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid peroxidation in conjunction with Lp PLA2 activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with anti-hyperlipidaemic or anti-atherosclerotic or anti-diabetic or anti-anginal or anti-inflammatory or anti-hypertension agents. Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository.

The compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

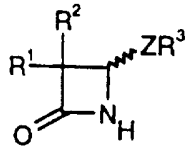
A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I).

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Compounds of formula (I) may be prepared by adapting processes previously described for ananlogous compounds in International patent applications WO 96/13484, WO 96/19451 and PCT EP96/02765 (SmithKline Beecham plc). Such processes include treating an azetidone of formula (II):



(II)

in which:
R^1, R^2, R^3, and Z are as hereinbefore defined;
with an alkylating agent of the formula (III):

$$R^7R^0 \qquad \text{(III)}$$

in which R^7 is a suitable leaving group such as halogen or triflate; and
$R^0$is as hereinbefore defined;
under alkylating conditions.

Suitable alkylating conditions are well known in the art and include carrying out the reaction in the presence of a suitable base such as sodium hydride or potassium hydroxide optionally with a quaternary ammonium salt such tetrabutyl ammonium bromide, in a suitable alkylating solvent such as tetrahydrofuran (THF), and at a temperature in the range -10 to 0°C.

In compounds of formula (I) in which Z is S(O)n, the preceding alkylation reaction is conveniently effected on compounds in which n is 0.

Compounds of formula (I) in which n is 1 or 2 can be readily prepared from compounds of formula (I) in which n is 0 by treatment thereof with a suitable oxidising agent such as m-chloroperbenzoic acid. Use of chiral oxidising agents such as (+)- or (-)-1,1'-bi-2-naphthol / titanium *iso*propoxide (N Komatsu et al, J Org

Chem, 1993, 58, 7624-7626) can give diastereoisomeric selectivity, if not chirally pure compounds.

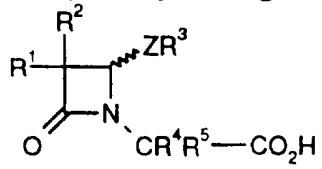
Compounds of formula (I) in which one of R^4 and R^5 is alkyl may also be prepared from corresponding compounds of formula (I) where both R^4 and R^5 are hydrogen by treatment thereof with an alkylating agent under the conditions described above. Such compounds may be obtained by treating a compound of formula (II) with an alkylating agent of formula (III) in which both of R^4 and R^5 is hydrogen, under alkylating conditions as hereinbefore described.

A second alkyl group for R^4/R^5 may be introduced by treating a first obtained compound of formula (I) in which one of R^4 and R^5 is hydrogen, with an alkylating agent in the presence of a suitable base such as sodium hydride, potassium hydroxide or lithium hexamethyldisilazide, in a suitable alkylating solvent such as tetrahydrofuran (THF), and at a temperature in the range -80 to 10°C.

Compounds of formula (II) in which Z is O may be obtained by treating 4-acetoxyazetidinone, 4-benzoyloxyazetidinone or 4-phenylsulfonylazetidinone with a phenol/alcohol HOR^3 in the presence of a base such as potassium *t*-butoxide, in a suitable solvent such as THF at a temperature in the range 0 to 5°C. Compounds of formula (IV) in which Z is S may be obtained by treating 4-acetoxyazetidinone with a thiol HSR^3 in the presence of a base such as sodium ethoxide, in a suitable solvent such as ethanol at a temperature in the range 0 to 5°C.

Compounds of formula (III) may be readily prepared by adapting known synthetic procedures, according to the specific value of $X^{1/2}$. A convenient starting material is an appropriately substituted aryl compound which may then be elaborated to introduce the side chain $R^7CR^4R^5\ X^{1/2}$-.

Compounds of formula (I) in which X^1 denotes a group $CONR^6$ or $CONR^6O$ may be conveniently prepared by treating an acid of the formula (IV):



(IV)

in which:

R^1, R^2, R^3, R^4, R^5 and Z are as hereinbefore defined;

with an amine of the formula (V):

$$NHR^6Y^1$$

(V)

or a hydroxylamine of the formula (VI):

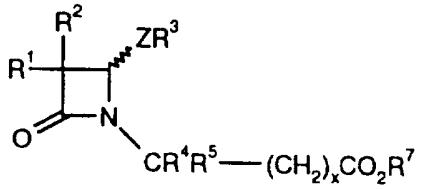
NH_2OY^1 (VI)

in which R^6 and Y^1 are hereinbefore defined,
in the presence of an activating agent such as ethyl chloroformate or dicyclohexylcarbodiimide (DCC), in a suitable solvent such as chloroform or dimethyl formamide, at a temperature in the range -10 to 20°C.

A similar process may be used for preparing a compound of formula (I) in which X^2 denotes a group $CONR^6(CH_2)_y$ or $CONR^6O(CH_2)_y$, but using an amine $NHR^6(CH_2)_yY^1$ or a hydroxylamine $NH_2O(CH_2)_yY^1$.

An acid of formula (IV) in which one of R^4 and R^5 is hydrogen may be obtained by treating a compound of formula (II) with a corresponding 2-bromo (C_{1-7}) alkanoate ester, under alkylating conditions as hereinbefore described; followed by the hydrolysis of the thus formed intermediate ester using standard conditions. A second alkyl group may be introduced by alkylating of the first formed monoalkyl ester.

Compounds of formula (I) in which X^1 denotes a group $(CH_2)_xCOO$ in which x is an integer from 1 to 6 may be conveniently prepared by transesterifying a compound of formula (VII):



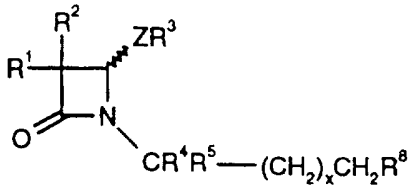
(VII)

in which:
R^7 is methyl; and
x, R^1, R^2, R^3, R^4, R^5 and Z are as hereinbefore defined;
using conditions well known in the art for such reactions, for instance heating in toluene in the presence of a catalytic amount of sodium methoxide and an alcohol.

A compound of formula (VII) in which one of R^4 and R^5 is hydrogen may be obtained by treating a compound of formula (II) with a methyl 2-bromoalkanoate, under alkylating conditions as hereinbefore described.

Alternatively, a compound of formula (I) in which X^1 denotes a group $(CH_2)_xCOO$ in which x is an integer from 1 to 6 may be prepared by treating a compound of formula (IV) in which R^7 is hydrogen with an alcohol Y^1OH or an activated derivative thereof, for instance a tosylate.

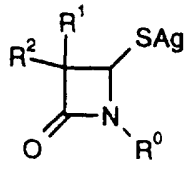
Compounds of formula (I) in which X^1 is CH_2O may be prepared by a suitable ether coupling reaction, for instance treating a compound of formula (VIII):



(VIII)

in which R^8 is a halogen or other suitable leaving group such as triflate or tosylate and R^1, R^2, R^3, R^4, R^5, x and Z are as hereinbefore defined;
with an alcohol Y^1OH or a suitable salt therof.

In addition, compounds of formula (I) in which Z is S(O)n and n is 0 may be prepared by a process which comprises treating a compound of formula (IX):



(IX)

in which R^0, R^1, R^2, X^1 and Y^1 are as hereinbefore defined;
with an alkylating agent of the formula (X):

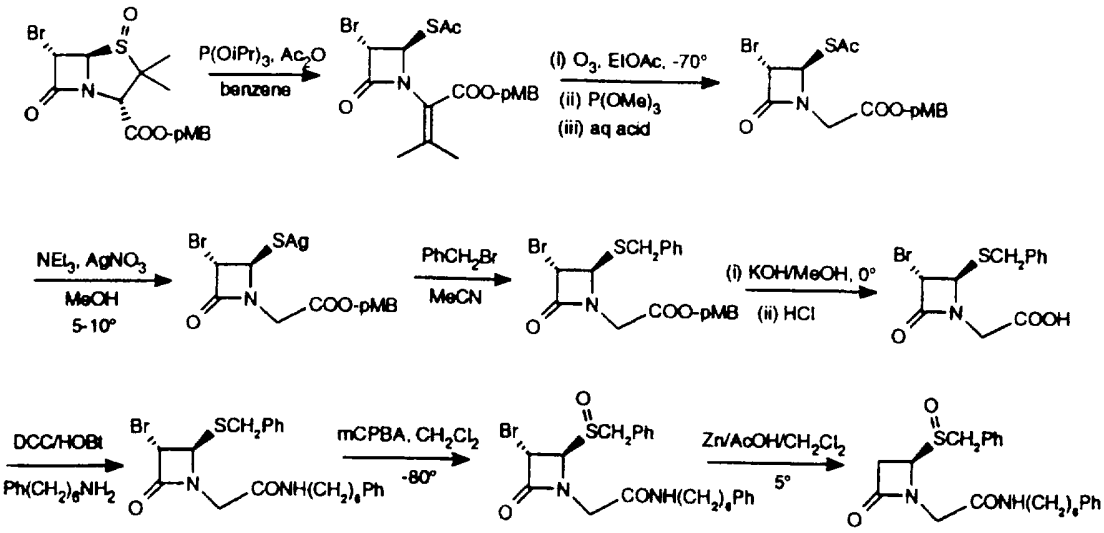
$$R^8R^3$$

(X)

in which R^3 and R^8 are as hereinbefore defined;
under suitable alkylating conditions, for instance, in a solvent such as acetonitrile, at a temperature in the region 25°C.

Compounds of formula (IX) may be obtained from the corresponding 4-acetylthioazetidinone by treatment with silver nitrate and a base in a suitable solvent such as methanol.

Mixtures of diastereoisomeric compounds of formula (I) may be resolved, if so desired, according to procedures well known in the art. For instance sulphoxides (n=1) may be separated by chromatography and/or crystallisation. Chirally pure compounds may be prepared by chiral chromatography, from chirally pure intermediates or by chiral synthesis using chiral reagents or catalysis. Suitable chiral intermediates may be obtained by resolution or chiral induction or by using chiral reagents, in particular natural chiral molecules, according to methods well known to those skilled in the art. For chiral synthesis, a convenient chiral starting material is a penicillin derivative which has the preferred configuration at C-4 of the β-lactam ring. This is illustrated in the following scheme:



The preparation of the starting material (4-methoxybenzyl-6-bromopenicillinate-1-oxide) is described by J. Chem. Soc., Perkin Trans. 1, 1994, 179-188.

The present invention will now be illustrated by the following examples. In these, the terms 'diastereoisomer 1' and 'diastereoisomer 2' are used for sulfoxide compounds to refer to the diastereoisomers having R,R/S,S and R,S/S,R configurations, respectively. Such configurations were obtained initially by X-ray analysis of a limited number of compounds and then extrapolated to the remaning compounds on the basis of their ^1H nmr spectra. Unless otherwise specified, all compounds are racemic. Chiral compounds are described as 4*R* or *S*, S*R* or *S* where the 4 describes the centre at the C4 position in the azetidinone and the S describes the sulfoxide centre.

Preparation 1 Methyl (4-benzylthio-2-oxoazetidin-1-yl)acetate

a. 4-(Benzylthio)azetidin-2-one

Sodium (8.1g, 0.35mol) was dissolved in ethanol (250ml) and benzyl mercaptan (45.2g, 0.37mol) added dropwise over 20 minutes keeping the temperature between 20°C - 25°C whilst bubbling nitrogen through the mixture. After 15 minutes, the reaction was cooled to 5°C and a solution of 4-acetoxyazetidin-2-one (45.0g, 0.35mol) in ethanol (50ml) was added dropwise over 15 minutes whilst maintaining the temperature at 5°C. The mixture was stirred at room temperature for 60 minutes and evaporated to dryness under reduced pressure. Water (400ml) was added, the mixture extracted with dichloromethane (2x300ml), the extracts dried ($MgSO_4$) and evaporated under reduced pressure to an oil. The oil was cooled to -20°C and titurated with ether (400ml) to give a white solid which was isolated by filtration (50.2g, 79%), m.p. 50-51.0°C.

^1H NMR δ ($CDCl_3$) 2.86(1H, m, $\underline{H}_{3a}$), 3.30 (1H, m, $\underline{H}_{3b}$), 3.85 (2H, s, $SC\underline{H}_2$), 4.68 (1H, m, $\underline{H}_4$), 7.31 (5H, m, Ph-$\underline{H}$).

b. Methyl (4-benzylthio-2-oxoazetidin-1-yl)acetate

To a solution of 4-(benzylthio)azetidin-2-one (5.0g, 25mmol), methyl bromoacetate (4.6g, 30mmol) and tetrabutylammonium bromide (0.9g, 0.28mmol) in dry THF (150ml) was added powdered potassium hydroxide (1.7g, 30mmol). The resulting mixture was stirred for two hours at room temperature before water (50 ml) was added. The solution was extracted with ethyl acetate (3x150ml portions) and the combined extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluted with petroleum ether 60°-80°:ethyl acetate 4:1 to give methyl (4-benzylthio-2-oxoazetidin-1-yl)acetate as a yellow oil (5g, 70%).

^1H NMR δ ($CDCl_3$) 2.96(1H, dd, J=2.5, 16 Hz $\underline{H}_{3a}$), 3.24,3.99 (each 1H, d, J=18.00 Hz, $NC\underline{H}_2$), 3.4 (1H, dd, J=5,12.5 Hz $\underline{H}_{3b}$), 3.70 (3H, s, OCH_3), 3.77 (2H, s, $SC\underline{H}_2$), 4.92 (1H, m, $\underline{H}_4$), 7.28 (5H, m, Ph-$\underline{H}$)

Preparation 2 (4-Benzylthio-2-oxoazetidin-1-yl)acetic acid To a solution of methyl (4-benzylthio-2-oxo-azetidin-1-yl)acetate (2.5g, 9.4mmol) in methanol (80ml) was added, dropwise at 0°C, a solution of 1 N sodium hydroxide (9.9ml, 9.9mmol). The reaction was stirred for 1 hr and evaporated to dryness. Water (50 ml) was added and the solution acidified to pH 3 with dilute hydrochloric acid and extracted with ethyl acetate (3x100ml) . The combined extracts were dried ($MgSO_4$), evaporated and the residue purified by recrystallisation (hexane/ether) to give (4-benzylthio-2-oxo-azetidin-1-yl)acetic acid as a white solid (1.3g, 55%), mp 110-111°C. ^1H NMR δ ($CDCl_3$) 2.99 (1H, dd, J=6.87,17.5 Hz, $\underline{H}_{3a}$), 3.27, 4.06 (each 1H, d, J=18.40 Hz, NCH_2), 3.39 (1H, dd, J=5,15.4 Hz, $\underline{H}_{3b}$), 3.77 (2H, s, $SC\underline{H}_2$), 4.91 (1H, m, $\underline{H}_4$), 7.27 (5H, m, Ph-$\underline{H}$).

Preparation 3: . (4-Benzylthio-2-oxoazetidin-1-yl)acetic acid

a. 4-(Benzylthio)azetidin-2-one

Sodium (8.1g, 0.35mol) was dissolved in ethanol (250ml) and benzyl mercaptan (45.2g, 0.37mol) added dropwise over 20 minutes keeping the temperature between 20°C - 25°C whilst bubbling nitrogen through the mixture. After 15 minutes, the reaction was cooled to 5°C and a solution of 4-acetoxyazetidin-2-one (45.0g, 0.35mol) in ethanol (50ml) was added dropwise over 15 minutes whilst maintaining

the temperature at 5°C. The mixture was stirred at room temperature for 60 minutes and evaporated to dryness under reduced pressure. Water (400ml) was added, the mixture extracted with dichloromethane (2x300ml), the extracts dried ($MgSO_4$) and evaporated under reduced pressure to an oil. The oil was cooled to -20°C and triturated with ether (400ml) to give a white solid which was isolated by filtration (50.2g, 79%), m.p. 50-51.0°C.

b. Methyl-(4-benzylthio-2-oxoazetidin-1-yl) acetate

To a solution of 4-(benzylthio)azetidin-2-one (5.0g, 25mmol), methyl bromoacetate (4.6g, 30mmol) and tetrabutylammonium bromide (0.9g, 0.28mmol) in dry THF (150ml) was added powdered potassium hydroxide (1.7g, 30mmol). The resulting mixture was stirred for two hours at room temperature before water (50 ml) was added. The solution was extracted with ethyl acetate (3x150ml portions) and the combined extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluted with petroleum ether 60°-80°:ethyl acetate 4:1 to give methyl (4-benzylthio-2-oxoazetidin-1-yl)acetate as a yellow oil (5g, 70%).
^{1}H NMR δ ($CDCl_3$) 2.96(1H, dd, J=2.5, 16 Hz $\underline{H}_{3a}$), 3.24,3.99 (each 1H, d, J=18.00 Hz, $NC\underline{H}_2$), 3.4 (1H, dd, J=5,12.5 Hz $\underline{H}_{3b}$), 3.70 (3H, s, $OC\underline{H}_3$), 3.77 (2H, s, $SC\underline{H}_2$), 4.92 (1H, m, $\underline{H}_4$), 7.28 (5H, m, Ph-$\underline{H}$)

c. (4-Benzylthio-2-oxoazetidin-1-yl)acetic acid

To a solution of methyl (4-benzylthio-2-oxo-azetidin-1-yl)acetate (2.5g, 9.4mmol) in methanol (80ml) was added, dropwise at 0°C, a solution of 1 N sodium hydroxide (9.9ml, 9.9mmol). The reaction was stirred for 1 hr and evaporated to dryness. Water (50 ml) was added and the solution acidified to pH 3 with dilute hydrochloric acid and extracted with ethyl acetate (3x100ml) . The combined extracts were dried ($MgSO_4$), evaporated and the residue purified by recrystallisation (hexane/ether) to give (4-benzylthio-2-oxo-azetidin-1-yl)acetic acid as a white solid (1.3g, 55%), mp 110-111°C. ^{1}H NMR δ ($CDCl_3$) 2.99 (1H, dd, J=6.87,17.5 Hz, $\underline{H}_{3a}$), 3.27, 4.06 (each 1H, d, J=18.40 Hz, NCH_2), 3.39 (1H, dd, J=5,15.4 Hz, $\underline{H}_{3b}$), 3.77 (2H, s, $SC\underline{H}_2$), 4.91 (1H, m, $\underline{H}_4$), 7.27 (5H, m, Ph-$\underline{H}$).

Preparation 4: 6-(4-Pyridyl)hexylamine

Sodamide (6.63g) was suspended in liquid ammonia (100ml) and cooled in a cardice/acetone bath. 4-Picoline (7.3ml) was added, the cooling bath removed and the mixture stirred at reflux for 2hrs. The mixture was cooled again and 5-bromopentylamine hydrobromide (18.53g) added and the mixture allowed to reflux for 5 hrs. The mixture was again cooled, quenched with ammonium chloride (10g) and the solvent allowed to evaporate overnight. The residue was dissolved in water (100ml), made strongly alkaline with NaOH and extracted with CH_2Cl_2 (2x100ml). The combined organics were partitioned with water at pH7 and the aqueous was washed with CH_2Cl_2 (100ml) then basified with NaOH and extracted with CH_2Cl_2 (2x100ml), dried over K_2CO_3 and evaporated to an orange oil. This was purified by vacuum distillation to give the title compound as a colourless oil (4.94g, 37% yield; b.p. 110-120°C/0.5mm)
^{1}H NMR δ ($CDCl_3$) 1.3-1.7 (8H, m, 4 x $C\underline{H}_2$), 2.6 (4H, m, $C\underline{H}_2Pyr + C\underline{H}_2NH_2$), 7.10 (2H, m, Pyr-3,5$\underline{H}$), 8.48 (1H, m, Pyr-2,6$\underline{H}$)

Preparation 5: 6-(2-Pyridyl)hexylamine

Treatment of 2-picoline with sodamine in liquid ammonia followed by 5-bromopentylamine using the procedure for 6-(4-pyridyl)hexylamine gave the title compound in 38% yield, b.p. 250°C at 0.3 mm Hg

Preparation 4: 2-Bromomethyl-4-(5-phenylpentyl)thiazole

a. 2-Benxoyloxy-4-(5-phenylpentyl)thiazole

A mixture of benzoyloxylthioacetamide (CA8923f) (2.0g, 0.0102moles) and 1-bromo-6-phenyl-2-hexanone (2.5g, 0.00929moles) in absolute alcohol (2.5ml) was stirred at reflux for 15 minutes. The reaction was cooled and poured into sat.$NaHCO_3$ (aq) and extracted with ethyl acetate (2x50ml). The organic extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated to an orange oil. Purification by column chromatography eluted with 20:1 to 10:1 P.E.: ethyl acetate gave 2-benxoyloxy-4-(5-phenylpentyl)thiazole as a colourless oil (2.39g, 71%).

b. 2-Hydroxymethyl-4-(5-phenylpentyl)thiazole

2-Benxoyloxy-4-(5-phenylpentyl)thiazole (2.29g, 0.00627moles) was treated with 5% ethanolic potassium hydroxide (100ml) and the mixture was heated on a steam bath for 10 minutes. The mixture was reduced in volume to 25ml under reduced pressure, water (100ml) was added and the mixture was reduced to 50ml under reduced pressure. The residue was acidified to pH7 with dilute HCl and extracted with diethyl ether (x2). The organic extracts were combined and washed with sat.$NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to a yellow oil. Purification by column chromatography eluted with 1:1 P.E.: ethyl acetate gave 2-hydroxymethyl-4-(5-phenylpentyl)thiazole as a yellow oil (1.55g, 94%).

c. 2-Bromomethyl-4-(5-phenylpentyl)thiazole

A mixture of 2-hydroxymethyl-4-(5-phenylpentyl)thiazole (1.47g, 0.00562moles) and triphenylphosphine (1.59g, 0.00606moles) in dry CH_2Cl_2 (25ml) was cooled to 0°C and treated with solid N-bromosuccinimide (1.08g, 0.00606moles) in portions over 10 minutes maintaining the temperature at 0°C. The cooling bath was removed and the reaction was stirred for 1h. Purification by column chromatography eluted with 10:1 to 5:1 P.E.: ethyl acetate gave the product as a colourless oil. The oil was dissolved in diethyl ether and washed with sat.$NaHCO_3$ (aq), brine, dried ($MgSO_4$) and evaporated to give 2-bromomethyl-4-(5-phenylpentyl)thiazole as colourless oil (1.52g, 83%).

Example 1 N-(6-Cyclohexylhexyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide

A mixture of (4-benzylthio-2-oxoazetidine-1yl)acetic acid (2.06g), 6-(cyclohexyl)hexylamine (1.50g), dicyclohexylcarbodiimide (1.69g) and 1-hydroxybenzotriazole (1.11g) in dry dimethylformamide (DMF) (20ml) was stirred at 20°C for 3 hours. Ethyl acetate (50ml) was added, the mixture filtered and the filtrate evaporated to an oil. This oil was taken up in ethyl acetate, washed with aq. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated to an oil which was purified by chromatography on silica gel (40-60 Petroleum ether/ethyl acetate) to give the title compound as a colourless oil (2.89g, 85% yield).

^1H NMR δ ($CDCl_3$) 0.7-1.8 (19H, m, 4 x $C\underline{H}_2$ + Cyclohexyl C$\underline{H}$, C$\underline{H}_2$), 2.95 (1H, dd, J=2, 15 Hz, $\underline{H}_3$), 3.25 (2H, m, NHC$\underline{H}_2$), 3.38 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.55, 3.73 (each 1H, d, J=17 Hz, NC$\underline{H}_2$), 3.82 (2H, s, SC$\underline{H}_2$), 4.82 (1H, m, $\underline{H}_4$), 6.06 (1H, br s, N$\underline{H}$), 7.2-7.4 (5H, m, Ph-$\underline{H}$)

Example 2 N-(6-Cyclohexylhexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Diastereoisomer 1)

N-(6-Cyclohexylhexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide (2.76g) was dissolved in dichloromethane (60ml), cooled to -60°C and a solution of 55-60% *m*-chloroperbenzoic acid (*m*CPBA) (1.84g;ca 6.62mM) in dichloromethane (80ml) was added dropwise over 15 mins, then the mixture was stirred at 20°C for 3 hours. The solution was washed with aq. $NaHCO_3/Na_2SO_3$, water, dried over $MgSO_4$ and evaporated to a colourless solid. This was recrystallised three times from EtOAc (cooling to 20°C only) to give the title compound as a colourless solid m.p. 150-1°C, (735mg, 26%).

^{1}H NMR δ ($CDCl_3$) 0.8-1.8 (19H, m, 4 x CH_2 + Cyclohexyl CH, CH_2), 2.95 (1H, dd, J=5, 15 Hz, H_3), 3.22 (2H, m, $NHCH_2$), 3.46 (1H, dd, J=2, 15 Hz, H_3), 3.72, 4.10 (each 1H, d, J=17 Hz, NCH_2), 3.90, 4.06 (each 1H, d, J=13 Hz, $SOCH_2$), 4.53 (1H, m, H_4), 6.62 (1H, br s, NH), 7.2-7.5 (5H, m, Ph-H)

$\nu_{c=o}$ 1791 cm^{-1}

Found: C, 66.4; H, 8.1; N, 6.6%; $C_{24}H_{36}N_2O_3S$ requires: C, 66.6; H, 8.4; N, 6.5%

Example 3 N-(6-Cyclohexylhexyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2)

The mother liquors from the first two recrystallisations in Example 2 above were combined and evaporated to a solid which was recrystallised from EtOAc, cooling to RT and filtering to remove the first formed solid, then refrigerating to obtain a solid which was recrystallised again from EtOAc to give the title compound as a colourless solid, m.p. 135-7°C, (1.32 g, 46%)

^{1}H NMR δ ($CDCl_3$) 0.8-1.8 (19H, m, 4 x CH_2 + Cyclohexyl CH, CH_2), 2.88 (1H, dd, J=2, 15 Hz, H_3), 3.2 (3H, m, H_3 + $NHCH_2$), 3.91, 4.20(each 1H, d, J=17 Hz, NCH_2), 4.00, 4.24 (each 1H, d, J=13 Hz, $SOCH_2$), 4.62 (1H, m, H_4), 7.2-7.5 (6H, m, Ph-H + NH);

$\nu_{c=o}$ 1793 cm^{-1}

Found: C, 66.2; H, 8.2; N, 6.5%; $C_{24}H_{36}N_2O_3S$ requires: C, 66.6; H, 8.4; N, 6.5%

Example 4 N-(6-Cyclohexylhexyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide

N-(6-Cyclohexylhexyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (0.95g) was dissolved in dichloromethane (40ml), a solution of 55-60% *m*CPBA (0.83g) in dichloromethane (40ml) was added and stirred at 20°C for 1.5 hours. The solution was washed with aq $NaHCO_3/Na_2SO_3$ and brine, dried over $MgSO_4$ and evaporated to a solid. This was purified by chromatography on silica gel (40-60 Pet ether/EtOAc) then recrystallisation from EtOAc to give the title compound as a colourless solid, m.p. 129-30°C, (630 mg, 64%)

^{1}H NMR δ ($CDCl_3$) 0.8-1.8 (19H, m, 4 x CH_2 + cyclohexyl CH, CH_2), 3.01 (1H, dd, J=2, 15 Hz, H_3), 3.12 (1H, dd, J=5, 15 Hz, H_3), 3.25 (2H, m, $NHCH_2$), 3.83, 3.97 (each 1H, d, J=17 Hz, NCH_2), 4.35 (2H, s, SO_2CH_2), 4.86 (1H, m, H_4), 5.96 (1H, br s, NH), 6.9, 7.4 (5H, m, Ph-H); $\nu_{c=o}$ 1796 cm^{-1}

Found: C, 64.2; H, 7.9; N, 6.4%; $C_{24}H_{36}N_2O_4S$ requires: C, 64.3; H, 8.1; N, 6.2%

Example 5 N-(Nonyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide

Treatment of (4-benzylthio-2-oxoazetidine-1yl)acetic acid with nonylamine under the conditions described for Example 1 gave the title compound as a colourless soild, m.p. 64-65°C, 88% yield

^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=6.8Hz, CH_3), 1.28 (12H, m, 6xCH_2), 1.50 (2H, m, NCH_2CH_2), 2.93, 2.97 (1H, dd, J=2.4, 15.4Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.36, 3.40 (1H, dd, J=5.2, 15.4Hz, H_3), 3.57, 3.72 (each 1H, d, J=16.7Hz, NCH_2), 3.82 (2H, s, SCH_2), 4.81 (1H, m, H_4), 6.0 (1H, m, NH), 7.30-7.33 (5H, m, Ph-H); $\nu_{c=o}$ 1773 cm^{-1}

Found: C, 67.0; H, 8.4; N, 7.6%; $C_{21}H_{32}N_2O_2S$ requires: C, 67.0; H, 8.6; N, 7.4%

Treatment of N-(nonyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide with *m*CPBA as described for Examples 2 and 3 gave the following two compounds (Examples 6 and 7) after separation by crystallisation.

Example 6 N-(Nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1)

Colourless solid, m.p. 162-164°C, 22% yield

^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=6.8Hz, CH_3), 1.28 (12H, m, 6xCH_2), 1.50 (2H, m, NCH_2CH_2), 2.93, 2.97 (1H, dd, J=4.8, 14.8Hz, H_3), 3.22 (2H, m, $NHCH_2$), 3.44, 3.48 (1H, dd, J=2.0, 14.8Hz, H_3), 3.73, 4.10 (each 1H, d, J=17.6Hz, NCH_2), 3.90. 4.05 (each 1H, d, J=12.8Hz, $SOCH_2$), 4.53 (1H, m, H_4), 6.6 (1H, m, NH), 7.26-7.40 (5H, m, Ph-H); $\nu_{c=o}$ 1791 cm^{-1}

Found: C, 64.0; H, 7.8; N, 7.4%; $C_{21}H_{32}N_2O_3S$ requires: C, 64.3; H, 8.2; N, 7.1%

Example 7 N-(Nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2)

Colourless solid, m.p. 107-108°C, 34% yield

^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=6.8Hz, CH_3), 1.28 (12H, m, 6xCH_2), 1.52 (2H, m, NCH_2CH_2), 2.85, 2.89 (1H, dd, J=2.4, 15.3Hz, H_3), 3.15, 3.19 (1H, dd, J=5.4, 15.3Hz, H_3), 3.26 (2H, m, $NHCH_2$), 3.91, 4.23 (each 1H, d, J=17.1Hz, NCH_2), 4.0, 4.20 (each 1H, d, J=13Hz, $SOCH_2$), 4.62 (1H, m, H_4), 7.2 (1H, m, NH), 7.26-7.40 (5H, m, Ph-H); $\nu_{c=o}$ 1794 cm^{-1}

Found: C, 63.9; H, 8.0; N, 7.2%; $C_{21}H_{32}N_2O_3S$ requires: C, 64.3; H, 8.2; N, 7.1%

Example 8 N-(Nonyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide

Treatment of N-(nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide with *m*CPBA as described for Example 4 gave the title compound as a colourless solid, m.p. 125-126°C, 76% yield

^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=6.8Hz, CH_3), 1.28 (12H, m, 6xCH_2), 1.50 (2H, m, NCH_2CH_2), 2.97, 3.03 (1H, dd, J=2.4, 15.4Hz, H_3), 3.09, 3.15 (1H, dd, J=5.1, 15.4Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.83, 3.98 (each 1H, d, J=16.9Hz, NCH_2), 4.32, 4.39 (each 1H, d, J=14.3Hz, SO_2CH_2), 4.85 (1H, m, H_4), 5.95 (1H, m, NH), 7.41 (5H, m, Ph-H)

$\nu_{c=o}$ 1796 cm^{-1}

Found: C, 61.4; H, 7.6; N, 7.0%; $C_{21}H_{32}N_2O_4S$ requires: C, 61.7; H, 7.9; N, 6.9%

Example 11 N-(6-(4-Pyridyl)hexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide

A mixture of 4-benzylthio-2-oxoazetidine-1ylacetic acid (2.26g), 6-(4-pyridyl)hexylamine (1.60g), dicyclohexylcarbodiimide (1.86g) and 1-

hydroxybenzotriazole (1.22g) in dry dimethylformamide (20ml) was stirred at 20-25°C for 3 hrs. Ethyl acetate (50ml) was added, the mixture was filtered and the filtrate evaporated to an oil. This oil was taken up in EtOAc, washed with $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated to an orange oil which was purified by chromatography on silica gel (EtOAc/EtOH) to give the title compound as a colourless oil (3.22g, 87% yield)

^1H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x CH_2), 2.59 (2H, t, J=8 Hz, CH_2Ph), 2.95 (1H, dd, J=2, 15 Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.37 (1H, dd, J=5, 15 Hz, H_3), 3.56, 3.72 (each 1H, d, J=17 Hz, NCH_2), 3.81 (2H, s, SCH_2), 4.82 (1H, m, H_4), 6.18 (1H, br s, NH), 7.09 (2H, m, Pyr-3,5H), 7.30 (5H, m, Ph-H), 8.47 (1H, m, Pyr-2,6H)

Example 12 N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Dia 1)

N-(6-(4-pyridyl)hexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide (3.04g)was dissolved in CH_2Cl_2 (50ml), cooled to -60°C and a solution of 55-60% *m*-chloroperbenzoic acid (*m*CPBA) (2.11g) in CH_2Cl_2 (100ml) was added dropwise over 15 mins. The solution was stirred at 20-25°C for 3 hrs then washed with aq $NaHCO_3/Na_2SO_3$, brine, dried over $MgSO_4$ and evaporated to a sticky solid. This was recrystallised twice from ethyl acetate to give the title compound as a colourless solid m.p. 167-8°C, (0.90g; 30%)

^1H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x CH_2), 2.59 (2H, t, J=8 Hz, CH_2Ph), 2.97 (1H, dd, J=5, 15 Hz, H_3), 3.23 (2H, m, $NHCH_2$), 3.47 (1H, dd, J=2, 15 Hz, H_3), 3.68, 4.15 (each 1H, d, J=17 Hz, NCH_2), 3.89, 4.07 (each 1H, d, J=13 Hz, $SOCH_2$), 4.50 (1H, m, H_4), 6.75 (1H, br s, NH), 7.10 (2H, m, Pyr-3,5H), 7.25, 7.40 (5H, 2 x m, Ph-H), 8.48 (2H, br s, Pyr-2,6H); $\nu_{c=o}$ 1792 cm^{-1}

Found: C, 64.4; H, 6.7; N, 9.8%; $C_{23}H_{29}N_3O_3S$ requires: C, 64.6; H, 6.8; N, 9.8%

Example 13 N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (95% Dia 2)

The mother liquor from the above recrystallisation in Example 12 was evaporated to a solid which was recrystallised twice from ethyl acatate to give the title compound as a colourless solid, m.p. 109-10°C, (1.41g, 46% yield)

^1H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.59 (2H, t, J=8 Hz, CH_2Ph), 2.92 (1H, dd, J=2, 15 Hz, H_3), 3.25 (3H, m, $NHCH_2$ + H_3), 3.87, 4.27 (each 1H, d, J=17 Hz, NCH_2), 3.98, 4.19 (each 1H, d, J=13 Hz, $SOCH_2$), 4.61 (1H, m, H_4), 7.10 (2H, m, Pyr-3,5H), 7.25,7.38 (6H, 2 x m, Ph-H + NH), 8.47 (2H, m, Pyr-2,6H); $\nu_{c=o}$ 1793 cm^{-1}

Found: C, 64.3; H, 6.6; N, 9.8%; $C_{23}H_{29}N_3O_3S$ requires: C, 64.6; H, 6.8; N, 9.8%

Example 14 N-(6-(4-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide

N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Dia 1) (1.15g) was dissolved in CH_2Cl_2 (50ml) and a solution of 55-60% *m*CPBA(1.10g;ca 3.5mM) in CH_2Cl_2(50ml) added and stirred at 20-25°C for 3hrs and allowed to stand at 20-25°C for 16 h. *m*CPBA (0.13g) was added and the solution stirred for a further 3 hrs then washed with aq $NaHCO_3/Na_2SO_3$, brine, dried over $MgSO_4$ and evaporated to an oil. This oil was chromatographed on silica gel (EtOAc/EtOH) to give the title compound as a solid which was recrystallised from EtOAc/Et_2O to give a colourless solid m.p. 106-8°C, (0.38g, 31%)

^{1}H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.60 (2H, t, J=8 Hz, CH_2Pyr), 3.00 (1H, dd, J=2, 15 Hz, H_3), 3.11 (1H, dd, J=5, 15 Hz, H_3), 3.25 (2H, m, $NHCH_2$), 3.86, 3.94 (each 1H, d, J=17 Hz, NCH_2), 4.34 (2H, s, SO_2CH_2), 4.83 (1H, m, H_4), 6.10 (1H, br s, NH), 7.10 (2H, m, Pyr-3,5H), 7.41 (5H, m, Ph-H), 8.47 (2H, m, Pyr-6H); $\nu_{c=o}$ 1797 cm^{-1}

Found: C, 62.0; H, 6.5; N, 9.5%; $C_{23}H_{29}N_3O_4S$ requires: C, 62.3; H, 6.6; N, 9.5%

Example 15 N-(6-(4-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide N-(pyridyl)oxide

N-(6-(4-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide N-(pyridyl)oxide was also produced in the oxidation of N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide with *m*CPBA (details in Example 14 above) and was obtained after chromatography and recrystallisation from ethyl acetate as a colourless solid (0.44g, 35%), m.p. 132-4°C.

^{1}H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.60 (2H, t, J=8 Hz, CH_2Pyr), 3.00 (1H, dd, J=2, 15 Hz, H_3), 3.12 (1H, dd, J=5, 15 Hz, H_3), 3.25 (2H, m, $NHCH_2$), 3.91 (2H, s, NCH_2), 4.36 (2H, s, SO_2CH_2), 4.83 (1H, m, H_4), 6.22 (1H, br s, NH), 7.09 (2H, m, Pyr-3,5H), 7.41 (5H, m, Ph-H), 8.12 (2H, m, Pyr-2,6H); $\nu_{c=o}$ 1783 cm^{-1}

Found; C, 59.6; H, 6.2; N, 9.1%; $C_{23}H_{29}N_3O_5S$ requires: C, 60.1; H, 6.4; N, 9.1%

Example 16 N-(6-(2-Pyridyl)hexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide

Treatment of of 4-benzylthio-2-oxoazetidine-1ylacetic acid with 6-(2-pyridyl)hexylamine, dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in dry dimethylformamide as described for Example 11 gave the title compound as a colourless oil in 90% yield.

^{1}H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.77 (2H, t, J=8 Hz, CH_2Pyr), 2.94 (1H, dd, J=2, 15 Hz, H_3), 3.23 (2H, m, $NHCH_2$), 3.36 (1H, dd, J=5, 15 Hz, H_3), 3.54, 3.75 (each 1H, d, J=17 Hz, NCH_2), 3.81 (2H, s, SCH_2), 4.83 (1H, m, H_4), 6.29 (1H, br s, NH), 7.15 (2H, m, Pyr-3,5H), 7.30 (5H, m, Ph-H), 7.59 (1H, m, Pyr-4H), 8.50 (1H, m, Pyr-6H)

Examples 17 and 18 were prepared by the methods described for Examples 12 and 13 and Examples 19 and 20 were prepared by the methods described for Examples 14 and 15.

Example 17 N-(6-(2-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Dia 1)

Colourless solid, m.p. 126-30°C, 30% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.9 (8H, m, 4 x CH_2), 2.77 (2H, t, J=8 Hz, CH_2Pyr), 2.95 (1H, dd, J=5, 15 Hz, H_3), 3.22 (2H, m, $NHCH_2$), 3.45 (1H, dd, J=2, 15 Hz, H_3), 3.75, 4.09 (each 1H, d, J=17 Hz, NCH_2), 3.90, 4.06 (each 1H, d, J=13 Hz, $SOCH_2$), 4.54 (1H, m, H_4), 6.75 (1H, br s, NH), 7.10 (2H, m, Pyr-3,5H), 7.30 (5H, m, Ph-H), 7.59 (1H, m, Pyr-4H), 8.50 (1H, m, Pyr-6H); $\nu_{c=o}$ 1791 cm^{-1}

Found: C, 64.5; H, 6.6; N, 9.8%; $C_{23}H_{29}N_3O_3S$ requires: C, 64.6; H, 6.8; N, 9.8%

Example 18 N-(6-(2-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (92% Dia 2)

Colourless solid, m.p. 93-6°C, 20% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.9 (8H, m, 4 x CH_2), 2.78 (2H, t, J=8 Hz, CH_2Pyr), 2.86 (1H, dd, J=2, 15 Hz, H_3), 3.25 (3H, m, $NHCH_2$ + H_3), 3.92, 4.23 (each 1H, d, J=17 Hz, NCH_2), 4.0, 4.20 (each 1H, d, J=13 Hz, $SOCH_2$), 4.63 (1H, m, H_4), 7.10 (2H, m, Pyr-3,5H), 7.30 (6H, m, Ph-H + NH), 7.58 (1H, m, Pyr-4H), 8.50 (1H, m, Pyr-6H); $\nu_{c=o}$ 1793 cm^{-1}

Found: C, 64.5; H, 6.7; N, 9.8%; $C_{23}H_{29}N_3O_3S$ requires: C, 64.6; H, 6.8; N, 9.8%

Example 19 N-(6-(2-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide

Colourless solid, m.p. 116-8°C, 9% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.78 (2H, t, J=8 Hz, CH_2Pyr), 2.99 (1H, dd, J=2, 15 Hz, H_3), 3.11 (1H, dd, J=5, 15 Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.82, 4.01 (each 1H, d, J=17 Hz, NCH_2), 4.36 (2H, s, SO_2CH_2), 4.87 (1H, m, H_4), 6.26 (1H, br s, NH), 7.12 (2H, m, Pyr-3,5H), 7.41 (5H, m, Ph-H), 7.60 (1H, m, Pyr-4H), 8.50 (1H, m, Pyr-6H); $\nu_{c=o}$ 1792 cm^{-1}

Found: C, 62.2; H, 6.5; N, 9.4%; $C_{23}H_{29}N_3O_4S$ requires: C, 62.3; H, 6.6; N, 9.5%

Example 20 N-(6-(2-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide N-(pyridyl)oxide

Colourless solid, m.p. 153-4°C, 61% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.8 (8H, m, 4 x CH_2), 2.96 (3H, m, CH_2Pyr + H_3), 3.13 (1H, dd, J=5, 15 Hz, H_3), 3.25 (2H, m, $NHCH_2$), 3.85, 4.09 (each 1H, d, J=17 Hz, NCH_2), 4.38 (2H, s, SO_2CH_2), 4.92 (1H, m, H_4), 6.61 (1H, br s, NH), 7.2 (3H, m, Pyr-3,4,5H), 7.41 (5H, m, Ph-H), 8.26 (1H, m, Pyr-6H); $\nu_{c=o}$ 1793 cm^{-1}

Found: C, 60.0; H, 6.3; N, 9.1%; $C_{23}H_{29}N_3O_5S$ requires: C, 60.1; H, 6.4; N, 9.1%

Example 21 1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylthio-2-oxoazetidine

To a mixture of 2-bromomethyl-4-(5-phenylpentyl)thiazole (0.5 g), 4-benzylthio-azetidin-2-one (0.3 g) and tetra-n-butylammonium bromide (0.05 g) in dry tetrahydrofuran (THF), cooled to 10°C, powdered potassium hydroxide (0.096 g) was added. The mixture was warmed to 20°C and stirred for 4 hours. Ethyl acetate and brine were added and the organic solution separated, washed and evapotated to give a brown oil. Chromatography on silica gel using petroleum ether/ethyl acetate gave the title compound as a pale yellow oil (0.48 g, 68% yield).

^{1}H nmr δ ($CDCl_3$) 1.40 (2H, m, CH_2), 1.63-1.75 (4H, m, 2xCH_2), 2.59 (2H, t, J=7.6 Hz, PhCH_2), 2.74 (2H, t, J=7.6Hz, thiazolylCH_2), 2.93, 2.97 (1H, dd, J=2.4, 15.2 Hz, H_3), 3.33, 3.37 (1H, dd, J=5.2, 15.2 Hz, H_3), 3.77 (2H, s, SCH_2), 4.33, 4.76 (each 1H, d, J=16.4 Hz, NCH_2), 4.78 (1H, m, H_4), 6.83 (1H, s, thiazole-H), 7.14-7.29 (10H, m, 2xPh-H); $\nu_{c=o}$ 1772 cm^{-1}

Example 22 1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulphinyl-2-oxoazetidine (Dia 1:Dia 2 22:78)

1-(4-(5-phenylpentyl)thiazol-2-ylmethyl)-4-benzylthio-2-oxoazetidine (1.1 equiv) was dissolved in CH_2Cl_2 (50ml), cooled to -60°C and a solution of 55-60% *m*-chloroperbenzoic acid (*m*CPBA) (2.11g) in CH_2Cl_2 (100ml) was added dropwise over 15 mins. The solution was stirred at 20-25°C for 3 hrs then washed with aq $NaHCO_3$/Na_2SO_3, brine, dried over $MgSO_4$ and solvent removed under reduced pressure to give the title compound as a mixture of diastereoisomers in the form of a colourless oil in 87% yield. $\nu_{c=o}$ 1785 cm^{-1}

Found: C, 66.2; H, 6.2; N, 5.9%; $C_{25}H_{28}N_2O_2S$ requires: C, 66.3; H, 6.2; N, 6.2%

Example 23 1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulphonyl-2-oxoazetidine

Treatment of 1-(4-(5-phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulfinyl-2-oxoazetidine with *m*CPBA (1.1 equiv) under the conditions described for Example 2 gave the title compound in the form of a colourless oil in 91% yield.

^{1}H nmr δ ($CDCl_3$) 1.40 (2H, m, $\underline{CH_2}$), 1.61-1.73 (4H, m, 2x$\underline{CH_2}$), 2.60 (2H, t, J=7.8 Hz, Ph$\underline{CH_2}$), 2.74 (2H, t, J=7.6Hz, thiazolyl$\underline{CH_2}$), 3.15 (2H, d, J=4Hz, 2x$\underline{H_3}$), 4.35 (2H, m, $SO_2\underline{CH_2}$), 4.50, 4.97 (each 1H, d, J=16.4 Hz, N$\underline{CH_2}$), 4.84 (1H, m, $\underline{H}$), 6.86 (1H, s, thiazole-$\underline{H}$), 7.14-7.39 (10H, m, 2xPh-$\underline{H}$); $\nu_{c=o}$ 1792 cm^{-1}

Found: C, 64.1; H, 6.2; N, 6.0%; $C_{25}H_{28}N_2O_3S$ requires: C, 64.1; H, 6.0; N, 6.0%

Example 24 4-Methylthio-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one

Treatment of 4-methylthioazetidin-2-one with 2-bromomethyl-5-phenyloxazole in the presence of lithium hexamethyldisilazide in THF at -70°C gave the title compound as a yellow gum.

Found: C, 61.3; H, 5.2; N, 10.2%; $C_{14}H_{14}N_2O_2S$ requires: C, 61.3; H, 5.1; N, 10.2%

Example 25 4-Methylsulfinyl-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one

Treatment of 4-methylthio-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one with *m*CPBA (1 eq) in dichloromethane at -78°C following the procedure of Example 2 gave the title compound as a mixture of diastereoisomers as a yellow gum. m/z 290 (M^+), 227, 158, 103, 77.

Found: C, 56.3; H, 4.9; N, 9.5%; $C_{14}H_{14}N_2O_3S$ (+ 0.4 H_2O + 0.02 CH_2Cl_2) requires: C, 56.2; H, 5.0; N, 9.4%; (solvents identified by nmr)

Example 26 4-Methylsulfinyl-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one

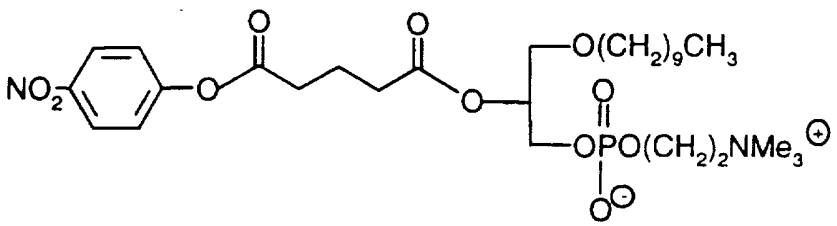
Treatment of 4-methylthio-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one with *m*CPBA (2 eq) in dichloromethane at 20°C gave the title as a cream solid

Found: C, 54.8; H, 4.7; N, 9.2%; $C_{14}H_{14}N_2O_4S$ requires: C, 54.9; H, 4.6; N, 9.1%;

Biological Data

Screen for Lp-PLA$_2$ inhibition.

Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

Assays were performed in 96 well titre plates.

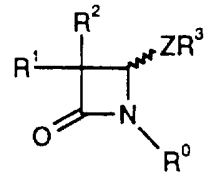
Lp-PLA_2 was partially purified by density gradient centrifugation of human plasma. Active fractions were pooled and used as the source of Lp-PLA_2. The enzyme was pre-incubated at 37 °C with vehicle or test compound for 10 min in a total volume of 180 µl. The reaction was then initiated by the addition of 20 µl 10x substrate (A) to give a final substrate concentration of 20 µM. The reaction was followed at 405 nm for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results:

The compounds of Example 3, 7, 8, 13, 18 and 22 had IC_{50} values in the range 5 to 200nM.

Claims

1. A compound of formula (I):



(I)

in which:

R^0 is $CR^4R^5\text{-}X^1\text{-}Y^1$, $CR^4R^5\text{-}X^2\text{-}Y^2$, or $(CH_2)_pX^3(CH_2)_qY^3$;

R^1 and R^2, which may be the same or different, is each selected from hydrogen, halogen or $C_{(1\text{-}8)}$alkyl;

R^4 and R^5 which may be the same or different is each selected from hydrogen and $C_{(1\text{-}6)}$alkyl, or R^4 and R^5 may be linked together to form the residue of a $C_{(3\text{-}7)}$ cycloalkyl ring;

X^1 is a linker group and Y^1 is optionally substituted $C_{(1\text{-}12)}$alkyl $C_{(2\text{-}12)}$alkenyl, $C_{(2\text{-}12)}$alkynyl, $C_{(3\text{-}7)}$-cycloalkyl$C_{(1\text{-}8)}$ alkyl;

X^2 is a linker group and Y^2 an optionally substituted heteroaryl group;

X^3 is a heteroaryl group and Y^3 is an optionally substituted aryl group, p is an integer from 1 to 6, q is 0 or an an integer from 1 to 6;

Z is O and R^3 is $C_{(1\text{-}8)}$alkyl, aryl$C_{(1\text{-}4)}$alkyl or aryl each of which may be optionally substituted, or

Z is S(O)n in which n is 0, 1 or 2 and R^3 is $C_{(1\text{-}8)}$alkyl, $C_{(3\text{-}8)}$cycloalkyl, $C_{(3\text{-}8)}$cycloalkyl$C_{(1\text{-}6)}$alkyl, aryl, aryl$C_{(1\text{-}4)}$alkyl or heteroaryl$C_{(1\text{-}4)}$alkyl each of which may be optionally substituted.

2. A compound of formula (I) as claimed in claim 1 in which R^1 and R^2 is each hydrogen.

3. A compound of formula (I) as claimed in claim 1 or 2 in which Z is SO and R^3 is arylmethyl or heteroarylmethyl

4. A compound as claimed in claim 3 in which R^3 is benzyl or furanylmethyl.

5. A compound as claimed in claim 4 in which R^3 includes a carboxy or ester substituent.

6. A compound as claimed in any one of claims 1 to 5 in which R^4 and R^5 are both hydrogen or R^4 is hydrogen and R^5 methyl.

7. A compound as claimed in any one of claims 1 to 6 in which:

X^1 is a direct bond or a group $(CH_2)_xX^4$ in which X^4 is CH_2O, CO, COO, $CONR^6$, $CONR^6CO$, or CONHO in which R^6 is hydrogen or $C_{(1-6)}$alkyl, x is 0 (for all except X^4 =COO) or an integer from 1 to 6; or

(ii) X^2 is:

(a) a direct bond;

(b) a group $X^5(CH_2)_y$ in which X^5 is CO, $CONR^6$, COO, $CONR^6CO$, or CONHO in which R^6 is hydrogen or $C_{(1-6)}$alkyl and y is 0 or an integer from 1 to 12;

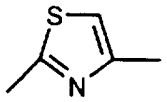
(c) a $C_{(1-12)}$alkylene chain optionally interupted by X^5;

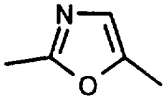
(d) a group A-B in which A is a direct bond or X^5 and B is a $C_{(1-12)}$alkylene chain interupted and/or terminated at the end remote from A by one or more groups M selected from O, S(O)n, NR^6, alkene or alkyne in which R^6 is hydrogen or $C_{(1-6)}$alkyl and n is 0, 1 or 2.

8. A compound as claimed in claim 7 in which X^1 is CONH or X^2 is $CONH(CH_2)_6$.

9. A compound as claimed in any one of claims 1 to 8 in which Y^1 is $C_{(6-10)}$ alkyl, $C_{(3-7)}$cycloalkyl$C_{(5-7)}$ alkyl or Y^2 is pyridyl or pyridyl N-oxide.

10. A compound as claimed in any one of claims 1 to 9 in which X^3 is:



or


p is 1, q is 0 or 5 and Y^3 is optionally substituted phenyl or naphthyl.

11. A compound of formula (I) selected from:

N-(6-Cyclohexylhexyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide;
N-(6-Cyclohexylhexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Diastereoisomer 1);
N-(6-Cyclohexylhexyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2);
N-(6-Cyclohexylhexyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide;
N-(Nonyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide;
N-(Nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1);
N-(Nonyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2);
N-(Nonyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Pyridyl)hexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide;
N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Dia 1);
N-(6-(4-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide (Dia 2);
N-(6-(4-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide;
N-(6-(4-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide N-(pyridyl)oxide;
N-(6-(2-Pyridyl)hexyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide;
N-(6-(2-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide

(Dia 1);
N-(6-(2-Pyridyl)hexyl)-4-benzylsulphinyl-2-oxoazetidin-1-ylacetamide
(Dia 2);
N-(6-(2-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide;
N-(6-(2-Pyridyl)hexyl)-4-benzylsulphonyl-2-oxoazetidin-1-ylacetamide N-(pyridyl)oxide;
1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylthio-2-oxoazetidine;
1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulphinyl-2-oxoazetidine ;
1-(4-(5-Phenylpentyl)thiazol-2-ylmethyl)-4-benzylsulphonyl-2-oxoazetidine;
4-Methylthio-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one;
4-Methylsulfinyl-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one; and
4-Methylsulfinyl-1-((5-phenyloxazol-2-yl)methyl)azetidin-2-one;

12. A pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

13. A compound of formula (I) for use in therapy.

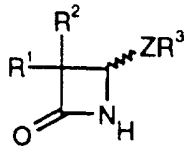
14. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating atherosclerosis.

15. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating diabetes, hypertension, angina pectoris, after ischaemia, reperfusion, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation, inflammatory conditions of the brain such as Alzheimer's Disease, neuropsychiatric disorders such as schizophrenia, and psoriasis.

16. A method of treating a disease state associated with activity of the enzyme Lp-PLA2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme.

17. A method as claimed in claim 15 in which the disease state is associated with:
(a) the increased involvement of monocytes, macrophages or lymphocytes;
(b) the formation of lysophosphatidylcholine and oxidised free fatty acids;
(c) lipid peroxidation in conjunction with Lp PLA2 activity; or
(d) endothelial dysfunction.

18. A process for preparing a compound of formula (I) as defined in claim 1 which comprises treating an azetidone of formula (II):



(II)

in which:

R^1, R^2, R^3, and Z are as hereinbefore defined;

with an alkylating agent of the formula (III):

$$R^7R^0$$

(III)

in which R^7 is a suitable leaving group such as halogen or triflate; and

$R^0$is as hereinbefore defined;

under alkylating conditions.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/EP 96/05588

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D205/09 C07D401/12 C07D417/06 C07D413/06 C07D205/08 A61K31/395

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 199 630 A (MERCK & CO. INC.) 29 October 1986 see page 11 - page 13; claims ---	1-18
A	GB 2 266 527 A (MERCK & CO. INC.) 3 November 1993 see page 19 - page 31; claims ---	1-18
A	WO 95 02579 A (ZENECA LTD.) 26 January 1995 see claims ---	1-18
P,Y	WO 96 13484 A (SMITHKLINE BEECHAM PLC) 9 May 1996 cited in the application see claims --- -/--	1-18

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 1997	07. 03. 97

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	Chouly, J

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/EP 96/05588

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 96 19451 A (SMITHKLINE BEECHAM PLC) 27 June 1996 cited in the application see claims -----	1-18

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 96/05588

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 16,17
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16,17 is(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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 1286304 A	16-07-91
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