AZETIDINONE DERIVATIVES FOR THE TREATMENT 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.

Lipoprotein Associated Phospholipase A_2 (Lp-PLA_2). The sequence of the enzyme, the isolation and purification thereof, isolated nucleic acids encoding the enzyme, recombinant host cells transformed with DNA encoding the enzyme are described in patent application WO 95/00649 (SmithKline Beecham plc). Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. 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 same enzyme, although calling it by the name 'Platelet Activating Factor Acetyl Hydrolase' (PAF acetyl hydrolase) and suggest that it may have potential as a therapuetic protein for regulating pathological inflammatory events.

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 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.

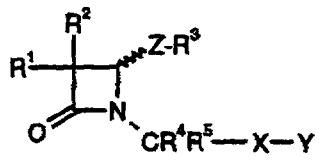
The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA_2 could therefore prove beneficial in the treatment of this phenomenon. A Lp-PLA_2 inhibitor could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

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.

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, 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).

We have now identified a series of compounds which have been found to act as inhibitors of Lp-PLA$_2$.

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



(I)

in which:

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

R^4 and R^5 which may be the same or different is each selected from hydrogen, $C_{(1-6)}$alkyl, $C_{(2-6)}$alkenyl, aryl, aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl each of which may be optionally substituted or R^4 and R^5 may be linked together to form the remainder of a (C_{3-7})cycloalkyl ring;

X is a linker group;

Y is an optionally substituted aryl group;

Z is oxygen and R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl, $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, aryl, or aryl(C_{1-4})alkyl, 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, heteroaryl, or heteroaryl(C_{1-4})alkyl, each of which may be optionally substituted; and

excluding compounds in which:

X is a direct bond; a group $X^1(CH_2)_m$ in which X^1 is CO, $CONR^6$, COO, $CONR^6CO$, or $CONR^6O$ in which R^6 and m are as hereinbefore defined; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;

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, or aryl(C_{1-4})alkyl, each of which may be optionally substituted; and

R^4 and R^5 is each hydrogen.

Suitably, X is a direct bond; a group $X^1(CH_2)_m$ in which X^1 is CO, $CONR^6$, COO, $CONR^6CO$, or $CONR^6O$ in which R^6 is hydrogen or $C_{(1-6)}$alkyl and m is 0 or an integer from 1 to 12; a group $(X^1)_aX^2$ in which a is 0 or 1 and X^2 is a $C_{(1-12)}$alkylene chain interupted and/or terminated at the end adjacent to Y by one or more groups X^3 selected from O, $S(O)_x$, NR^6, alkene or alkyne, in which x is 0, 1 or 2; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1.

Suitable sub-sets of compounds within formula (I) include those in which:
(a) X is a direct bond; a group $X^1(CH_2)_m$ as hereinbefore defined; a group $(X^1)_aX^2$ as hereinbefore defined; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;
Z is oxygen and R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl, $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, aryl, or aryl(C_{1-4})alkyl, 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 heteroaryl or heteroaryl(C_{1-4})alkyl, each of which may be optionally substituted;
R^4 and R^5 are as hereinbefore defined; or
(b) X is a direct bond; a group $X^1(CH_2)_m$ as hereinbefore defined; a group $(X^1)_aX^2$ as hereinbefore defined; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;
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 or aryl(C_{1-4})alkyl, each of which may be optionally substituted;
R^4 and R^5 which may be the same or different is each selected from hydrogen, $C_{(1-6)}$alkyl, $C_{(2-6)}$alkenyl, aryl, aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl each of which may be optionally substituted or R^4 and R^5 may be linked together to form the remainder of a (C_{3-7})cycloalkyl ring, with the proviso that R^4 and R^5 are not both hydrogen; or
(c) X is a group $(X^1)_aX^2$ as hereinbefore defined;
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 or aryl(C_{1-4})alkyl, each of which may be optionally substituted; and
R^4 and R^5 is each hydrogen.

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 above.

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 values for when R^3 is aryl(C_{1-4})alkyl include aryl$C_{(1-3)}$alkyl. Within this, representative examples of the aryl group include phenyl and naphthyl. Suitable examples of R^3 include benzyl, 2-phenylethyl and 3-phenylpropyl in each of which the phenyl ring may be optionally substituted by up to three substituents.

Suitable substituents for a phenyl or naphthyl ring in R^3 include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkoxycarbonyl, $C_{(2-6)}$alkenyloxycarbonyl, carboxy, carboxy$C_{(1-6)}$alkyl and $C_{(1-6)}$alkoxycarbonyl$C_{(1-6)}$alkyl. More preferably, R^3 is 4-carboxybenzyl or a corresponding $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl ester thereof.

Representative examples of the aryl group for when R^3 is aryl 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, $C_{(1-6)}$alkoxycarbonyl, $C_{(2-6)}$alkenyloxycarbonyl, carboxy, carboxy$C_{(1-6)}$alkyl and $C_{(1-6)}$alkoxycarbonyl$C_{(1-6)}$alkyl.

Representative examples for R^3 when R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl or $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl include methyl, n-butyl, t-butyl and n-hexyl, cyclohexyl and cyclohexyl methyl, suitably n-butyl, t-butyl or n-hexyl. Suitable substituents for the alkyl or cycloalkyl group in R^3 include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkoxycarbonyl, $C_{(2-6)}$alkenyloxycarbonyl, carboxy, carboxy$C_{(1-6)}$alkyl and $C_{(1-6)}$alkoxycarbonyl$C_{(1-6)}$alkyl.

Further representative values for R^3 include heteroaryl$C_{(1-3)}$alkyl, preferably heteroarylmethyl. Representative examples of the heteroarylaryl group for use in R^3 include pyridyl, pyridyl N-oxide, furanyl, thienyl and thiazolyl. Suitable substituents for a heteroaryl ring in R^3 include halo, hydroxy, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkoxycarbonyl, $C_{(2-6)}$alkenyloxycarbonyl, carboxy, carboxy$C_{(1-6)}$alkyl and $C_{(1-6)}$alkoxycarbonyl$C_{(1-6)}$alkyl.

It will be appreciated that within R^3, an optional substituent may be located in the alkyl, cycloalkyl, aryl and/or heteroaryl portion. Preferably, the substituent is carboxy or a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenylester thereof.

Preferably, R^3 is aryl$C_{(1-3)}$alkyl or heteroaryl$C_{(1-3)}$alkyl, more preferably aryl$C_{(1-3)}$alkyl, most preferably benzyl, which may be optionally substituted, in particular by a carboxy group or a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenylester thereof.

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

Preferably, $S(O)_nR^3$ is optionally substitued benzylsulphinyl, more preferably 4-carboxybenzylsulphinyl or a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenylester thereof.

Representative examples of R^4 and R^5 when an alkyl group include methyl, ethyl and propyl. Representative examples of a $C_{(2-6)}$alkenyl group include allyl. Representative examples of a (C_{3-7})cycloalkyl ring include cyclopropyl. Representative examples of aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl include benzyl and furylmethyl, respectively. Representative examples of R^4 and R^5 when aryl or aralkyl include phenyl and benzyl. Suitably, R^4 and R^5 are both hydrogen or R^4 is hydrogen and R^5 methyl.

Representative examples of X include $CO(CH_2)_m$, $CONH(CH_2)_m$, $COO(CH_2)_m$, $CONHCO(CH_2)_m$, $CONHO(CH_2)_m$ and $C_{(1-12)}$alkylene. Preferably,

X^1 is CO or $CONR^6$, more preferably CONH. Preferably, m is 1, 2, 5, 6, 7 or 9, preferably 6.

Further representative examples of X include $X^4(CH_2)_pCH=CH(CH_2)_q$, $X^4(CH_2)_pC\equiv C(CH_2)_q$ or $X^4(CH_2)_p(O)_r(CH_2)_q(O)_s$ in which X^4 is a direct bond or $CONR^6$, p is an integer from 1 to 12, q is 0 or an integer from 1 to 12 such that $p+q \leq 12$, suitably ≤ 6, r is 0 or 1 and s is 1 or r is 1 and s is 0, with the proviso that if r and s are both 1, then $q \geq 1$. In preferred examples in this subset of compounds, X is $CONR^6(CH_2)_4C\equiv C$ or $(CH_2)O(CH_2)_6$.

Preferred examples of X include $CONH(CH_2)_6$, $CONR^6(CH_2)_4C\equiv C$ and $(CH_2)O(CH_2)_6$.

Suitably, Y is a benzene ring, optionally substituted by up to three further substituents. Suitable substituents include halo, hydroxy, $C_{(1-8)}$alkyl and $C_{(1-8)}$alkoxy. Preferably, Y is phenyl optionally substituted by halo.

Useful combinations of substituents for compounds of formula (I) which are exemplified herein are summarised in the following table:

R^3	R^4	R^5	X
4-carboxy-benzylsulfinyl	hydrogen	methyl	$CONH(CH_2)_6$
5-carboxyfuran-2-methylsulfinyl	hydrogen	hydrogen	$CONH(CH_2)_6$
benzylsulfinyl	hydrogen	hydrogen	$(CH_2)O(CH_2)_6$
benzylsulfinyl	hydrogen	hydrogen	$CONR^6(CH_2)_4C\equiv C$

Compounds of formula (I) in which the group R^3 incorporates a carboxy substituent are generally found to have improved activity against the target enzyme in *in vivo* models, in particular, a superior ability to inhibit plaque associated Lp PLA_2. In such studies, it is however found that such compounds have better pharmacokinetic properties if initially adminstered as an alkyl or alkenyl ester 'pro-drug'. The ester grouping is then rapidly hydrolysed in the liver to release free carboxyl. Generally, compounds with an α-methyl substituent, that is those in which one of R^4/R^5 is methyl are more potent than the corresponding des-methyl compounds.

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 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.

It will be further readily appreciated by the skilled person that, in compounds of formula (I) in which n is 1, that is sulphoxide compounds, the presence of the SO

moiety will introduce an additional chiral centre into the molecule and therefore 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, 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, 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, (C_{1-6})alkylcarbonyloxy, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkylcarbonyloxy, (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 'heteroaryl' includes single and fused rings, each ring suitably comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A fused heteroaryl ring may include carbocyclic rings and need include only one heteroaryl ring. Suitable fused heteroaryl rings include bicyclic systems.

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.

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:
[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide, in particular diastereoisomers 1b, 2a and 2b, especially isomer 2b;
(α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-carboxybenzylsulphinyl]-2-oxoazetidin-1-ylpropionamide and the corresponding allyl ester;
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide;
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-carboxyfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2) and the corresponding allyl and methyl esters thereof;
N-(6-[4-Chlorophenyl]hexyl)-4-(5-carboxyfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2) and the corresponding allyl and methyl esters thereof.
N-[6-(4-chlorophenyl)hexyl]-[4-(4-carboxymethylphenoxy)-2-oxo-azetidin-1-yl]-acetamide;
N-[6-(4-Chlorophenyl)hexyl]-[4-(2-fluorophenoxy 2-oxo azetidin-1 yl) acetamide;
N-(6-(4-Chlorophenyl)hexyl)-(4-(4-allyloxycarbonyl-methylphenoxy)-2-oxoazetidin-1-yl)acetamide;
1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2);
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (Diastereoisomer 2); and
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2).

More preferred compounds include:
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide, in particular diastereoisomers 1b, 2a and 2b, especially isomer 2b(1);
(α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-carboxybenzylsulphinyl]-2-oxoazetidin-1-ylpropionamide and the corresponding allyl ester;

N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-carboxyfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2) and the corresponding allyl and methyl esters thereof;

N-(6-{4-Chlorophenyl}hexyl)-4-(5-carboxyfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2) and the corresponding allyl and methyl esters thereof;

1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2);

1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (Diastereoisomer 2); and

1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2).

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.

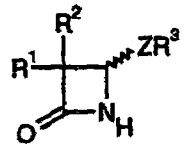
A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

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 from convenient starting materials by adapting synthetic procedures well known in the art. A suitable process comprises treating an azetidone of formula (II):



(II)

in which:

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

with an alkylating agent of the formula (III):

$$L^1CR^4R^5XY$$

(III)

in which L^1 is a suitable leaving group such as halogen or triflate; and R^4, R^5, X and Y are as hereinbefore defined;

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.

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

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 (I) in which Z is $S(O)_n$ and n is 1 or 2 can be readily prepared from corresponding 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.

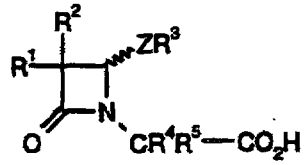
Compounds of formula (II) in which in which Z is $S(O)_n$ and n is 0 may be obtained by treating 4-acetoxyazetidinone, 4-benzoyloxyazetidinone or 4-phenylsulfonylazetidinone with a thiol R^3SH in the presence of a base such as sodium ethoxide, in a suitable solvent such as ethanol at a temperature in the range 0 to 5°C. When this displacement is conducted in the presence of a chiral base, such as chinchonidine or cinchonine, enantiomerically enriched compounds (II) can be obtained (J Chem Soc, Chem Commun, 1982, 1324-5).

Compounds of formula (II) in which Z is O may be obtained by treating 4-acetoxyazetidinone, 4-benzoyloxyazetidinone or 4-phenylsulfonyl-azetidinone with a phenol/alcohol R^3OH 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 (III) may be readily prepared by adapting known synthetic procedures, according to the specific value of X. A convenient starting

material is an appropriately substituted aryl compound which may then be elaborated to introduce the side chain $L^1CR^4R^5X$-.

Compounds of formula (I) in which X denotes a group $CONR^6(CH_2)_m$, $CONR^6X^2$, $CONR^6O(CH_2)_m$ or $CONR^6OX^2$ may be conveniently prepared by treating an acid of the formula (IV):



(IV)

in which:

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

with an amine of the formula (V):

$$NHR^6X^5Y$$

(V)

or a hydroxylamine of the formula (VI):

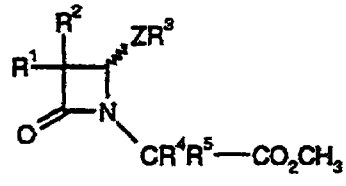
$$NH_2OX^5Y$$

(VI)

in which X^5 is $(CH_2)_m$ or X^2 and m, R^6, Y and X^2 are as 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.

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 ester, for instance a (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 group, for instqance an alkyl group, may then be introduced by alkylating of the first formed monoalkyl ester.

Compounds of formula (I) in which X denotes a group $COO(CH_2)_m$ or $COOX^2$ may be conveniently prepared by a transesterification reaction from another ester, in particular the methyl ester of formula (VII):



(VII)

in which:

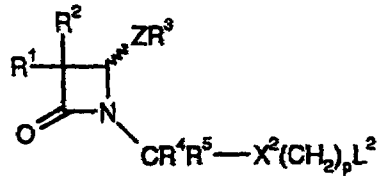
Z, R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined;

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-bromo(C_{1-7}) alkanoate, under alkylating conditions as hereinbefore described.

Alternatively, a compound of formula (I) in which X denotes a group $COO(CH_2)_m$ or $COOX^2$ may be prepared by treating a compound of formula (IV) with an alcohol YX^5OH or an activated derivative thereof, for instance a tosylate.

Compounds of formula (I) in which the linker group X contains an ether function may be prepared by a suitable ether coupling reaction, for instance treating a compound of formula (VIII):



(VIII)

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

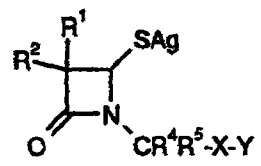
with a compound of formula (IX):

$$L^3(CH_2)_qY$$

(IX)

in which one of L^2 and L^3 is a halogen or other suitable leaving group such as triflate or tosylate and the other is OH or a suitable salt therof, and p and q are as hereinbefore defined; under standard ether forming conditions.

Compounds of formula (I) in which Z is $S(O)_n$ and n is 0 may also be prepared by a process which comprises treating a compound of formula (X):



(X)

in which R^1, R^2, R^4, R^5, X and Y are as hereinbefore defined;

with an alkylating agent of the formula (XI):

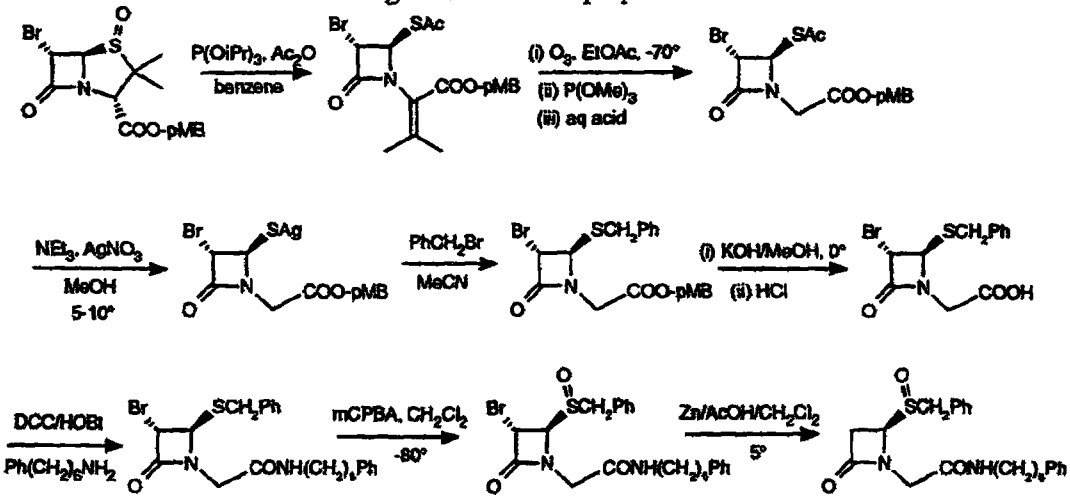
R^3L^1 (XI)

in which R^3 and L^1 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 (X) 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 for the preparation of suitable intermediates



The preparation of the starting material (4-methoxybenzyl-6-bromopenicillinate-1-oxide) is described by J. Chem. Soc., Perkin Trans. 1, 1994, 179-188. An alkyl substituent (R4/R5) may be introduced at a late stage in the sequence, using alkylating conditions hereinbefore described.

The present invention will now be illustrated by the following examples. The relative configurations of the centre at the C4 position in the azetidinone and the centre alpha to the N of the azetidinone are unknown in the two diastereoisomers (a and b) described below but are thought to be R,R/S,S (diastereoisomer a) and R,S/S,R

(diastereoisomer b). The relative configurations of the C4 and sulfoxide centres are also unknown, but are thought to be *R,R/S,S* (diastereoisomer 1) or *R,S/S,R* (diastereoisomer 2). Such configurations were obtained initially by x-ray analysis of a limited number of compounds and then extrapolated to the remaining compounds on the basis of their ^{1}H NMR spectra. Unless otherwise specified (e.g. isomer (-)b2) all compounds are racemic (e.g. diastereoisomer b2). All compounds are predominantly the (diastereo)isomer described. All compounds are characterised by NMR and most by microanalysis and mass spec. Melting points are uncorrected. Isomers and enantiomers are labelled as described above to facilitate description of the syntheses and to indicate preferred compounds.

Preparations

4-(5-Allyloxycarbonylfuran-2-methylthio)azetidin-2-one

a. Methyl 5-(chloromethyl)-2-furoate

A stirring mixture of paraformaldehyde (25.22 g, 0.84 mol), anhydrous zinc chloride (108.06 g), and methyl 2-furoate (100 g, 0.793 mol) were cooled to 15 °C (ice bath) and a stream of HCl gas bubbled through with stirring. The temperature was allowed to rise to 25-30 °C, and after 1 hr the mixture was poured onto ice-water. The organic layer was separated off and the aqueous layer further extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to a dark brown oil. Distillation under reduced pressure gave the product as a pale yellow solid (72.5g, 52% yield), b.p.(88°C/0.8 mm Hg). ^1H NMR δ (DMSO-d_6) 3.82 (3H, s, C$\underline{H}_3$), 4.90 (2H, s, C$\underline{H}_2$), 6.75, 7.29 (each 1H, d, furan-$\underline{H}$)

b. Methyl 5-(acetylthiomethyl)-2-furoate

Methyl (5-chloromethyl)-2-furoate (50 g, 0.286 mol) was dissolved in dry dimethylformamide (300 ml) and potassium thioacetate (32.68 g, 0,286 mol) added with stirring. The initial exotherm was controlled by cooling (ice bath), then the reaction was stood at room temperature for 2 hr. The solvent was evaporated and the residue treated with water and thoroughly extracted with ether. The combined extracts were dried ($MgSO_4$), evaporated and purified by flash chromatography (silica, ethyl acetate/petroleum ether) to give the product as an oil (40.9g, 67% yield). ^1H NMR δ ($CDCl_3$) 2.36 (3H, s, C$\underline{H}_3$CO), 3.88 (3H, s, C$\underline{H}_3$O), 4.16 (2H, SC$\underline{H}_2$), 6.36, 7.09 (each 1H, d, furan-$\underline{H}$)

c. 4-(5-(Allyloxycarbonyl)furan-2-methylthio)azetidin-2-one

Potassium t-butoxide (12.77 g, 0.114 mol) was stirred in allyl alcohol (60 ml) until complete solution was obtained. Methyl 5-(acetylthiomethyl) furoate (22.17 g, 0.104 mol) in allyl alcohol (60 ml) was then added, and after 2 hr the mixture was cooled (ice bath) and a solution of 4-acetoxyazetidin-2-one (13.36 g, 0.104 mol) in dry tetrahydrofuran (100 ml) added dropwise over 20 min. After a further 30 min, the cooling bath was removed, then the mixture stirred for 3 hr at room temperature. The solvent was evaporated and the residue treated with brine and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated to give the product as a pale yellow oil (22.5g, 81% yield). ^1H NMR δ ($CDCl_3$) 2.87 (1H, m, $\underline{H}_{3a}$), 3.43 (1H, m, H_{3b}), 3.89 (2H, m, SCH_2), 4.79 (2H, m, C$\underline{H}_2$O), 4.94 (1H, m, $\underline{H}_4$), 5.38 (2H, m, C$\underline{H}_2$CH-), 6.01 (1H, m, C$\underline{H}$CH$_2$), 6.33, 7.13 (each 1H, d, furan-$\underline{H}$), 6.74 (1H, N$\underline{H}$)

4-(2-Fluorophenoxy)azetidin-2-one

A solution of 2-fluorophenol (4.5g, 40mmol) and 18-crown-6 (5 mg) in dry THF (100ml) was treated with potassium *t*-butoxide (4.5g, 40mmol) and a solution of 4-benzoyloxyazetidin-2-one (7.7g, 40mmol) in dry THF added. The mixture was stirred for 1 h and quenched with aqueous citric acid and ethyl acetate. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. On trituration under ether/excess n-hexane and filtration the title compound was obtained as a solid (5.8g, 80%) m.p. 95-6°

^{1}H NMR δ ($CDCl_3$) 3.17 (1H, dd), 3.34 (1H, m), 5.66 (1H, m), 6.59 (1H, bs), 6.93-7.18 (4H, m)

The following were prepared from 4-acetoxyazetidinone (or 4-acetoxy-3-methylazetidin-2-one) and the required phenol in a similar manner:

4-(Phenoxy)azetidin-2-one m.p. 107-8°C

4-(2-Methylphenoxy)azetidin-2-one m.p.105-6°C

4-(2-Benzyloxyphenoxy)azetidin-2-one m.p. 86-7°C

4-(2-Methylthiophenoxy)azetidin-2-one m.p. 131-2°C

4-(4-Allyloxycarbonylphenoxy)azetidin-2-one m.p. 51-2°

4-(4-Chlorophenoxy)azetidin-2-one m.p. 115-6°C

4-(4-Methoxyphenoxy)azetidin-2-one m.p. 96-7°C

4-(4-Methylthiophenoxy)azetidin-2-one m.p. 118-20°C

***trans*-3-Methyl-4-(phenoxy)-azetidin-2-one** ^{1}H NMR δ ($CDCl_3$) 1.35 (3H, d,7.6Hz), 3.55 (1H, m), 5.63 (1H, d, 4.0Hz), 6.83-7.38 (6H,m)

N-(6-phenylhexyl)bromoacetamide

A cooled solution of 6-phenylhexylamine (26.6 g) (Morse M. A. et al., Cancer Research, 1991, 1846) and Hunig's base (19.5 g) in dry dichloromethane (300 ml) was treated with bromoacetylchloride (23.38g) in dichloromethane (50 ml) at 0-5 °C. After aqueous workup and chromatography N-(6-phenylhexyl)-1-bromoacetamide was obtained as a colourless solid, 35.4 g (83%), m.p. 29-32°C.

N-(6-(4-chlorophenyl)hexyl)bromoacetamide

6-(4-Chlorophenyl)hexylamine (Lamattina J. L. EP 138464 A2 850424 (CA 103:142000)) was treated with bromoacetylbromide in a similar manner to give the title compound as a colourless solid, m.p 67-8°C, (93%).

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%), mp 50-51.0°C.

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-$\underline{H}$)

(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, $NC\underline{H}_2$), 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-$\underline{H}$).

1-(Amino)-6-(3-chlorophenyl)hex-1-yne

a. 6-(3-chlorophenyl)hexyn-1-ol

A stirred mixture of 3-chloroiodobenzene (14.3g, 60mmol), tetrakis(triphenylphosphine) palladium (2.1g, 1.8mmol) and 5-hexyn-1-ol (5.9g, 60mmol) in triethylamine (120ml) was stirred at 25°C for 3h and partitioned between water and ether. The ether layer was separated and the aqueous extracted with ether. The combined ether extracts were washed with 1N HCl and dried (Na_2SO_4). The ether was evaporated and the residue purified by flash chromatography on silica using dichloromethane as eluant. Evaporation of the appropriate fractions gave the product as an oil (11.5g, 92%)

b. 1-(Phthalimido)-6-(3-chlorophenyl)hex-1-yne

A solution of 6-(3-chlorophenyl)hexyn-1-ol (11.5g, 55mmol), triphenylphosphine (14.5g, 55mol) and phthalimide (8.1g, 55mol) in dry THF (110ml) was treated with a solution of DEAD (9.6g, 55mmol) in THF (20ml) over several minutes. After 16h, volatiles were removed in vacuo and the residue treated with ether. The precipitated solid was removed, the filtrate evaporated and the residue purified by flash chromatography on silica using dichloromethane as eluant. Evaporation of the appropriate fractions gave 1-(phthalimido)-6-(3-chlorophenyl)hex-1-yne as a solid (16.5g, 89%)

c. 1-(Amino)-6-(3-chlorophenyl)hex-1-yne

A mixture of 1-(phthalimido)-6-(3-chlorophenyl)hex-1-yne (6.6 g) and hydrazine hydrate (2.24 g) in ethanol (100 ml) was heated at reflux temperature for 18 h. After cooling and filtering the solvent was evaporated to give an oil which was dissolved in diethyl ether and washed with brine, dried and evaporated to give 1-(amino)-6-(3-chlorophenyl)hex-1-yne as a brown oil (3.1 g, 77%).

The following 2 amines were prepared in an analogous manner:

1-(Amino)-6-(2-chlorophenyl)hex-1-yne

1-(Amino)-6-(1-naphthyl)hex-1-yne

6-phenyl-3-hexynamine

a. N-(6-phenyl-3-hexynyl)phthalimide

A mixture of phthalimide (8.78 g), 6-phenyl-3-hexynol (J.Dijkink, N.Speckamp, Tetrahedron, Vol.34, 173-178, 1978) (8.0 g) and triphenylphosphine (12.04 g) in dry THF (75 ml) was cooled to 5°C under nitrogen. A solution of diethyl azodicarboxylate (8.0 g) in dry THF (20 ml) was added over 10 minutes maintaining the temperature at 10°C. The reaction was stirred at room temperature for 20h, evaporated to dryness, dissolved in $CHCl_3$ (250 ml) and washed with 1N NaOH, brine, 2N HCl, sat. $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to a cream solid (28.1 g). Purification by flash column chromatography eluted with 10:1 to 2:1 petroleum ether:ethyl acetate and recrystallisation from ethanol gave N-(6-phenyl-3-hexynyl)phthalimide as a colourless solid (8.25 g, 59%) m.p. 95-96°C.

b. 6-phenyl-3-hexynamine

N-(6-phenyl-3-hexynyl)phthalimide (3.0 g) in ethanol (150 ml) was treated with hydrazine monohydrate (0.96ml) and stirred at reflux for 4h. The reaction was cooled, evaporated to dryness and azeotroped with water. The residue was treated with 1N NaOH and extracted with diethyl ether (x2). The organic extracts were combined and extracted with 2N HCl (x2). The aqueous extracts were combined and basified with NaOH(aq) and extracted with diethyl ether (x2). The organic extracts were combined, washed with water, dried ($MgSO_4$), evaporated to give 6-phenyl-3-hexynamine as an oil (1.52 g, 89%).

***Z*-6-phenyl-3-hexenylamine**

a. *Z*-N-(6-phenyl-3-hexenyl)phthalimide

N-(6-Phenyl-3-hexynyl)phthalimide (4.4 g) in ethanol (140 ml) was hydrogenated at 40psi/20°C with Lindlar's cayalyst (60 mg) for 105 minutes. The reaction was filtered and evaporated to a yellow oil (4.51 g). Purification by flash column chromatography eluted with 6:1 to 4:1 petroleum ether : ethyl acetate gave *Z*-N-(6-phenyl-3-hexenyl)phthalimide as a colourless oil (4.15g, 94%). $\nu_{C=C}$ 1656 cm^{-1}; nmr homonuclear decoupling gives $^3J_{H3-H4}$ (alkene) = 10.8Hz.

b. *Z*-6-phenyl-3-hexenylamine

Z-N-(6-phenyl-3-hexenyl)phthalimide (1.95 g) in ethanol (100 ml) was treated with hydrazine monohydrate (0.64 g) and the mixture was stirred at reflux for 4.5 h and stirred at room temperature for 22 h. The reaction was evaporated to dryness and azeotroped with water. The residue was mixed with 1N NaOH and extracted with diethyl ether (x2). The organic extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated to dryness. Purification by Kugelrohr distillation at 185-200°C/0.2mmHg gave *Z*-6-phenyl-3-hexenylamine as a colourless oil (contains 6-phenylhexylamine 10%) (0.89g, 80%).

***E*-6-phenyl-3-hexenylamine**

***a. E*-N-(6-phenyl-3-hexenyl)phthalimide**

A mixture of *E*-6-Phenyl-3-hexenol (J.Dijkink, N.Speckamp, Tetrahedron, Vol.34, 173-178, 1978) (6.35 g), phthalimide (6.89 g) and triphenylphospine (9.45 g) in dry THF (50 ml) was cooled under nitrogen. Diethyl azodicarboxylate (6.27g) in dry THF was added over 10 minutes maintaining the temperature at 10°C. The reaction was

stirred at room temperature for 20 h and evaporated to dryness. The residue was mixed with CH_2Cl_2 (100 ml) and washed with 1N NaOH, brine, 1N HCl, brine, dried ($MgSO_4$) and evaporated to dryness. Purification by flash column chromatography eluted with 8:1 to 4:1 petroleum ether:ethyl acetate gave trans-N-(6-phenyl-3-hexenyl)phthalimide as a colourless solid (6.96 g, 63%) m.p. 75°C. $\nu_{c=c}$ 1670 cm^{-1} and nmr homonuclear decoupling gives $^3J_{H3-H4}$ (alkene) = 15Hz.

b. *E*-6-phenyl-3-hexenylamine

E-N-(6-phenyl-3-hexenyl)phthalimide (4.79 g) and propylamine (5 g) in ethanol (200 ml) were stirred at reflux for 2h and then at 70°C for 18h. The reaction mixture was evaporated to dryness and azeotroped with ethanol. The residue was mixed with 1N NaOH and extracted with diethyl ether (x2). The organic extracts were combined, washed with 2N HCl (x2). The aqueous extracts were combined, washed with diethyl ether and then basified with NaOH(aq) and extracted with diethyl ether (x2). The organic extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by Kugelrohr distillation at 180°C/0.5mmHg gave *E*-6-phenyl-3-hexenylamine as a colourless oil (0.98g, 36%).

5-Phenoxypentylamine

a. 5-Chloro-1-phenoxypentane

A mixture of phenol (2.67 g, 0.028mol), 1,5-dichloropentane (20 g, 0.148mol) and K2CO3 (20 g, 0.144mol) in methyl ethyl ketone (300ml) was refluxed for 24 hours. After cooling, the reaction mixture was filtered, and evaporated to a yellow oil (37.8 g). This was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate 15:1 to give a yellow oil (18 g). This was evaporated using a high vacuum with a water bath temperature >80oC to remove the excess 1,5-dichloropentane (b.p. 63-65°C) to give a yellow oil (5.8g). The oil was further purified by flash chromatography on silica gel eluted with hexane to give 5-chloro-1-phenoxypentane as a yellow oil (2.50 g, 44%).

b. N-5-Phenoxypentyl phthalimide

5-Chloro-1-phenoxypentane (2.50 g,12.6mmol) was dissolved in DMF (75 ml) and potassium phthalimide (4.65 g, 25.13mmol) was added and the mixture stirred at 100oC overnight for 18 hours. The DMF was evaporated and the solid was partitioned between ethyl acetate (75 ml) and water (50 ml). The organic layer was washed with H_2O (50ml), dried ($MgSO_4$) and evaporated to yellow solid. The yellow solid was purified by re crystallisation from ether/pet ether to give a white solid. The white solid was re crystallised again from ether to give N-5-phenoxypentyl phthalimide as a white solid (2.50 g, 64%), m.p. 62-64°C.

c. 5-Phenoxypentylamine

N-(phenoxy)-5-pentyl phthalimide (2.50 g, 8.08mmol) in ethanol (200ml) and hydrazine monohydrate (1.21 g, 24.17mmol) was refluxed for 18 hours overnight. Then filtered and evaporated, then evaporated from water a few times then evaporated from ethanol. 2M NaOH (500 ml) was added and extracted with ether (200 ml x2). The organic layer was washed with water several times until pH of solution was neutral, then dried ($MgSO_4$) and evaporated to give 5-phenoxypentylamine as a a yellow oil (1.13 g, 78%).

2-(2-phenoxyethyloxy)ethylamine

Sequential treatment of 2,2'-dichlorodiethylether with phenol/K2CO3/2-butanone and potassium phthalimide/DMF as described in the previous Preparation (at a and b) above gave N-(2-(2-phenoxyethyloxy)ethyl)phthalimide as a colourless solid. Treatment of this phthalimide (2.99 g) with hydrazine hydrate (1.44 g) in ethanol (200 ml) by the procedure in the previous Preparation (at c) gave the title amine as a yellow oil (0.81 g, 47%)/

2-(3-phenylpropyloxy)ethylamine

Ethanolamine (1.53 g) was added to NaH (1.0 g) in dimethyl sulfoxide (DMSO) (10 ml) at room temperature, followed by 1-bromo-3-phenylpropane (5 g) and the mixture stirred at room temperature for 0.5 h. After aqueous work-up the title compound was obtained as a yellow oil (1.6 g, 36%).

6-Phenylhexyloxy triflate

a. 2-(6-Phenylhexyloxy)ethanol

6-Phenylhexyl bromide (6.10 g) and ethylene glycol (15.5g) were added to a solution of sodium hydroxide (1.08 g) in water (1.1 ml) and the mixture heated at 100°C for 30hrs. Ether (75 ml) and water (75 ml) were added, separated and the ether layer was washed with water then brine, dried over $MgSO_4$ and evaporated to an orange oil. This was purified by Kugelrohr distillation (225°C/0.2mm) followed by chromatography on silica gel (40-60 petroleum ether/ethyl acetate) to give a colourless oil (3.04g; 54%)

b. 2-(6-Phenylhexyloxy)ethyl triflate

2-(6-Phenylhexyloxy)ethanol (2.88g), pyridine (1.23 g) and DMAP (20 mg) were dissolved in dry CH_2Cl_2 (15ml), cooled to -5°C and triflic anhydride(4.37 g) in CH_2Cl_2 (10 ml) was added over 5 mins keeping temp <0°C. The mixture was stirred at 0°C for 1 hr then washed with water, brine, dried over $MgSO_4$ and evaporated to a colourless oil (4.54g, 99%).

The following 2 triflates were prepared in an analogous manner.

2-(6-(4-Chlorophenyl)hexyloxy)ethyl triflate

2-(6-(4-Fluorophenyl)hexyloxy)ethyl triflate

3-Phenoxy-1-trifluoromethanesulphonylpropane

A mixture of 3-phenoxypropan-1-ol (2.38 g), pyridine (1.19 g) and 4-dimethylaminopyridine (DMAP) (0.10 g) was cooled to -5°C under a N_2 atmosphere. Trifluoromethane sulfonic anhydride (4.4 g) dissolved in dry dichloromethane (15 ml) was added dropwise over 30 minutes between 0°C to -5°C, then stirred for 2 hours at 0°C. The mixture was poured into water and the organic layer was separated, washed with water (x2), dried ($MgSO_4$), evaporated under reduced pressure to a dark brown oil which was purified by silica gel flash chromatography, eluted with petroleum ether 40°C - 60°C/ethyl acetate 2:1, to give the title compound as a clear oil pale brown/orange oil (3.22g, 73%).

2-Phenoxy-1-trifluoromethanesulphonylethane was prepared in an analogous manner from the corresponding alcohol.

(4-(4-ethoxycarbonyl)benzylthio)azetidin-2-one

a. Ethyl 4-(bromomethyl)benzoate

4-(Bromomethyl)benzoic acid (25.75g, 0.1197moles) was suspended in thionyl chloride (50ml) and dimethylformamide (0.25ml) was added. The mixture was heated under reflux for 25 minutes until clear, evaporated and azeotroped with toluene (x2). The resulting oil was dissolved in dichloromethane (75ml) and added dropwise over 10 minutes to a solution of absolute alcohol (8.6ml, 0.1465moles), pyridine (10.5ml, 0.1298moles) in dry dichloromethane (50ml), cooled to 10°C. The ice bath was removed and the reaction was stirred for 45 minutes, then washed with water, 2NHCl, water, sodium hydrogen carbonate solution and brine. The organic solution was dried ($MgSO_4$) and evaporated to give a mixture of 60:40 ethyl 4-(bromomethyl)benzoate: ethyl 4-(chloromethyl)benzoate as an oil (25.6g, 94%)

^1H nmr δ ($CDCl_3$) 1.40 (3H, m, $C\underline{H}_3$), 4.40 (2H, m, $C\underline{H}_2O$), 4.50, 4.61 (2H, 2xs, $C\underline{H}_2Cl/Br$), 7.45 (2H, m, Ar-$\underline{H}$), 8.01 (2H, m, Ar-$\underline{H}$)

b. Ethyl 4-(acetylthiomethyl)benzoate

60:40 Ethyl 4-(bromomethyl)benzoate: ethyl 4-(chloromethyl)benzoate (25.0g, 0.111moles) in dry dimethylformamide (150ml), cooled to 5°C, was treated with potassium thioacetate (13.3g, 0.117moles) and the temperature rose to 20°C. The reaction was stirred at room temperature for 2 hours, poured into water (250ml) and extracted with diethyl ether (3x100ml). The organic extracts were combined, washed with water, dried ($MgSO_4$), charcoaled and evaporated to give ethyl 4-(acetylthiomethyl)benzoate as a brown soild (26.0g, 99%), m.p. 36-37°C.

^1H nmr δ ($CDCl_3$) 1.38 (3H, t, J=7.1Hz, $C\underline{H}_3$), 2.36 (3H, s, $COC\underline{H}_3$), 4.14 (2H, s, $C\underline{H}_2S$), 4.36 (2H, q, $C\underline{H}_2O$), 7.35 (2H, d, J = 8.2Hz, Ar-$\underline{H}$), 7.97 (2H, d, J= 8.2Hz, Ar-$\underline{H}$)

c. 4-(4-(Ethoxycarbonyl)benzylthio)azetidin-2-one

A solution of sodium (1.87g, 0.0813moles) in absolute alcohol (300ml) was treated with a solution of ethyl 4-(acetylthiomethyl)benzoate (19.4g, 0.0814moles) in absolute alcohol (75ml) over 3 minutes. The reaction was stirred at room temperature for 30 minutes, cooled to -5°C and treated with a solution of 4-acetoxyazetidin-2-one (10.0g, 0.07745moles) over 5 minutes. The cooling bath was removed and reaction was stirred for 2 hours, evaporated to dryness and treated with brine (200ml) and extracted with ethyl acetate (200ml, 100ml). The organic extracts were combined washed with brine, dried ($MgSO_4$) and evaporated to a red oil. Purified by flash column chromatography on silica gel eluted with 3:1 to 1:2 petroleum ether 40-60°C:ethyl acetate to give 4-(4-(ethoxycarbonyl)benzylthio)azetidin-2-one as an orange oil (18.64g, 91%).

^1H nmr δ ($CDCl_3$) 1.38 (3H, t, J=7.1Hz, $C\underline{H}_3$), 2.82, 2.89 (1H, 2xm, $\underline{H}_3$), 3.29, 3.35 (1H, 2xm, $\underline{H}_3$), 3.88 (2H, s, $C\underline{H}_2S$), 4.37 (2H, q, $C\underline{H}_2O$), 4.70 (1H, m, $\underline{H}_4$), 5.70 (1H,bs, N$\underline{H}$), 7.40 (2H, d, J = 8.3Hz, Ar-$\underline{H}$), 8.00 (2H, m, Ar-$\underline{H}$)

Examples

Example 1 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

a. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)propionate

A mixture of 4-benzylthioazetidin-2-one (1.93 g, 0.01 mol), methyl DL-2-bromopropionate (1.23 ml, 0.011 mol) and tetra-n-butylammonium bromide (0.32 g, 0.001 mol) in dry tetrahydrofuran (50 ml) was treated with freshly powdered potassium hydroxide (0.62 g, 0.011 mol) and stirred at ambient temperature for 1 hour. Following treatment with ethyl acetate and water, an insoluble yellow solid was removed by filtration and discarded, and the filtrate separated. The aqueous layer was extracted again with ethyl acetate and the combined extracts dried ($MgSO_4$) and evaporated to a brown oil. Purification by flash chromatography (silica, ethyl acetate/petrol) gave the title compound as a mixture of diastereoisomers (colourless oil), 0.5 g, 18% yield.

^1H NMR δ ($CDCl_3$) 1.55 (2x3H, d), 2.93 (2x1H, m), 3.29(2x1H, m), 3.74 and 3.75 (each 3H, s), 3.80 and 3.84 (each 2H, s), 3.91 and 4.41 (each 1H, q), 4.70 and 4.96 (each 1H, m), 7.30 (2x5H, m)

b. 2-(4-Benzylthio-2-oxoazetidin-1-yl)propionic acid

A stirred solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)propionate (1.39 g, 0.005 mol) in methanol (12 ml) was treated with 1 molar potassium hydroxide (5.47 ml). After 2 hours, the methanol was evaporated and the residue diluted with water and extracted twice with ether. The aqueous layer was acidified with cooling (ice bath) and the oil which precipitated was extracted into ether. The combined extracts were dried ($MgSO_4$) and evaporated to give the title compound as a white solid (mixture of diastereoisomers), m.p. 78-82°C, 0.98 g, 74% yield.

^1H NMR δ ($CDCl_3$) 1.58 (2x3H, d), 2.94 (2x1H, m), 3.29(2x1H, m), 3.80 and 3.83 (each 2H, s), 3.80 and 4.39 (each 1H, q), 4.73 and 4.95 (each 1H, m), 6.94 (2x1H, s), 7.30 (2x5H, m)

c. N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

A mixture of 6-(4-chlorophenyl)hexylamine (0.54 g,0.00256 mol,Lamattina J. L. EP 138464 A2 850424 (CA 103:142000)), 1-hydroxybenzotriazole hydrate (0.35 g, 0.00256 mol), 2-(4-benzylthio-2-oxoazetidin-1-yl) -propionic acid (0.68 g, 0.00256 mol) and dicyclohexylcarbodiimide (0.53 g, 0.00256 mol) in dimethylformamide (10 ml) was stirred for 16 h at ambient temperature. The solvent was evaporated and the residue treated with ethyl acetate. The insoluble dicyclohexylurea was filtered off and discarded, and the filtrate washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and evaporated to an oil. The diastereomeric mixture was separated by flash chromatography (silica, tert. butyl methyl ether/petrol) and fractions containing the more slowly eluting diastereoisomer were combined and evaporated to give the title compound as an oil (0.14 g, 11.8% yield)

^1H NMR δ ($CDCl_3$) 1.32 (4H, m), 1.51 (3H, d), 1.53 (4H, m), 2.55 (2H,t), 2.87 (1H, dd), 3.24 (3H, m), 3.82 (2H, s), 4.06 (1H, q), 4.69(1H, dd), 6.51 (1H, m), 7.06-7.33 (9H, m).

Example 2 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

Evaporation of the fractions containing the faster eluting diastereoisomer in the above example gave the other diastereoisomer as a colourless oil (0.54g, 46% yield)

^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.53 (3 H, d), 1.57 (4H, m), 2.55 (2H, t), 2.83 (1H, dd), 3.26 (3H, m), 3.84 (2H, s), 3.92(1H, q), 4.77 (1H, dd), 6.58(1H, m), 7.05-7.36(9H, m).

Example 3 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomers b1 &b2)

A solution of N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b) (0.96 g, 0.0021 mol) in dichoromethane (25 ml) was cooled to -65 to -70°C and a solution of m-chloroperbenzoic acid (0.43 g, 0.0025 mol) in dichloromethane (10 ml) added dropwise over 15 min. After 45 min the mixture was washed with a mixture of saturated sodium hydrogen carbonate and saturated sodium sulphite, dried ($MgSO_4$) and evaporated to an oil. Crystallisation from ethyl acetate - ether gave the title compound as a 40:60 mixture of diastereoisomers b1:b2, m.p. 70-73°C

Example 4 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (-)b2)

The solid was purified by chromatography (HPLC, Chiralcell OJ column, ethanol/hexane), followed by silica, ethanol/hexane) to give the title compound, a white solid, as a single enantiomer.

$[a]_D^{20}$ = -41.6° (c 0.11, ethanol)

^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m),1.61 (3H, d), 2.56 (2H, t), 2.76 (1H, dd), 3.12 (1H, dd), 3.23 (2H, m), 3.96, 4.09 (each 1H, d), 4.45 (1H, q), 4.58 (1H, dd), 7.07-7.39 (9H, m)

The other 3 components of the mixture (Examples 5-7) were obtained by the same chromatographic procedure.

Example 5 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (+)b2)

$[a]_D^{20}$ = +34.5° (c 0.112, ethanol); 99.2% pure.

^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m),1.61 (3H, d), 2.56 (2H, t), 2.76 (1H, dd), 3.12 (1H, dd), 3.23 (2H, m), 3.96, 4.09 (each 1H, d), 4.45 (1H, q), 4.58 (1H, dd), 7.07-7.39 (9H, m)

Example 6 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (+)b1)

$[a]_D^{20}$ = +80.7° (c 0.03, ethanol); 96.2% pure.

1H NMR δ (CDCl3) 1.32 (4H,m), 1.42 (3H, d), 1.55 (4H, m), 2.55 (2H, t), 2.90 (1H, dd), 3.20 (2H, m), 3.45 (1H, dd), 3.88, 4.06 (each 1H, d), 4.34 (1H, q), 4.48 (1H, dd), 6.95 (1H, m), 7.08-7.41 (9H, m)

Example 7 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (-)b1)

$[a]_D^{20}$ = -95.5° (c 0.11, ethanol); 99.4% pure.

1H NMR δ (CDCl3) 1.32 (4H,m), 1.42 (3H, d), 1.55 (4H, m), 2.55 (2H, t), 2.90 (1H, dd), 3.20 (2H, m), 3.45 (1H, dd), 3.88, 4.06 (each 1H, d), 4.34 (1H, q), 4.48 (1H, dd), 6.95 (1H, m), 7.08-7.41 (9H, m)

Example 8 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulfinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1)

Treatment of N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a) with *m*CPBA as described in Example 3 gave the title compound as a mixture of diastereoisomers. Recrystallisation of this mixture from ethyl acetate gave N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulfinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1) as colourless crystals, m.p. 168-170°C.

^{1}H NMR δ ($CDCl_3$) 1.32 (4H, m), 1.49 (2H, m), 1.55 (3 H, d), 1.60 (2H, m), 2.56 (2 H, t), 2.83 (1H, dd), 3.20 (2H, m), 3.38 (1H, dd), 3.88, 3.97 (each 1H, d), 4.08 (1H, q), 4.67 (1H, dd), 6.38 (1H, m), 7.08-7.40 (9H, m)

Example 9 N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulfinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2)

Treatment of the mother liquors form the above recrystallisation with petroleum ether (b. p. 40-60) gave the title compound as a white crystalline solid, m.p. 79-81°C.

^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.52 (4H, m), 1.61 (3H, d), 2.56 (2H, t), 2.77(1H, dd), 3.15 (1H, dd), 3.24 (2H, m), 4.01 (1H, q), 4.01. 4.12 (each 1H, d), 4.58 (1H, dd), 7.08-7.41 (9H, m)

Example 10 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

a. 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-$\underline{H}$)

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

A stirring solution of methyl (4-benzylthio-2-oxoazetidin-1-yl) acetate (13.27 g, 0.05 mol) in dry tetrahydrofuran was cooled to -70°C (acetone-cardice bath) and a 1 molar solution of lithium bis(trimethylsilyl)amide (60 ml) was added under nitrogen over 15 min, followed by 1,3-dimethyl-2-imidazolone (33 ml). After 30 min, iodomethane (5.6 ml, 0.09 mol) was added dropwise. After a further hour, the reaction temperature was allowed to rise to -20°C, then the mixture recooled to -70°C and glacial acetic acid (5.6 ml) added dropwise. The reaction was quenched with water and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oil

which was purified by flash chromatography (fine silica, ethyl acetate/light petrol) to give the product as a mixture of diastereoisomers, contaminated with 9% of the dimethylated product, as a yellow oil, 13.7 g, 89% yield

^{1}H NMR δ ($CDCl_3$) 1.55 (2x3H, d), 2.93 (2x1H, m), 3.29(2x1H, m), 3.74 and 3.75 (each 3H, s), 3.80 and 3.84 (each 2H, s), 3.91 and 4.41 (each 1H, q), 4.70 and 4.96 (each 1H, m), 7.30 (2x5H, m)

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

A stirred solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)propionate (1.39 g, 0.005 mol) in methanol (12 ml) was treated with 1 molar potassium hydroxide (5.47 ml). After 2 hours, the methanol was evaporated and the residue diluted with water and extracted twice with ether. The aqueous layer was acidified with cooling (ice bath) and the oil which precipitated was extracted into ether. The combined extracts were dried ($MgSO_4$) and evaporated to give the title compound as a white solid (mixture of diastereoisomers), m.p. 78-82°C, 0.98 g, 74% yield.

^{1}H NMR δ ($CDCl_3$) 1.58 (2x3H, d), 2.94 (2x1H, m), 3.29(2x1H, m), 3.80 and 3.83 (each 2H, s), 3.80 and 4.39 (each 1H, q), 4.73 and 4.95 (each 1H, m), 6.94 (2x1H, s), 7.30 (2x5H, m)

d. N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

A mixture of 6-(4-fluorophenyl)hexylamine (3.0 g, 0.0154 mol,), 1-hydroxybenzotriazole hydrate (2.08 g, 0.0154 mol), 2-(4-benzylthio-2-oxoazetidin-1-yl)-propionic acid (4.08 g, 0.0154 mol) and dicyclohexylcarbodiimide (3.17 g, 0.0154 mol) in dimethylformamide (60 ml) was stirred for 16 h at ambient temperature. The solvent was evaporated and the residue treated with ethyl acetate. The insoluble dicyclohexylurea was filtered off and discarded, and the filtrate washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and evaporated to an oil. The diastereomeric mixture was separated by flash chromatography (fine silica, tert. butyl methyl ether/petrol) and fractions containing the more slowly eluting diastereoisomer were combined and evaporated to give the title compound as an oil, yield 1.89 g (28%)

^{1}H NMR ($CDCl_3$) δ 1.33 (4H, m), 1.51 (3H, d), 1.53 (4H, m), 2.55 (2H,t), 2.87 (1H, dd), 3.24 (3H, m), 3.82 (2H, s), 4.06 (1H, q), 4.69(1H, dd), 6.51 (1H, m), 6.91-7.33 (9H, m).

Example 11 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

The more rapidly eluting diastereoisomer was also obtained from the above column chromatography as an oil, yield 2.8 g (41%)

^{1}H NMR δ (CDCl3) 1.33 (4H, m), 1.53 (3 H, d), 1.57 (4H, m), 2.55 (2H, t), 2.83 (1H, dd), 3.26 (3H, m), 3.84 (2H, s), 3.92(1H, q), 4.77 (1H, dd), 6.58(1H, m), 6.91-7.36(9H, m).

Example 12 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomers b1+b2)

A solution of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b) (Example 11) (1.82 g, 0.0041 mol) in dichoromethane (30 ml) was cooled to -65 to -70°C and a solution of *m*-chloroperbenzoic acid (0.85 g, 0.0049 mol) in dichloromethane (30 ml) added

dropwise over 30 min. After 2 h the mixture was washed with a mixture of saturated sodium hydrogen carbonate and saturated sodium sulphite, dried ($MgSO_4$) and evaporated to an oil. Crystallisation from ethyl acetate - light petrol gave a mixture of diastereomers (1.18 g) (b1:b2, 1:3), m.p. 75-78°C.

Example 13 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer (-)b2)

The above mixture of diastereoisomers b1 + b2 was separated by HPLC (Dynamax silica column, ethanol/hexane) into b1 and b2. Diastereoisomer b2 was then separated into its component enantiomers by chiral HPLC (Chiralcel OD column, ethanol/hexane) to give the title compound as a white solid, 0.06 g

^1H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m),1.61 (3H, d), 2.56 (2H, t), 2.75(1H, dd), 3.11(1H, dd), 3.23 (2H, m), 3.96, 4.09 (each 1H, d), 4.45 (1H, q), 4.58 (1H, dd), 6.92-7.40 (9H, m)

$[a]_D^{20}$ = -36.2 (c 0.46, ethanol)

Example 14 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer (+)b2)

Also obtained was the (+) enantiomer as a white solid, yield 0.06 g.

^1H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 1.61 (3H, d), 2.56 (2H, t), 2.75(1H, dd), 3.11(1H, dd), 3.23 (2H, m), 3.96, 4.09 (each 1H, d), 4.45 (1H, q), 4.58 (1H, dd), 6.92-7.40 (9H, m)

$[a]_D^{20}$ = +32.7 (c 0.42, ethanol)

Treatment of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (1.15 g) (diastereoisomer a, Example 10) with mCPBA (0.54 g) by the procedure described in Example 12 gave the following two diastereoisomers after chromatography (Examples 15, 16)

Example 15 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1)

0.5 g, white solid, m.p. 165-7°C, ^1H NMR d ($CDCl_3$) (selected diagnostic peaks) 4.11 (1H, q, a-H), 4.70 (1H, m, H4); Found: C, 65.2; H, 6.7; N, 5.8% $C_{25}H_{31}FN_2O_3S$ requires: C, 65.5; H, 6.8; N, 6.1%

Example 16 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2)

0.28 g, white solid, m.p. 73-5°C, ^1H NMR d ($CDCl_3$) (selected diagnostic peaks) 4.00 (1H, q, a-H), 4.58 (1H, m, H4); Found: C, 65.3; H, 6.65; N, 5.7% $C_{25}H_{21}FN_2O_3S$ requires: C, 65.5; H, 6.8; N, 6.1%

Example 17 N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphonyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

Treatment of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (2.7 g) (diastereoisomer a, Example 10) with *m*CPBA (2.43 g) at room temperature gave the title compound as a white solid (2.43 g), m.p. 85-7°C; ^1H NMR d ($CDCl_3$) (selected diagnostic peaks) 3.96 (1H, q, a-H), 4.75 (1H, m, H4); Found: C, 63.2; H, 6.45; N, 5.9% $C_{25}H_{31}FN_2O_4S$ requires: C, 63.3; H, 6.6; N, 5.9%

Example 18 N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphonyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

Treatment of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (0.39 g) (diastereoisomer b, Example 11) with *m*CPBA (0.22 g) at room temperature gave the title compound as a white solid (0.29 g), m.p. 90-2°C; ^{1}H NMR d ($CDCl_3$) (selected diagnostic peaks) 4.27 (1H, q, a-H), 4.64 (1H, m, H4); Found: C, 63.0; H, 6.4; N, 5.85% $C_{25}H_{31}FN_2O_4S$ requires: C, 63.3; H, 6.6; N, 5.9%

Example 19 N-(Benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

Treatment of 2-(4-benzylthio-2-oxoazetidin-1-yl)propionic acid (Example 10b) with benzylamine under the conditions described in Example 10c gave the title compound as the higher rf product after chromatography: 1.19 g, clear oil; ^{1}H NMR d ($CDCl_3$) (selected diagnostic peaks) 4.27 (1H, q, a-H), 4.80 (1H, m, H4);

Example 20 N-(Benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

From the above chromatographic separation the lower rf fractions were combined to give the title compound as a colourless solid, m.p. 70-2°C, 1.44 g; ^{1}H NMR d ($CDCl_3$) (selected diagnostic peaks) 4.10 (1H, q, a-H), 4.69 (1H, m, H4);

Example 21 N-[6-(4-Fluorophenylhexyl)]-2-[4-(allyloxycarbonylbenzylthio)-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

a. Allyl 4-(bromomethyl)benzoate

4-(Bromomethyl)benzoic acid (103 g, 0.48 moles) was suspended in thionyl chloride (200 ml) and dimethylformamide (1 ml) was added. The mixture was heated under reflux until clear, evaporated and azeotroped with toluene (2 x 150 ml). The resulting oil was dissolved in dichloromethane and added dropwise to a cooled solution of pyridine (42 ml) and allyl alcohol (40 ml) in dichloromethane. The mixture was stirred at room temperature for 1 hour, then washed with water, 2M hydrochloric acid, sodium hydrogen carbonate solution and brine. The organic solution was dried and evaporated to give allyl 4-(bromomethyl)benzoate as a clear oil (98g, 84% yield). ^{1}H NMR d ($CDCl_3$) 4.61 (2H, s, CH_2), 4.82 (2H, m, $C\underline{H}_2O$), 5.34 (2H, m, $C\underline{H}_2CH$-), 6.05 (1H, m, $C\underline{H}CH_2$), 7.45 (2H, d, Ph-H), 8.03 (2H, d, Ph-H).

b. Allyl 4-(acetylthiomethyl)benzoate

Allyl 4-(bromomethyl)benzoate (98 g, 0.4 moles) in dry dimethylformamide (100 ml) was added dropwise to a cooled suspension of potassium thioacetate (46 g, 0.4 moles) in dry dimethylformamide (200 ml). The cooling bath was removed and the mixture was stirred overnight. The rection mixture was poured into water and extracted with ethyl acetate (x3). The combined extracts were washed with water and brine. The mixture was dried and evaporated to give allyl 4-(acetylthiomethyl)benzoate as an orange oil (100g, 100% yield). ^{1}H NMR d ($CDCl_3$) 2.36 (3H, s, $COC\underline{H}_3$), 4.13 (2H, s, CH2), 4.82 (2H, m, $C\underline{H}_2O$), 5.32 (2H, m, $C\underline{H}_2CH$-), 6.05 (1H, m, $C\underline{H}CH_2$), 7.35 (2H, d, Ph-H), 7.98 (2H, d, Ph-H).

c. 4-(4-(Allyloxycarbonyl)benzylthio)azetidin-2-one

Allyl alcohol (27 ml) in dry tetrahydrofuran (50 ml) was added dropwise to a solution of potassium *tert*-butoxide (4.93 g, 0.044 moles) in dry tetrahydrofuran (100 ml). After stirring for 5 minutes a solution of allyl 4-(acetylthiomethyl)benzoate (10.1 g, 0.04 moles) in dry tetrahydrofuran (100 ml) was added dropwise. After stirring for 15

minutes a solution of 4-acetoxyazetidin-2-one (5.16 g, 0.04 moles) was added dropwise. The mixture was stirred for 1 hour and evaporated. The residue was partitioned between ethyl acetate and water and the aqueouse was extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated. Flash chromatography (silica gel, ethyl acetate-petrol) gave 4-(4-Allyloxycarbonylbenzylthio)azetidin-2-one as an oil (9.1g, 82% yield). ^{1}H NMR d ($CDCl_3$) 2.84 (1H, dd, H3a), 4.31 (1H, dd, H3b), 3.88 (2H, s, S-CH2), 4.68 (1H, dd, H4), 4.78 (2H, m, $C\underline{H}_2O$), 5.35 (2H, m, $C\underline{H}_2CH$-), 6.05 (1H, m, $C\underline{H}CH_2$), 6.07 (1H, br. singlet, N-H), 7.40 (2H, d, Ph-H), 8.03 (2H, d, Ph-H).

d. **Methyl 4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate**

To a stirring solution of 4-(4-(allyloxycarbonyl)benzylthio)azetidin-2-one (2.55 g, 9.2 mmol), tetrabutylammonium bromide (0.33 g, 1.02 mmol) and methyl bromoacetate (1.06 ml, 11.2 mmol) in dry tetrahydrofuran (40 ml) was added powdered potassium hydroxide (0.63 g, 11.2 mmol) keeping the reaction temperature below 30 by means of a cold water bath. After 2 h, the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed (fine silica, ethyl acetate-petrol) to give the title compound as a clear oil, yield 2.66 g (83%).

^{1}H NMR δ ($CDCl_3$) 2.97 (1H, dd, H3a), 3.26, 4.07 (each 1H, $C\underline{H}_2CO$, d), 3.42 (1H, dd, H3b), 3.70 (3H, s, $C\underline{H}_3O$), 3.81 (2H, s, $SC\underline{H}_2$), 4.83 (2H, m, $C\underline{H}_2O$), 4.93 (1H, dd, H4), 5.35 (2H, m, $C\underline{H}_2CH$), 6.03 (1H, m, $C\underline{H}CH_2$), 7.39 (2H, d, Ph-H), 8.02 (2H, d, Ph-H)

e. **Methyl 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-2-ylpropionate**

Methyl 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate (23.8 g, 68 mmoles) was stirred at -65°C in dry tretahydrofuran under nitrogen and treated with lithium bis(trimethylsilyl)amide (81.6 ml of a 1.0 molar solution in hexane), keeping the temperature to -65°C. The mixture was stirred for 5 minutes, then treated with 1,3-dimethylimidazolidinone (44.6 ml) dropwise ensuring the temperature did not rise. This mixture was stirred for 30 minutes then methyl iodide (7.6 ml) was added dropwise. The mixture was stirred for a further 1 hour then allowed to warm to -20C. After re-cooling, the mixture was treated with acetic acid (7 ml), poured into water and extracted with ethyl acetate (x6). The combined extracts were dried and evaporated to an orange oil. Flash chromatography (fine silica, 20% ethyl acetate in petrol) gave the required methyl 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-2-ylpropionate as a yellow oil as a mixture of diastereoisomers (15.2 g, 62%).

^{1}H NMR δ ($CDCl_3$) 1.56 (3H, d), 2.85-2.96 (2H, m, diastereomer A and B, $\underline{H}_{3a}$), 3.24-3.35 (2H, m, diastereomer A and B, $\underline{H}_{3b}$), 3.74 (3H, s), 3.76 (3H, s), 3.87 (2H, d), 3.97 (1H, q, diastereomer B, N-C$\underline{H}$), 4.43 (1H, q, diastereomer A, N-C$\underline{H}$), 4.71 (1H, m, diastereomer B, H_4), 4.82 (2H, m), 4.97 (1H, m, diastereomer A, H_4), 5.27-5.46 (2H, m), 5.96-6.10 (1H, m), 7.39 (2H, d), 8.02 (2H, d).

f. **4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-2-ylpropionic acid**

29.7 ml of 1 M potassium hydroxide solution was added dropwise over 20 minutes to a solution of methyl 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-2-ylpropionate (9.0 g, 0.0248 moles) in tetrahydrofuran (100 ml), keeping the temperature to 0-5°C. The mixture was stirred for a further 20 minutes then diluted with water and extracted

with ether (x2). The aqueous solution was recooled and acidified with dilute hydrochloric acid then extracted with ether (x2). The combined extracts were dried and evaporated to give the title compound as a yellow oil, 8.5g, 98% yield
^{1}H NMR δ ($CDCl_3$) 1.50-1.6 (3H, m), 2.86-2.98 (2H, m, diastereomer A and B, H_{3a}), 3.24-3.35 (2H, m, diastereomer A and B, H_{3b}), 3.87 (2H, d), 3.95 (1H, q, diastereomer B, N-CH), 4.45 (1H, q, diastereomer A, N-CH), 4.75 (1H, m, diastereomer B, H_4), 4.82 (2H, m), 4.98 (1H, m, diastereomer A, H_4), 5.27-5.46 (2H, m), 5.96-6.10 (1H, m), 7.39 (2H, d), 8.02 (2H, d).

g. (+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(allyloxycarbonylbenzylthio)-2-oxoazetidin-1-yl]propionamide (diastereoisomer a)

Dicyclohexylcarbodiimide (4.75 g, 23 mmoles) in dry dimethylformamide (50 ml) was added dropwise to a cooled solution of 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-2-ylpropionic acid (8.0 g, 23 mmoles), 1-hydroxybenzotriazole hydrate (3.11 g, 23 mmoles) and 6-(4-fluorophenyl)hexylamine (4.5 g, 23 mmoles) in dry dimethylformamide (50 ml). Cooling was removed and the mixture was stirred overnight. The dimethylformamide was evaporated and the residue was purified by flash chromatography (fine silica, *tert*-butylmethyl ether then ethyl acetate) to provide samples which were predominantly diastereoisomer a (4.6 g), diastereoisomer b (2.7 g) and mixed fractions.

Diastereoisomer a: yellow oil, 4.6 g, 38% yield
^{1}H NMR δ ($CDCl_3$) 1.23-1.63 (11H, m), 2.55 (2H, t), 2.81 (1H, dd, H_{3a}), 3.20-3.30 (3H, m, CH_2 and H_{3b}), 3.90 (2H, d), 4.04 (1H, q, N-CH), 4.78-4.84 (3H, m, CH_2 and H_4), 5.27-5.45 (2H, m), 5.95-6.09 (1H, m), 6.50 (1H, br. triplet, NH), 6.90-6.98 (2H, m), 7.06-7.26 (2H, m), 7.40 (2H, d), 8.02 (2H, m).

Example 22 (+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-(allyloxycarbonyl-benzylthio)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b)

From the above chromatography diastereoisomer b was obtained as a yellow oil, 2.7 g, 22% yield
1H NMR δ ($CDCl_3$) 1.23-1.63 (11H, m), 2.55 (2H, t), 2.85 (1H, dd, H_{3a}), 3.19-3.23 (2H, m), 3.28(1H, dd, H_{3b}), 3.91 (2H, s), 4.09 (1H, q, N-CH), 4.69 (1H, dd, H_4), 4.82 (2H, d), 5.25-5.45 (2H, m), 5.95-6.09 (1H, m), 6.43 (1H, br. triplet, NH), 6.90-6.98 (2H, m), 7.06-7.26 (2H, m), 7.40 (2H, d), 8.02 (2H, m).

Example 23 (+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)- 2-oxoazetidin-1-yl]propionamide (diastereoisomers b2+b1 3:2)

A solution of (+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(allyloxycarbonylbenzylthio)- 2-oxoazetidin-1-yl]propionamide (diastereoisomer b) (2.5 g, 4.75 mmoles) in dichloromethane (50 ml) was stirred at -65°C and treated with a solution of *m*-chloroperbenzoic acid (1.0 g, 5.7 mmoles) in dichloromethane (30 ml). The mixture was stirred for 1 hour, poured into a solution of sodium hydrogen carbonate and sodium sulphite, separated and the aqueous extracted with dichloromethane. The combined extracts were washed with brine, dried and evaporated to an oil which was purified by flash chromatography (fine silica, ethyl acetate) to give the title compound as a yellow oil, 1.3 g, 50% yield as a 3:2 mixture of sulfoxide diastereoisomers 2 and 1.

Example 24 (+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b2)

The sulfoxide diastereoisomers above were separated by HPLC to give the title compound as a yellow oil, 100 mg

^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.44-1.63 (4H, m), 1.61 (3H, d), 2.55 (2H, t), 2.84 (1H, dd, H_{3a}), 3.15-3.31 (3H, m, H_{3b} and CH_2), 4.01 and 4.09 (1H each, d), 4.50 (1H, q, N-C<u>H</u>), 4.61 (1H, dd, H_4), 4.83 (2H, d), 5.29-5.45 (2H, m), 5.95-6.09 (1H, m), 6.90-6.98 (2H, m), 7.06-7.26 (2H, m), 7.37 (2H, d), 8.08 (2H, m).

Example 25 (+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b1)

The above chromatography also gave the title compound as an oil, 50 mg

^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.44-1.63 (4H, m), 1.45 (3H, d), 2.54 (2H, t), 2.90 (1H, dd, H_{3a}), 3.18-3.22 (2H, m, CH_2), 3.43 (1H, dd, H_{3b}) 3.94 and 4.02 (1H each, d), 4.34 (1H, q, N-C<u>H</u>), 4.53 (1H, dd, H_4), 4.83 (2H, d), 5.29-5.45 (2H, m), 5.95-6.09 (1H, m), 6.80 (1H, br. triplet, NH), 6.90-6.98 (2H, m), 7.06-7.26 (2H, m), 7.37 (2H, d), 8.08 (2H, m).

Example 26 (+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(allyloxycarbonyl)benzylsulphinyl)- 2-oxoazetidin-1-yl]propionamide (diastereoisomer a1)

Treatment of N-[6-(4-fluorophenylhexyl)]- 2-[4-(allyloxycarbonylbenzylsulphinyl)- 2-oxoazetidin-1-yl]propionamide (diastereoisomer a, Example 21) with *m*CPBA by the method described in Example 23 gave the title compound as white crystals after chromatography and recrystallisation from ethyl acetate, m.p. 175-177°C, 27% yield

^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.38-1.65 (4H, m), 1.54 (3H, d), 2.55 (2H, t), 2.82 (1H, dd, H_{3a}), 3.20 (2H, dt, CH_2), 3.35 (1H, dd, H_{3b}) 3.94 (2H, d), 4.17 (1H, q, N-C<u>H</u>), 4.78 (1H, dd, H_4), 4.83 (2H, d), 5.29-5.45 (2H, m), 5.95-6.09 (1H, m), 6.35 (1H, br. triplet, NH), 6.90-6.98 (2H, m), 7.06-7.26 (2H, m), 7.37 (2H, d), 8.08 (2H, m).

Example 27 (+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2)

From the above reaction (Example 26) the title compound was obtained as off-white crystals after chromatography and recrystallisation from diethyl ether, m.p. 75-76°C, 22% yield

^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.38-1.65 (4H, m), 1.62 (3H, d), 2.56 (2H, t), 2.82 (1H, dd, H_{3a}), 3.17-3.30 (3H, m, CH_2 and H_{3b}), 4.00-4.15 (3H, m, CH_2 and N-C<u>H</u>), 4.63 (1H, dd, H_4), 4.83 (2H, d), 5.29-5.45 (2H, m), 5.95-6.09 (1H, m), 6.90-6.98 (2H, m), 7.06-7.26 (3H, m), 7.37 (2H, d), 8.08 (2H, m).

Example 28 (+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(carboxy)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomers b2+b1 3:2)

Treatment of (+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)-benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide as the mixture of diastereoisomers

produced in Example 23 (b2+b1 3:2) (0.32 g) with triphenylphosphine (0.165 g), pyrrolidine (0.045 g) and tetrakis triphenylphosphinepalladium(0) (0.02 g) in dichloromethane (40 ml) under nitrogen for 16 h, followed by aqueous work-up gave the title compound as a white solid, m.p. 122-150°C, 0.155 g, 51 % yield as a 3:2 mixture of diastereoisomers b2 and b1.

^{1}H NMR - some diagnostic peaks: δ ($CDCl_3$) 4.7 (m, H4 of dia b2) 4.6 (m, H4 of dia b1).

Example 29 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomers a and b)

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%), mp 50-51.0°C.

^{1}H 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%).

^{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. 3-Bromomethylfuran

A solution of triphenylphosphine (8.45g, 0.0322moles) and 3-(hydroxymethyl)-furan (2.93g. 0.02987moles) in dry dichloromethane (30ml) at 0°C was treated with N-bromosuccinimide (5.74g, 0.03225moles) in solid portions over 10 minutes. The reaction was stirred at 0°C for 30 minutes and the allowed to warm to 15°C over 1.5 hours. The reaction was then purified by flash column chromatography on silica gel eluted with petroleum ether 40-60°C to give 3-bromomethylfuran as a pale yellow oil (3.25g, 68%).

d. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionate).

A solution of methyl-(4-benzylthio-2-oxoazetidin-1-yl)acetate (3.0g, 0.01131moles) in dry tetrahydrofuran (60ml) at -78°C under nitrogen was treated with a 1M solution of lithium bis(trimethylsilyl)amide in THF (13.8ml, 0.0186moles) over 10 minutes keeping the temperature below -74°C. 1,3-Dimethylimidazolidin-2-one (7.5ml, 0.0687moles) was added keeping the temperature below -74°C. The resulting suspension was stirred at -78°C for 30 minutes and then treated with a solution of 3-bromomethylfuran (3.0g, 0.0186moles) in dry THF (10ml) over 10 minutes keeping the temperature below -73°C. The reaction was stirred at -78°C for 1 hour and then allowed to warm to -20°C over 30 minutes. The reaction was cooled to -75°C and quenched with glacial acetic acid (1.5ml), partitioned between brine (150ml) and ethyl acetate (150ml). The organic layer was washed with water, dried ($MgSO_4$) and evaporated to a coloured oil (7.81g). Purified by flash column chromatography on silica gel eluted with 2:1 petroleum ether 40-60°C:ethyl acetate to give methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionate as yellow oil (2.35g, 60%, 85:15 diastereoisomer A:B)

^{1}H NMR δ ($CDCl_3$) 2.83, 2.90 (dd, J=2.4, 15.5 Hz, 1 of $\underline{H}_{3A}$), 3.17 (m, $C\underline{H}_2$-furyl, $\underline{H}_{3B,3A}$), 3.54, 3.80 (2H, 2xs, $SC\underline{H}_{2A+B}$), 3.77 (3H, s, $CO_2C\underline{H}_3$), 3.95,4.26 (1H, 2xm, $C\underline{H}_{A+B}$), 4.60, 4.64 (1H, 2xm, $\underline{H}_{4A+B}$), 6.30 (1H, m, furyl-$\underline{H}$), 7.30 (6H, m, Ph-$\underline{H}$, furfyl-$\underline{H}$)

e. 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionic acid

A solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionate (2.93g, 0.00848 moles) in methanol (50ml) at 10°C was treated with a 1N sodium hydroxide solution (8.5ml, 0.0085moles) over 30 minutes. The cooling bath was removed and the reaction was stirred for 1 hour. 1N NaOH (1.0ml) was added and the reaction was stirred for 30 minutes, diluted with water (50ml) and evaporated to remove methanol. The residue was mixed with water (50ml) and extracted with diethyl ether (50ml). The aqueous was acidified with dilute Hcl and extracted with diethyl ether (2x75ml). The organic extracts were combined , washed with brine, dried ($MgSO_4$), and evaporated to give 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionic acid as a cream solid m.p. 77-80°C (2.73g, 97%, 50:50 distereoisomer A:B)

^{1}H NMR δ ($CDCl_3$) 2.86, 2.92 (dd, J=2.3, 15.4 Hz, $\underline{H}_3$), 3.10 (m, $C\underline{H}_2$-furyl, $\underline{H}_3$), 3.54, 3.79 (2H, m+s, $SC\underline{H}_{2A+B}$), 3.89 (m, $C\underline{H}_B$), 4.19 (m, $C\underline{H}_A$), 4.23 (1H, bs, $CO_2\underline{H}$), 4.57, 4.64 (1H, 2xm, $\underline{H}_{4A+B}$), 6.30, 6.37 (1H, 2xbs, furyl-$\underline{H}_{A+B}$), 7.30 (6H, m, Ph-$\underline{H}$, furfyl-$\underline{H}$)

f. N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomers a and b)

6-(4-Fluorophenyl)hexylamine (1.59g, 0.00814moles) in dry DMF (75ml) was added to a mixture of 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-(3-furyl)propionic acid (2.7g, 0.00814 moles), 1-hydroxybenzotriazole (1.1g, 0.00814moles), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluene sulfonate (3.5g, 0.00826moles) and the resulting solution was stirred at room temperature for 19h. The suspension was partitioned between aq.NaHCO3 (175ml) and diethyl ether (75ml). The layers were separated and the aqueous layer was washed with diethyl ether (75ml). The organic extracts were combined and washed with brine (x2), dried ($MgSO_4$) and evaporated to an orange oil (3.76g). Purified by flash column chromatography on silica gel eluted

with 2:1 petroleum ether 40-60°C:ethyl acetate to give the title compounds as colourless oils.

Diastereoisomer a, 1.17g, 28% (contains 20% diastereoisomer b)

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.55 (2H, t, J=7.9 Hz, CH_2Ph), 2.75, 2.80 (dd, H_3), 3.15 (m, CH_2-furyl, H_3), 3.75 (3H, m, CH, SCH_2), 4.30 (1H, m, H_4), 6.23 (1H, bs, furyl-H), 6.85 (1H, m, NH), 6.9-7.4 (11H, m, pF-Ph-H, Ph-H, furyl-H)

Diastereoisomer b, 1.36g, 33% (contains 20% diastereoisomer a)

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.55 (2H, t, J=7.9 Hz, CH_2Ph), 2.81, 2.87 (dd, H_3), 3.15 (m, CH_2-furyl, H_3), 3.70 (2H, s, SCH_2), 4.12 (1H, m, CH), 4.57 (1H, m, H_4), 6.25 (1H, bs, furyl-H), 6.4 (1H, m, NH), 6.9-7.4 (11H, m, pF-Ph-H, Ph-H, furyl-H)

Example 30 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide

A solution of (+/-)-N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (80% diastereoisomer b) (0.30g, 0.00256moles) in dichloromethane (25ml), cooled to -70°C, was treated with a solution of 3-chloroperoxy benzoic acid (0.80g, 0.00255moles) in dichloromethane (25ml) over 1 hour maintaining the temperature at -70°C. The cooling bath was removed and the reaction mixture was stirred for 1 hour giving a colourless solution. The reaction mixture was diluted with dichloromethane (50ml) and washed with 10% aq sodium sulphite solution, sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to a colourless oil which contained a mixture of diastereoisomers b1+b2. Purification by repeated flash column chromatography on silica gel eluted with 1:1 to 3:1 petroleum ether 40-60°C: ethyl acetate followed by recrystallisation from ethyl acetate/petroleum ether 40-60°C gave (+/-)-N-[6-(4-fluorophenyl)hexyl]-2-[4-benzylsulphinyl]-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomer b2) as colourless solid. (0.38g, 28%) m.p. 90-91°C.

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.57 (2H, t, J=7.6Hz, CH_2Ph), 2.67, 2.73 (1H, dd, J=2.5, 15.4Hz, H_3), 2.94, 3.01 (1H, dd, J=5.5, 15.4Hz, H_3), 3.22 (4H, m, CH_2-furyl, CH_2NH), 3.92, 4.05 (each 1H, 2xd, J=13.1Hz, $SOCH_2$), 4.41 (1H, m, H_4), 4.58 (1H, dd, J=6, 10 Hz, CH), 6.29 (1H, d, J=0.77Hz, furyl-H), 6.9-7.4 (12H, m, pF-Ph-H, furyl-H, Ph-H, NH)

Example 31 N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomer a2)

A solution of N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (80% diastereoisomer a) (1.13g, 0.00222moles) in dichloromethane (25ml), cooled to -70°C, was treated with a solution of 3-chloroperoxy benzoic acid (0.70g, 0.00223moles) in dichloromethane (25ml) over 1 hour maintaining the temperature at -70°C. The cooling bath was removed and the reaction was stirred for 1 hour giving a colourless solution. The reaction mixture was diluted with dichloromethane (50ml), washed with 10% aq sodium sulphite solution, sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to a colourless oil which contained a mixture of diastereoisomers. Purification by flash column chromatography on silica gel eluted with 1:1 to 4:1 petroleum ether 40-60°C:ethyl acetate gave (+/-)-N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-

oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomer a2) as colourless oil. (0.31g, 26%).
^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.57 (2H, t, J=7.6Hz, CH_2Ph), 2.76, 2.79 (1H, dd, J=2, 15.2Hz, H_3), 3.00, 3.04 (1H, dd, J=5.2, 15.2Hz, H_3), 3.30 (4H, m, CH_2-furyl, CH_2NH), 3.93, 4.08 (4H, 2xm, CH, H_4, SOCH_2), 6.29 (1H, s, furyl-H), 6.9-7.4 (11H, m, pF-Ph-H, furyl-H, Ph-H), 7.88 (1H, m, NH)

Example 32 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenyl)propionamide (95% diastereoisomer a)

a. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionate.

A solution of methyl-(4-benzylthio-2-oxoazetidin-1-yl) acetate (2.03g, 0.00765moles) in dry tetrahydrofuran (40ml) at -75°C under nitrogen was treated with a 1M solution of lithium bis(trimethylsilyl)amide in hexanes (9.2ml, 0.0092moles) over 5 minutes keeping the temperature below -68°C. 1,3-Dimethylimidazolidin-2-one (5.0ml, 0.0457moles) was added keeping the temperature below -70°C. The resulting suspension was stirred at -75°C for 30 minutes and then treated with a solution of benzyl bromide (2.36g, 0.0138moles) over 5 minutes keeping the temperature below -70°C. The reaction was stirred for 1.5 hours during which time it reached -20°C. The reaction was cooled to -75°C and quenched with glacial acetic acid (1.0ml), partititioned between brine (100ml) and ethyl acetate (100ml). The organic layer was washed with water, dried ($MgSO_4$), and evaporated to a coloured oil. Purification by flash column chromatography on silica gel eluted with 2:1 petroleum ether 40-60°C:ethyl acetate gave methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionate as yellow soild (1.78g, 65%, 9:1 diastereoisomer a:b) m.p. 66-67°C.
^{1}H NMR δ ($CDCl_3$) 2.83 (1H, m , H_3), 3.12 (1H, m, H_3), 3.35 (2H, m, CH_2Ph), 3.76 (5H, m, OCH_3, SCH_2), 4.06 (m, CH_B), 4.75 (m, H_4, CH_A), 7.23 (10H, m, 2xPh-H)

b. 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionic acid

A solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionate (1.75g, 0.00492 moles) in methanol (75ml) at 10°C was treated with a 1N sodium hydroxide solution (4.92ml, 0.00492moles) over 40 minutes. The cooling bath was removed and the reaction was stirred for 2 hour. 1N NaOH (0.2ml) was added and the reaction was stirred for 60 minutes, diluted with water (50ml) and evaporated to remove methanol. The residue was mixed with water (75ml) and extracted with ethyl acetate (50ml). The aqueous was acidified with 1NHCl and extracted with ethyl acetate (2x75ml). The organic extracts were combined washed with brine, dried ($MgSO_4$), and evaporated to give 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenyl)propionic acid as a cream solid m.p. 125-131°C (1.37g, 82%, 40:60 distereoisomer a:b)
^{1}H NMR δ ($CDCl_3$) 2.8 (1H,m, H_3), 3.15, 3.35 (3H, 2xm, CH_2-furyl, H_3), 3.53 (m, SCH_{2B}), 3.73 (s, SCH_{2A}), 4.0, 4.15 (1H, 2xm, CH_{A+B}), 4.07, 4.59 (1H, 2xm, H_4), 5.47 (1H, bs, CO_2H), 7.08-7.37 (10H, m, 2xPh-H)

c. (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenyl)propionamide

6-(4-Fluorophenyl)hexylamine (0.76g, 0.00389moles) in dry DMF (40ml) was added to a mixture of 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionic acid (1.33g, 0.00389moles), 1-hydroxybenzotriazole (0.52g, 0.00385moles), N,N'-dicyclohexylcarbodiimide (0.8g, 0.00388moles) and was stirred at room temperature

for 4h. The suspension was diluted with ethyl acetate (100ml) and filtered to remove urea. The filtrate was evaporated to remove ethyl acetate and the residue was mixed with aq.NaHCO3 (125ml) and washed with diethyl ether (2x75ml). The organic extracts were combined and washed with brine, dried ($MgSO_4$), and evaporated to an oil. This was combined with product from separate reactions (from 0.33g, 0.96g of 2-(4-benzylthio-2-oxoazetidin-1-yl)-3-phenylpropionic acid) and purified by repeat flash column chromatography on silica gel eluted with 3:1 P.E.:ethyl acetate to give the title compound as a waxy colourless solid, 0.79g, 20% (contains 5% diastereoisomer b), nmr for a:

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.8 Hz, CH_2Ph), 2.68, 2.74 (1H, dd, J=2.3, 15.4Hz, H_3), 2.99, 3.05 (1H, dd, J=5.2, 15.4Hz, H_3), 3.26 (4H, m, NHCH_2, CH_2Ph), 3.70 (2H, s, SCH_2), 3.81 (2H, m, CH, H_4), 6.9-7.4 (15H, m, pF-Ph-H, 2xPh-H,NH)

Example 33 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenyl)propionamide (98% diastereoisomer b)

The above chromatography gave the title compound as a colourless soild, 1.01g, m.p. 78-80°C, 25% yield (contains 2% diastereoisomer a)

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.8 Hz, CH_2Ph), 2.76, 2.80 (1H, dd, J=2.4, 15.6Hz, H_3), 3.06, 3.10 (1H, dd, J=5.2, 15.6Hz, H_3), 3.24, 3.34 (4H, m, NHCH_2, CH_2Ph), 3.51 (2H, s, SCH_2), 4.16 (1H, dd, J=5.6, 10.4 Hz, CH), 4.54 (1H, m, H_4), 6.35 (1H, m, NH), 6.9-7.4 (14H, m, pF-Ph-H, 2xPh-H)

Example 34 N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer a2)

A solution of N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenylpropionamide (0.76g, 0.00147moles) in dichloromethane (25ml), cooled to -70°C, was treated with a solution of 3-chloroperoxy benzoic acid (0.46g, 0.00147moles) in dichloromethane (25ml) over 1 hour maintaining the temperature at -70°C. The cooling bath was removed and the reaction was stirred for 2 hour giving a colourless solution. The reaction was washed with 10% aq sodium sulphite solution, sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to a colourless oil (0.89g). Purification by repeat flash column chromatography on silica gel eluted with 1:1 to 2:3 petroleum ether 40°-60°C:ethyl acetate followed by recystallisation from diethyl ether / petroleum ether gave N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer a2) as colourless solid. (0.26g, 33%) m.p. 62-63°C.

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.57 (2H, t, J=7.6Hz, CH_2Ph), 2.77, 2.87 (1H, dd, J=2.2, 15.3Hz, H_3), 2.88, 2.93 (1H, dd, J=5.2, 15.3Hz, H_3), 3.38 (4H, m, CH_2Ph, CH_2NH), 3.61 (1H, m, H_4), 3.83, 4.05 (each 1H, 2xd, J=13Hz, SOCH_2), 3.99 (1H, m, CH), 6.9-7.4 (14H, m, pF-Ph-H, 2x Ph-H), 8.06 (1H, m, NH)

$\nu_{C=O}$ 1785 cm^{-1}; Found: C, 69.3; H, 6.5; N, 5.3%; $C_{31}H_{35}FN_2O_3S$ requires: C, 69.6; H, 6.6; N, 5.2%

Example 35 N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (79% diastereoisomer a1)

Evaporation of column fractions from the above chromatography gave the title compound as a colourless foam, 0.21g, 27% yield, (contains 22% diastereoisomer a2); nmr for a1:

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.57 (2H, t, J=7.8 Hz, CH_2Ph), 2.62, 2.68 (1H, dd, J=4.7, 14.8Hz, H_3), 3.3 (5H, m, H_3, CH_2-Ph, CH_2NH), 3.80 (4H, m, H_4, $SOCH_2$, CH), 6.60 (1H, m, NH), 6.9-7.4 (14H, m, pF-Ph-H, 2xPh-H)

Example 36 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer b1)

A solution of (+/-)-N-[6-(4-fluorophenyl)hexyl]-2-{4-benzylthio}-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer b) (0.95g, 0.00183moles) in dichloromethane (25ml), cooled to -70°C, was treated with a solution of 3-chloroperoxy benzoic acid (0.57g, 0.00182moles) in dichloromethane (25ml) over 45 minutes maintaining the temperature at -70°C. The cooling bath was removed and the reaction was stirred for 2 hour giving a colourless solution. The reaction was washed with 10% aq sodium sulphite solution, sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to a colourless oil (0.89g). Purified by repeat flash column chromatography on silica gel eluted with 1:1 to 1:3 petroleum ether 40-60°C: ethyl acetate to separate the diastereoisomer products. Cooling the higher running isomer in diethyl ether gave N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer b1) as colourless solid. (0.071g, 7%) m.p. 128°C. (contains 4.8% diastereoisomer b2)

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.8 Hz, CH_2Ph), 2.62, 2.68 (1H, dd, J=4.9, 14.7Hz, H_3), 2.85 (1H, m), 3.25 (2H, m, CH_2NH), 3.36, 3.42 (1H, dd, J=2.2, 14.7Hz, H_3), 3.52 (1H, m, 1 of $CHCH_2$), 3.70, 4.05 (each 1H, 2xd, J=10Hz, $SOCH_2$), 4.20 (1H, m, H_4), 4.67 (1H, dd, J=5, 11Hz, CH), 6.7-7.4 (15H, m, pF-Ph, 2xPh-H, NH)

Found: C, 68.9; H, 6.5; N, 5.1%; $C_{31}H_{35}FN_2O_3S$ requires: C, 69.6; H, 6.6; N, 5.2%

Example 37 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer b2)

The lower running isomer fractions from the above chromatography were recrystallised from ethyl acetate/diethyl ether to give N-[6-(4-fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer b2) as colourless solid. (0.328g, 33%) m.p.84-85°C.

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.8 Hz, CH_2Ph), 2.60, 2.65 (1H, dd, J=2.4, 15.6Hz, H_3), 2.84, 2.87 (1H, dd, J=5.6, 15.6Hz, H_3), 3.21 (3H, m, 1 of PhCH_2CH), 3.53, 3.59 (1H, dd, J=6.4,14.9Hz, 1 of PhCH_2CH), 3.91, 4.02 (each 1H, 2xd, J=13.1Hz, $SOCH_2$), 4.34 (1H, m, H_4), 4.70, 4.74 (1H, dd, J=6.4, 10, CH), 6.9-7.4 (15H, m, pF-Ph-H, 2xPh-H, NH)

Found: C, 69.0; H, 6.5; N, 5.1%; $C_{31}H_{35}FN_2O_3S.1.0\%H_20$ requires: C, 68.9; H, 6.6; N, 5.2%

Example 38 (+)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer (+)-b2)

The above b2 diastereoisomer was separated by chiral HPLC to give the title compound as a gum

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.8 Hz, CH_2Ph), 2.60,

2.65 (1H, dd, J=2.4, 15.6Hz, $\underline{H}_3$), 2.84, 2.87 (1H, dd, J=5.6, 15.6Hz, $\underline{H}_3$), 3.21 (3H, m, 1 of $C\underline{H}_2NH$), 3.53, 3.59 (1H, dd, J=6.4,14.9Hz, 1 of $C\underline{H}_2Ph$), 3.91, 4.02 (each 1H, 2xd, J=13.1Hz, $SOC\underline{H}_2$), 4.34 (1H, m, $\underline{H}_4$), 4.70, 4.74 (1H, dd, J=6.4, 10, $C\underline{H}$), 6.9-7.4 (15H, m, pF-Ph-$\underline{H}$, 2xPh-$\underline{H}$, $N\underline{H}$)

a_D = +35.8° (c=0.4%w/v ethanol) at 20°C

Example 39 (-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer (-)-b2)

The title compound was a so obtained from the b2 diastereoisomer by chiral HPLC and was isolated a gum

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4x$C\underline{H}_2$), 2.56 (2H, t, J=7.8 Hz, $C\underline{H}_2Ph$), 2.60, 2.65 (1H, dd, J=2.4, 15.6Hz, $\underline{H}_3$), 2.84, 2.87 (1H, dd, J=5.6, 15.6Hz, $\underline{H}_3$), 3.21 (3H, m, 1 of $C\underline{H}_2NH$), 3.53, 3.59 (1H, dd, J=6.4,14.9Hz, 1 of $C\underline{H}_2Ph$), 3.91, 4.02 (each 1H, 2xd, J=13.1Hz, $SOC\underline{H}_2$), 4.34 (1H, m, $\underline{H}_4$), 4.70, 4.74 (1H, dd, J=6.4, 10, $C\underline{H}$), 6.9-7.4 (15H, m, pF-Ph-$\underline{H}$, 2xPh-$\underline{H}$, $N\underline{H}$)

a_D = -43.7° (c=0.3%w/v ethanol) at 20°C

Example 40 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (diastereoisomer a)

a. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-2-allylacetate

A solution of methyl-(4-benzylthio-2-oxoazetidin-1-yl) acetate (5.0g, 0.01884moles) in dry tetrahydrofuran (100ml) at -75°C under nitrogen was treated with a 1M solution of lithium bis(trimethylsilyl)amide in THF (23.0ml, 0.023moles) over 10 minutes keeping the temperature below -68°C. 1,3-Dimethylimidazolidin-2-one (12.5ml, 0.1143moles) was added keeping the temperature below -70°C. The resulting suspension was stirred at -75°C for 30 minutes and then treated with allyl iodide (3.1ml, 0.0339moles) over 5 minutes . The temperature rose to -65°C. The reaction was stirred at -78°C for 30 minutes and then allowed to warm to -20°C over 30 minutes. The reaction was cooled to -75°C and quenched with glacial acetic acid (5ml), partititioned between brine (150ml) and ethyl acetate (175ml). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to a coloured oil. Purification by flash column chromatography on silica gel eluted with 4:1 petroleum ether 40-60°C:ethyl acetate gave methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-2-allylacetate as yellow oil (4.48g, 78%, 85:15 diastereoisomer a:b)

^{1}H NMR δ ($CDCl_3$) 2.7 (2H, m, $C\underline{H}_2$), 2.90 (1H, m, $\underline{H}_3$), 3.27 (1H, m, $\underline{H}_3$), 3.80 (5H, m, $CO_2C\underline{H}_3$,$SC\underline{H}_2$), 3.92, 4.23 (1H, 2xm ,$C\underline{H}_A$+$C\underline{H}_B$), 4.55, 4.90 (1H, 2xm, $\underline{H}_4$), 5.16 (2H, m, CH=$C\underline{H}_2$), 5.80 (1H, m, $C\underline{H}$=CH2), 7.31 (5H, m, Ph-$\underline{H}$,)

b. 2-(4-benzylthio-2-oxoazetidin-1-yl)-2-allyl acetic acid

A solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)-2-allyl acetate (4.38g, 0.01434 moles) in methanol (100ml) at 10°C was treated with a 1N sodium hydroxide solution (14.3ml, 0.0143moles) over 15 minutes. The cooling bath was removed and the reaction was stirred for 1.5 hour. 1N NaOH (2.0ml) was added and the reaction was stirred for 30 minutes, diluted with water (100ml) and evaporated to remove methanol. The residue was extracted with diethyl ether (100ml). The aquous was acidified with dilute HCl, and extracted with diethyl ether (100ml, 50ml). The extracts were combined , washed with brine, dried ($MgSO_4$), and evaporated to give 2-(4-

benzylthio-2-oxoazetidin-1-yl)-2-allylacetic acid as a yellow oil (3.97g, 95%) 60:40 distereoisomer a:b

^{1}H NMR δ ($CDCl_3$) 2.7 (2H, m, CH_2), 2.90 (1H, m, H_3), 3.27 (1H, m, H_3), 3.80 (m, CH_B, CO_2CH_3,SCH_2), 4.12 (m ,CH_A), 4.65, 4.85 (1H, 2xm, H_4), 5.16 (2H, m, $CH=CH_2$), 5.80 (1H, m, CH=CH2), 7.31 (5H, m, Ph-H,)

c. (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (90% diastereoisomer a)

6-(4-Fluorophenyl)hexylamine (2.5g, 0.0128moles) in dry DMF (75ml) was added to a mixture of 2-(4-benzylthio-2-oxoazetidin-1-yl)-2-allylacetic acid (3.73g, 0.0128moles), 1-hydroxybenzotriazole (1.75g, 0.0129moles), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluene sulfonate (5.42g, 0.0128moles) and was stirred at room temperature for 19h. The suspension was partitioned between sodium hydogen carbonate solution (300ml) and diethyl ether (150ml). The layers were separated and the aqueous was washed with diethyl ether (100ml). The organic extracts were combined washed with water, dried ($MgSO_4$), and evaporated to an oil (5.92g). Purified by repeat flash column chromatography on silica gel eluted with 2:1 petroleum ether 40-60°C:ethyl acetate to give the title compound as a colourless oil, 1.27g, 21 %yield

1H NMR δ ($CDCl_3$) 1.35-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7Hz, CH_2Ph), 2.65 (2H, m, CH_2), 2.79, 2.85 (1H, dd, J=2.4, 15.4Hz, H_3), 3.25 (3H, m, H_3, NHCH_2), 3.71 (1H, dd, J=6Hz, CH), 3.82 (2H, s, SCH_2), 4.65 (1H, m, H_4), 5.15 (2H, m, $CH=CH_2$),

5.72 (1H, m, $CH=CH_2$), 6.85 (1H, m, NH), 6.9-7.3 (9H, m, Ph-H, Ar-H)

Example 41 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (80% diastereoisomer b)

From the above chromatography the title compound was isolated as a colourless oil, 1.11g, 19% yield

^{1}H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7Hz, CH_2Ph), 2.78 (2H, m, CH_2), 2.84, 2.91 (1H, dd, J=2.3, 15.3Hz, H_3), 3.25 (3H, m, H_3, NHCH_2), 3.82 (2H, s, SCH_2), 4.03 (1H, dd, J=6Hz, CH), 4.65 (1H, m, H_4), 5.08 (2H, m, $CH=CH_2$),

5.72 (1H, m, $CH=CH_2$), 6.51 (1H, m, NH), 6.9-7.3 (9H, m, Ph-H, Ar-H)

Example 42 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-2-allylacetamide (diastereoisomers a2+a1)

Treatment of 1.2g (0.00256moles) of (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (90% diastereoisomer a) with *m*CPBA using the procedure described in Example 34 gave, after similar work-up and chromatography the title compound as a colourless oil, 0.41g, 33% yield

^{1}H NMR (diastereoisomer a2) δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7Hz, CH_2Ph), 2.7-3.3 (6H, m, $CHCH_2$,H_3, NHCH_2), 3.80-4.20 (3H, m, $SOCH_2$, CH), 4.48 (1H, m, H_4), 5.13 (2H, m, $CH=CH_2$), 5.72 (1H, m, $CH=CH_2$), 6.9-7.4 (10H, m, Ph-H, Ar-H), 7.46 (1H, m, NH)

Example 43 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-2-allylacetamide

Treatment of 1.05g of (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (80% diastereoisomer b) with *m*CPBA using the procedure described in Example 34 gave, after similar work-up and chromatography the title compound as a pale yellow oil, 0.38g, 35% yield

^{1}H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2), 2.56 (2H, t, J=7Hz, CH_2Ph), 2.6-3.3 (6H, m, $CHCH_2$,H_3, $NHCH_2$), 3.95, 4.09 (each 1H, 2xd, J=11.6 Hz, $SOCH_2$), 4.47 (1H, m, CH), 4.57 (1H, m, H_4), 5.11 (2H, m, CH=CH_2), 5.72 (1H, m, CH=CH_2), 6.9-7.4 (10H, m, NH, Ph-H, Ar-H)

Example 44 (+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butyramide

a. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)butanoate

A mixture of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)acetate(1.2 g, 0.0045 mol) in dry tetrahydrofuran (20 ml) was treated with lithium hexamethyldisilazide solution (1 Mol solution in hexane,5.4 ml, 0.0054 mol) and stirred at -78°C for 30 minutes forming a precipitate which was broken up with vigorous stirring. Following treatment with ethyl iodide (0.64 ml,0.008 mol) at -78°C, the insoluble yellow solid dissolved forming a yellow solution. The reaction mixture was then left 16 hours at -20°C. After cooling to -78°C the solution was treated with acetic acid (0.5 ml) followed by partitiong between ethyl acetate and water. The aqueous layer was extracted again with ethyl acetate and the combined extracts dried ($MgSO_4$) and evaporated to a brown oil. Purification by flash chromatography (silica, ethyl acetate/petrol) gave the title compound as a mixture of diastereoisomers (colourless oil), 0.3 g, 23% yield.

^{1}H NMR δ ($CDCl_3$) 1.02 (3H, d of d, CH_2CH_3), 2.07 (2H, m, SCH_2), 2.92 and 3.25 (each 1H, m, H4s), 3.76 (2H, d, CH_2), 3.83 (2H, d, CH_2), 3.67, 4.16 (1H, m, CH), 4.64 and 4.94 (1H, m, H3), 7.28 (2x5H, m, Ph)

b. 2-(4-Benzylthio-2-oxoazetidin-1-yl)butanoic acid

A stirred solution of methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)butanoate (1.40 g, 0.0047 mol) in methanol (12 ml) was treated with 1 molar potassium hydroxide (5.47 ml). After 16 hours, the methanol was evaporated and the residue diluted with water. The aqueous layer was acidified with cooling (ice bath) and the oil which precipitated was extracted into ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated to give the title compound as a white oily solid (mixture of diastereoisomers), 1.36g, 100% yield.

^{1}H NMR δ ($CDCl_3$) 1.02 (3H, m, CH_2CH_3), 2.07 (2H, m, SCH_2), 2.92 and 3.35 (each 1H, m, H4s), 3.74 (2H, s, CH_2), 3.84 (2H, s, CH_2), 3.53, 4.10 (1H, m, CH), 4.71 and 4.94 (1H, m, H3),6.99, (1H,bs, OH), 7.28 (2x5H, m, PhH)

c. N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]butanamide (mixture of diastereoisomers a + b)

A mixture of 6-(4-fluorophenyl)hexylamine (0.95g,0.0048 mol,Lamattina J. L. EP 138464 A2 850424 (CA 103:142000)), 1-hydroxybenzotriazole hydrate (0.56g, 0.0042 mol), 2-(4-benzylthio-2-oxoazetidin-1-yl)-butanoic acid (1.2 g, 0.0043 mol) and dicyclohexylcarbodiimide (0.89 g, 0.0043 mol) in dimethylformamide (50 ml) was stirred for 16 h at ambient temperature. The solvent was evaporated and the residue treated with ethyl acetate. The insoluble dicyclohexylurea was filtered off and

discarded, and the filtrate washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and evaporated to an oil. This was purified by flash chromatography (silica, ethyl acetate/petrol) to give the title compound as an oil (1.47 g, 75% yield)
^{1}H NMR δ ($CDCl_3$) 0.83-.98,(3H,m,CH_3),1.1-17(6H,m,CH_2),1.8-2.15(4H,m,CH_2) 2.55 (2H, t,CH_2),2.88 (1H,m,CH_2), 2.99,(2H,m,CH_2), 3.46,(1H,q,CH_2), 3.85, 4.12(1H,q,CH), 3.85 (2H,s,CH_2), 3.86 (1H,d,CH_2), 4.65(1H,m,H4), 6.5(1H,t,NH), 6.75(1H, t,NH), 6.9-7.33(9H, m,PhH).

Example 45 N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide.

A solution of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]butyramide (diastereoisomers a &b) (1.27 g, 0.0028 mol) in dichoromethane (50 ml) was cooled to -65 to -70°C and a solution of *m*-chloroperbenzoic acid (0.58 g, 0.0033 mol) in dichloromethane (20 ml) added dropwise over 15 min. After 3 hours the mixture was washed with a mixture of saturated sodium hydrogen carbonate and saturated sodium sulphite, dried ($MgSO_4$) and evaporation gave the title compound as a mixture of diastereoisomers a1, a2, b1, b2 as an oil, 1.47g 100% yield.
^{1}H NMR δ ($CDCl_3$) 0.93-1.04,(3H,m,CH_2CH_3),1.1-1.7(6H,bm,-CH_2),1.8-2.25(2H,m,CH_3CH_2) 2.55 (2H, t,CH_2Ar),2.6-3.0 (1H,m,3H), 3.05-3.55 (3H,m,CH_2,H3),3.7 (1H,q,CH),3.85,4.12(1H,q,CH),3.85-4.25(2H,m,SCH_2), 4.5-4.85(1H,m,H4),6.45(1H,t,NH), 6.85(1H, t,NH), 6.9-8.1(9H, m,PhH).
0.8g of the above oil was purified by chromatography (HPLC, Beckman silica column, ethanol/hexane), to give the isomers described in Examples 46-48.

Example 46 (+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (Isomer a1)

Isomer a1, oil, (0.05g)
^{1}H NMR δ ($CDCl_3$) 0.83-.98,(3H,t,CH_3),1.2-1.75(6H,m,CH_2), 1.99 (2H, q,CH_3CH_2),2.56 (2H,m,CH_2Ar), 2.78,3.34,(2H,m,H3)3.21,(2H,m,$NHCH_2$), 3.87 (3H,m,CH,$PhCH_2$), 4.71(1H,m,H4),6.25(1H,t,NH), 6.9-7.39(9H, m,PhH).

Example 47 (+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (isomer b1 and b2, 1:3)

The above procedure yielded 0.05g of the title compounds (b1:b2, 1:3) as an oil
^{1}H NMR δ ($CDCl_3$) 0.93,(3H,t,CH_3),1.01,(3H,t,CH_3),1.22-1.38(6H,m,CH_2), 1.99-2.1 (2H, m,CH_3CH_2), 2.1-2.25 (2H, m,CH3CH_2), 2.56 (2H,m,CH_2Ar), , 2.55,3.08,(2H,m,H3) 2.68,3.55,(2H,m,H3),3.18,3.25,(2H,2xm,$NHCH_2$), 3.87-4.25 (3H,m,CH,$PhCH_2$), 4.45,4.51(1:3)(1H,2xm,H4),6.75(1H,t,NH), 6.9-7.40(9H, m,PhH).

Example 48 N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (isomer a2)

The above procedure yielded 0.05g of the title compound as an oil
^{1}H NMR δ ($CDCl_3$) 098,(3H,t,CH_3),1.3-1.61(6H,m,CH_2), 2.08 (2H, q,CH_3CH_2),2.56 (2H,m,CH_2Ar),2.75,3.19 (each 1H,m,H3),3.26 (2H,m,$NHCH_2$), 3.85 (1H,m,CH,), 4.05 (1H,d of d,ArCH_2), 4.54(1H,m,H4), 6.92-7.40(9H, m,PhH).

Example 49 (+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]pentanamide

a. Methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)pentanoate

Substituting propyl iodide (4g, 0.023 mol) for ethyl iodide and using the corresponding amounts of the other reagents in Example 44a gave after purification by flash chromatography (silica, ethyl acetate/petrol) the title compound as a mixture of diastereoisomers (colourless oil), 1.05 g, 25.3% yield.

^{1}H NMR δ ($CDCl_3$) 0.96 (3H, d of d, $CH_2\underline{CH_3}$), 1.36 (2H, m, $CH_3\underline{CH_2}$),1.96 (2H, m, $CH_2\underline{CH_2}$),2.90,3.29 (each 1H, m, H3s), 3.74 (3H, d, OCH_3,), 3.79 (2H, d, SCH_2), 4.27 (1H, m, CH), 4.64 and 4.94 (1H, m, H4), 7.29 (5H, m, Ph)

b. 2-(4-Benzylthio-2-oxoazetidin-1-yl)pentanoic acid

Substituting methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)pentanoate (1.04g, 0.0033 mol) for methyl 2-(4-benzylthio-2-oxoazetidin-1-yl)butanoate and using the corresponding amounts of the other reagents in Example 44b gave the title compound as a mixture of diastereoisomers (colourless oil), 0.8 g, 82% yield.

^{1}H NMR δ ($CDCl_3$) 0.96 (3H, d of d, $CH_2\underline{CH_3}$), 1.40 (2H, m, $CH_3\underline{CH_2}$),1.91 (2H, m, $CH_2\underline{CH_2}$),2.90,3.29 (each 1H, m, H3s), 3.64 (1H, m, OCH_3,), 3.84 (2H, d, SCH_2), 4.24 (1H, m, CH), 4.64, 4.94 (1H, m, H4),6.4(1H,bs,OH),7.29 (5H, m, Ph)

c. (+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propanamide

Substituting 2-(4-benzylthio-2-oxoazetidin-1-yl)propanoic acid (0.8g, 0.0027 mol.) for 2-(4-benzylthio-2-oxoazetidin-1-yl)butanoic acid and using corresponding quantities of the other reagents in Example 44c gave the title compound as an oil, 1.4g 100%yield

^{1}H NMR (complex spectrum) δ ($CDCl_3$) 0.93,(3H,m,CH_3),1.2-1.6(4H,m,CH_2),1.8-2.15(4H,m,CH_2)

2.55 (2H, t,CH_2),2.88 (1H,m,CH_2), 2.8,3.3 (1H,d of d,3H), 2.9,(2H,s,CH_2) 2.95,(2H,s,CH_2)3.28,(2H,m,CH_2), 3.85

(2H,m,CH_2),4.62(1H,q,CH),4.74(1H,m,H4),6.5(1H,t,NH), 6.76(1H, t,NH), 6.9-7.3 (9H, m,PhH).

Example 50 (+/-)-N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propanamide

A solution of N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]pentanamide (diastereoisomers a &b) (0.2g, 0.00042 mol) in dichoromethane (5 ml) was cooled to -65 to -70°C and a solution of *m*-chloroperbenzoic acid (0.09 g, 0.00051 mol) in dichloromethane (5 ml) added dropwise over 15 min. After 1 hour the mixture was washed with a mixture of saturated sodium hydrogen carbonate and saturated sodium sulphite, dried ($MgSO_4$) and evaporation gave the title compound as a mixture of diastereoisomers a1, a2, b1, b2 as an oil, 0.2g 100% yield.

^{1}H NMR (complex spectrum) δ (DMSO d_6) 0.83-0.95,(3H,m,$CH_2\underline{CH_3}$), 1.1-1.7(6H,bm,-$\underline{CH_2}$), 2.7 (2H, s,CH_2Ar), 2.9 (2H, s,CH_2Ar), 3.05-3.55 (3H,m,$\underline{CH_2}$,H3), 3.7 (1H,q,CH), 3.85, 4.12 (1H,q,CH), 3.70-4.25 (2H,m,SCH_2), 4.6-5.15 (1H,m's,H4), 7.0-8.2 (9H, m,PhH).

Example 51 N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer b1&b2 1:1.5)

Treatment of N-(benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b, Example 20) (1.31 g) with *m*CPBA under the conditions described in Example 12 gave the title compound as a mixture of diastereoisomers (b1:b2 1:1.5) 1.14 g, colourless solid, m.p. 110-3°C

Example 52 N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (89% diastereoisomer a1)

Treatment of N-(benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a, Example 19) (1.31 g) with *m*CPBA under the conditions described in Example 12 gave the title compound as a mixture of diastereoisomers which were separated by crystallisation to give predominantly diastereoisomer a1 as a colourless solid, m.p. 150-3°C

Example 53 N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (82% diastereoisomer a2)

The mother liquors from the above recryatallisation were evaporated and recrystallised to give the title compound as predominantly the diastereoisomer a2, 0.67 g, m.p. 134-5°C.

Example 54 R-Methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate

a. (-)-(R)-4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid

4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid (3.41 g, 10.2 mmol) and cinchonidine (2.99 g, 10.2 mmol) in ethanol (40 ml) were heated to boiling when a clear solution was obtained. On standing for 90 min, the crystalline salt which had precipitated was filtered off, and recrystallised from ethanol (20 ml). The solid obtained was stirred vigorously with ether and water whilst acidifying with dil. hydrochloric acid, and when complete solution was obtained the layers were separated and the aqueous layer further extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oil which crystallised on trituration with light petrol to give the title compound as white crystals, m.p. 74-6°C, 6.7 g, 50% yield

α_D^{25} = -24.2 (c. 0.7 w/v $CHCl_3$, 25°C)

^{1}H NMR δ ($CDCl_3$) 2.97 (1H, dd, H3a), 3.26, 4.07 (each 1H, $C\underline{H}_2CO$, d), 3.42 (1H, dd, H3b), 3.70 (3H, s, $C\underline{H}_3O$), 3.81 (2H, s, $SC\underline{H}_2$), 4.83 (2H, m, $C\underline{H}_2O$), 4.93 (1H, dd, H4), 5.35 (2H, m, $C\underline{H}_2CH$), 6.03 (1H, m, $C\underline{H}CH_2$), 7.39 (2H, d, Ph-H), 8.02 (2H, d, Ph-H)

b. R-methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate

A suspension of anhydrous potassium carbonate (8.88g), R-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetic acid (21.55g) in N-methylpyrollidinone (100ml) was treated with methyl iodide (10.94g) and stirred at room temperature for 2 hours. After a further (1.0g) methyl iodide was added the reaction was stirred for 30 minutes, partitioned between brine (500ml) and diethyl ether (500ml). The aqueous layer was washed with diethyl ether (500ml) and the organic extracts were combined, washed with water (x2), brine, dried ($MgSO_4$),and evaporated to an orange oil (22.1g). Purified by flash column chromatography on silica gel eluted with [1:1] P.E. 40-60°C: ethyl acetate to give R-methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate as a yellow oil (20.0g, 89%).

^{1}H NMR δ ($CDCl_3$) 2.94, 3.01 (1H, dd, J=2.2, 15.3Hz, $\underline{H}_3$), 3.26 (1H, d, J=18.1Hz, 1 of $NC\underline{H}_2$), 3.39, 3.46 (1H, dd, J=5.1, 15.3Hz, $\underline{H}_3$), 3.7 (3H, s, $CO_2C\underline{H}_3$), 3.81 (2H,

s, SCH_2), 4.03 (1H, d, J=18.1Hz, 1 of NCH_2), 4.83 (2H, m, CO_2CH_2), 4.93 (1H, m, H_4), 5.37 (2H, m, CH_2=CH), 6.04 (1H, m, CH_2=CH), 7.39 (2H, m, Ar-H), 8.02 (2H, m, Ar-H)

c. R,R-Methyl-2-(4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl)propionate and S,R- Methyl-2-(4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl)propionateA solution of R-methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate (13.2g) in anhydrous tetrahydrofuran (250ml), cooled to -75°C under nitrogen, was treated with a 1M solution of lithium bis(trimethylsilyl)amide in THF (46.3ml) over 10 minutes keeping the temperature below -70°C. The red solution was cooled back to -75°C and 1,3-dimethyl-imidazolidinone (30.5ml) was added keeping the temperature below -70°C. The resulting suspension was stirred at -75°C for 30 minutes and then treated with methyl iodide (4.3ml) over 1 minute and the temperature rose to -68°C. The reaction was stirred at -75°C for 1.5 hours and then allowed to warm to -20°C over 30 minutes. The reaction was cooled to -75°C and quenched with glacial acetic acid (3.5ml), partititioned between water (300ml) and diethyl ether (250ml). The aqueous was washed with ether (250ml) and the organic extracts were combined washed with brine (x3), dried ($MgSO_4$) and evaporated to a coloured oil (7.81g). ^{1}H nmr indicates a ratio of approximately 50% R,R (diastereoisomer a): 35% S,R (diastereoisomer b) : 15% starting material. Purified by repeat flash column chromatography on silica gel eluted with [2:1] petroleum ether 40-60°C:ethyl acetate to give the products as various mixtures (12.06g, 88%).

d. R,R-2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionic acid and S,R-2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionic acidA solution of methyl-2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionate (2.65g) in tetrahydrofuran (50ml) was cooled to 3°C and treated with 1N sodium hydroxide solution (7.5ml) over 1 hour. The cooling bath was removed and reaction mixture was stirred for 30 minutes and a further 1.0ml of 1N sodium hydroxide solution was added. The reaction was stirred for 30 minutes, brine (75ml) was added and the reaction mixture was extracted with diethyl ether (75ml). The aqueous was acidified with 2NHCl and extracted with diethyl ether (2x75ml). the extracts were combined, washed with water, dried ($MgSO_4$), and evaporated to give a mixture of (R,4-R) and (S,4-R)-2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionic acid and des α-methyl analogue as an orange oil (2.50g, 98%).

e. (S,4-R)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyoxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide

A mixture of 6-(4-fluorophenyl)hexylamine (1.38g), 2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionic acid (mixture of diasteroisomers) (2.47g), 1-hydroxybenzotriazole (0.95g) and dicyclohexylcarbodiimide(1.46g) in dimethylformamide (50ml) was stirred at room temperature for 4 hours. The reaction mixture was treated with diethyl ether (100ml) and filtered to remove dicyclohexylurea. The filtrate was washed with saturated sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and evaporated to dryness. Purified by flash column chromatography on silica gel eluted with [2:1] P.E. 40-60°C

to give S,R-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyoxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide (diastereoisomer b) as a yellow oil (0.479g, 13.4%)
^{1}H NMR δ ($CDCl_3$) 1.32-1.6 (13H, m, CH_3, 4xCH_2), 2.56 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.87 (1H, dd, J=2.3, 15.3Hz, H_3), 3.1-3.3 (3H, m, NHCH_2, H_3), 3.86 (2H, s, SCH_2), 4.10 (1H, q, CHCH$_3$), 4.69(1H, m, H_4), 4.83 (2H, m, CO_2CH_2), 5.37 (2H, m, CH_2=CH), 6.02 (1H, m, CH_2=CH), 6.43 (1H, m, NH), 6.94 (2H, m, p-F-Ph-H), 7.10 (2H, m, p-F-Ph-H), 7.37 (2H, m, Ar-H), 8.09 (2H, m, Ar-H)

Example 55. (α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide

A solution of S,R-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyoxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide (1.20g) in dichloromethane (25ml), cooled to -75°C, was treated with a solution of mcpba (0.71g, 1eq) in dichloromethane (25ml) dropwise over 1 hour. The cooling bath was removed and the reaction mixture was stirred for 2 hours, diluted with dichloromethane (25ml) and washed with 10% aqueous sodium sulphite (50ml), saturated sodium hydrogen carbonate solution (50ml), water. dried ($MgSO_4$) and evaporated to an orange oil. Intially purified by flash column chromatography on silica gel eluted with ethyl acetate and then by preparative hplc to give S,R,S-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide (diastereoisomer b2) as colourless oil. Solidifies on standing (0.24g, 19.4%).
^{1}H NMR δ ($CDCl_3$) 1.32-1.6 (13H, m, CH_3, 4xCH_2), 2.56 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.87 (1H, dd, J=2.4, 15.3Hz, H_3), 3.1-3.3 (3H, m, NHCH_2, H_3), 3.96, 4.08 (2H, 2xd, J=13Hz, SOCH_2), 4.4 (1H, q, CHCH$_3$), 4.60 (1H, m, H_4), 4.84 (2H, m, CO_2CH_2), 5.,37 (2H, m, CH_2=CH), 6.04 (1H, m, CH_2=CH), 6.94 (3H, m, NH, p-F-Ph-H), 7.10 (2H, m, p-F-Ph-H), 7.37 (2H, m, Ar-H), 8.09 (2H, m, Ar-H)

Example 56. (α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-carboxybenzylsulphinyl]-2-oxoazetidin-1-ylpropionamide

A solution of (α-*S*, 4-*R*, *SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyoxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide (Example 55, dia b2) (0.24g) , terakis(triphenylphosphine)palladium (0) (15mg) and triphenylphosphine (6mg)i in dry dichloromethane (5ml) was treated with pyrollidine (0.039ml) and the reaction was stirred at room temperature for 20 hours. The reaction mixturewas treated with dichloromethane (50ml) and water (25ml) and acidified with 2NHCl. Brine (75ml) was added to the emulsion, the layers were separated and the aqueous was washed with dichloromethane (2x50ml). The organic extracts were dried ($MgSO_4$) and evaporated to a yellow gum (0.22g) and purified by flash column chromatography on silica gel eluted with 50:50:1 dichloromethane:acetone:acetic acid to give (α-*S*, 4-*R*, *SS*)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyoxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide as a brown foam (0.123g, 56%).
^{1}H NMR δ ($CDCl_3$) 1.32-1.6 (13H, m, CH_3, 4xCH_2), 2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.84, 2.88 (1H, dd, J=2.4, 15.2Hz, H_3), 3.1-3.3 (3H, m, NHCH_2, H_3), 4.04, 4.10 (2H, 2xd, J=13Hz, SOCH_2), 4.4 (1H, q, CHCH$_3$), 4.68 (1H, m, H_4), 6.94 (3H, m, NH, p-F-Ph-H), 7.10 (2H, m, p-F-Ph-H), 7.39 (2H, m, Ar-H), 8.06 (2H, m, Ar-H)

Example 101 - (+/-)-4-(Pyrid-2-ylmethylthio)-1-(4-phenyl-2-oxobutyl)azetidin-2-one

a) (+/-)-4-(Pyrid-2-ylmethylthio)azetidin-2-one

Sodium (0.935 g, 40 mmol) was dissolved in ethanol (100 ml), then 2-(mercaptomethyl)pyridine (5.0 g, 40 mmol) was added and stirred 10 min at room temperature. A solution of 4-acetoxyazetidin-2-one in ethanol (50 ml) was added dropwise, and stirring continued for a further 30 min. The solvent was evaporated, water was added, and the product extracted into ethyl acetate. Drying and evaporation gave an oil which slowly crystallised and was triturated with petroleum ether to give the title compound (5.3 g), m.p. 99-100°C. ^{1}H NMR ($CDCl_3$) δ 2.84 (1H, dd), 3.34 (1H, dd), 3.95 (2H, s), 4.86 (1H, dd), 6.58 (1H, br s), 7.17-7.34 (2H, m), 7.65-7.72 (1H, m), 8.50-8.53 (1H, m).

b) (+/-)-4-(Pyrid-2-ylmethylthio)-1-(4-phenyl-2-oxobutyl)azetidin-2-one

A mixture of (+/-)-4-(pyrid-2-ylmethylthio)azetidin-2-one (5.3 g, 27 mmol), 1-bromo-4-phenyl-2-butanone (6.8 g, 30 mmol), tetrabutylammonium bromide (0.87 g, 2.7 mmol), finely powdered KOH (1.7 g, 30 mmol) and dry THF (100 ml) was stirred at room temperature for 2 hours, then poured into water and extracted with ether. Chromatography (silica, dichloromethane) of the organic extracts and crystallisation from ether gave the desired product (2.5 g), m.p. 56-58°C. ^{1}H NMR ($CDCl_3$) δ 2.70 (2H, t), 2.90 (2H, t), 3.01 (1H, dd), 3.43 (1H, dd), 3.57 (1H, d), 4.11 (1H, d), 3.84 (2H, s), 4.98 (1H, dd), 7.15-7.32 (7H, m), 7.60-7.67 (1H, m), 8.48-8.51 (1H, m).

Example 102 - (+/-)-4-(Pyrid-2-ylmethylsulphinyl)-1-(4-phenyl-2-oxobutyl)azetidin-2-one (diastereomer 1)

A solution of (+/-)-4-(pyrid-2-ylmethylthio)-1-(4-phenyl-2-oxobutyl)azetidin-2-one (2.4 g, 7 mmol) in dichloromethane (50 ml) was cooled to -60°C and a solution of *m*-chloroperoxybenzoic acid (1.46 g, 8.4 mmol) in dichloromethane (50 ml) was added dropwise. Stirring was continued at this temperature for 1 hour, then the mixture was poured into an aqueous solution of sodium sulphite and sodium bicarbonate. The organic layer was dried and evaporated, and the residue triturated with ethyl acetate. Recrystallisation from ethyl acetate gave a single diastereomer (0.66 g), m.p. 123-125°C. ^{1}H NMR δ ($CDCl_3$) 2.74 (2H, t), 2.92 (2H, t), 3.01 (1H, dd), 3.33 (1H, dd), 3.84 (1H, d), 3.98 (1H, d), 4.13 (1H, d), 4.40 (1H, d), 4.92 (1H, dd), 7.15-7.35 (7H, m), 7.70-7.80 (1H, m), 8.56 (1H, m). $\nu_{c=o}$ 1785 cm^{-1} (CCl_4)

Found: C, 63.63; H, 5.62; N, 7.97%

$C_{19}H_{20}N_2O_3S$ requires: C, 64.02; H, 5.66; N, 7.86%

Example 103 - (+/-)-4-(Pyrid-2-ylmethylsulphinyl)-1-(4-phenyl-2-oxobutyl)azetidin-2-one (diastereomer 2)

The mother liquors from the ethyl acetate trituration in example 102 were recrystallised twice from ethyl acetate/ether to obtain a sample of the second diastereomer, contaminated with 20% of diastereomer 1 (0.34 g), m.p. 70-72°C. ^{1}H NMR δ ($CDCl_3$) 2.69-2.77 (2H, m), 2.77 (1H, dd), 2.90 (2H, t), 3.26 (1H, dd), 4.17 (2H, s), 4.22 (1h, d), 4.37 (1H, d), 4.79 (1H, dd), 7.14-7.34 (7H, m), 7.69-7.74 (1H, m), 8.56-8.57 (1H, m).

$\nu_{c=o}$ 1785 cm^{-1} (CCl_4)

Found: C, 64.07; H, 5.65; N, 8.22%

$C_{19}H_{20}N_2O_3S$ requires: C, 64.02; H, 5.66; N, 7.86%

Example 104 - (+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-4-(Pyrid-2-ylmethylthio)azetidin-2-one

The synthesis was carried out as in example 1a, using 20 mmol each of 4-(acetylthiomethyl)pyridine and 4-acetoxyazetidin-2-one. Chromatography (silica, 0-4% MeOH in CH_2Cl_2) gave the title compound as an oil (2.7 g). 1H NMR δ ($CDCl_3$) 2.87 (1H, dd), 3.34 (1H, dd), 3.80 (2H, s), 4.70 (1H, dd), 7.03 (1H br. singlet), 7.26-7.30 (2H, m), 8.51-8.59 (2H, m).

b) (+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using 8.5 mmol of (+/-)-4-(pyrid-2-ylmethylthio)azetidin-2-one (8.5 mmol), N-(6-phenylhex-1-yl)-2-bromoacetamide (9.4 mmol), tetrabutylammonium bromide (0.94 mmol) and powdered KOH (9.4 mmol) in dry THF (50 ml). Chromatography (silica, 0-2% MeOH in EtOAc) gave the title compound as an oil (2.2 g). ^{1}H NMR δ ($CDCl_3$) 1.27 (4H, m), 1.46-1.66 (4H, m), 2.59 (2H, t), 2.91 (1H, dd), 3.22 (2H, m), 3.39 (1H, dd), 3.47, (1H, d), 3.72-3.89 (3H, m), 4.91 (1H, dd), 6.23 (1H, br. triplet), 7.14-7.30 (7H, m), 8.53-8.57 (2H, m).

Example 105 - (+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-phenylhex-1-yl)-4-(pyrid-4-ylmethylthio)-2-oxoazetidin-1-ylacetamide (2.1 g, 5.1 mmol). Recrystallisation of the crude product from ethyl acetate/ether gave a single diastereomer (0.55 g), m.p. 126-127°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.35 (4H, m), 1.48-1.64 (4H, m), 2.59 (2H, t), 3.01 (1H, dd), 3.23 (2H, dt), 3.46 (1H, dd), 3.82-3.90 (3H, m), 4.03 (1H, d), 4.70 (1H, dd), 6.36 (1H, br triplet), 7.15-7.29 (7H, m), 8.64-6.66 (2H, 7m). $\nu_{C=O}$ 1794, 1745cm^{-1} (CCl_4)

Found: C, 64.37; H, 6.74; N, 9.75%

$C_{23}H_{29}N_3O_3S$ requires: C, 64.61; H, 6.84; N, 9.83%

Example 106 - (+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 105 crystallised from ethyl acetate/ether to give a sample containing 86% of the second diastereomer (0.5 g) , m.p. 89-91°C. ^{1}H NMR δ ($CDCl_3$) 1.33-1.37 (4H, m) 1.50-1.60 (4H, m) 2.60 (2H, t), 3.00 (1H, dd), 3.21-3.33 (3H, m), 3.95-4.03 (3H, m), 4.18 (1H, d), 4.71 (1H, dd), 6.70 (1H, br. triplet), 7.15-7.29 (8H, m), 8.64-8.66 (2H, m). $n_{C=O}$ (CCl_4) 1795, 1766.

Found: C, 64.53; H, 6.72; N, 9.84%

$C_{23}H_{29}N_3O_3S$ requires: C, 64.61; H, 6.84; N, 9.83%

Example 107 - (+/-)-N-(6-Phenylhex-1-yl)-4-(1-oxopyrid-4-ylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

A solution of (+/-)-N-(6-phenylhex-1-yl)-4-(pyrid-4-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (0.2 g, 0.47 mmol) and *m*-chloroperoxybenzoic acid (excess) in dichloromethane (30 ml) was stirred at room temperature for 2 hours, then worked up as in example 102. Chromatography (silica, 0-5% MeOH in CH_2Cl_2) gave the title compound (0.17 g), m.p. 72-74°C. ^{1}H NMR δ ($CDCl_3$) 1.33-1.37 (4H, m), 1.50-1.65

(4H, m), 2.60 (2H, t), 3.24-3.30 (2H, m), 3.38 (1H, dd), 3.86 (1H, d), 4.06 (1H, d), 4.30 (1H, d), 4.54 (1H, d), 5.00 (1H, dd), 5.76 (1H, br. triplet), 7.15-7.20 (3H, m) 7.26-7.30 (2H, m), 7.40 (2H, d), 8.22 (2H, d). $\nu_{c=o}$ 1780 cm^{-1} (KBr)

Found: C 59.41; H 6.18; N 9.05

$C_{23}H_{29}N_3O_5S$:0.2H_2O requires: C 59.64; H 6.41; N 9.07

Example 108 - (+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-(2-Furylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using furfuryl mercaptan (42.5 mmol) and 4-acetoxyazetidin-2-one (38 mmol). Chromatography (silica, 1:1 pet. ether/CH_2Cl_2) gave the title compound as an oil (5.5 g). ^1H NMR δ ($CDCl_3$) 2.86 (1H, dd), 3.36 (1H, dd), 3.86 (2H, s), 4.79 (1H, dd), 6.06 (1H, br. singlet), 6.21-6.23 (1H, m), 6.33-6.35 (11H, m), 7.37-7.39 (1H, m).

b) (+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(2-furylmethylthio)-azetidin-2-one (10 mmol), N-(6-phenylhex-1-yl)-2-bromoacetamide (10 mmol), tetra-butylammonium bromide (1 mmol), and powdered KOH (11 mmol) in dry THF (150 ml). Chromatography (silica, EtOAc/pet. ether) gave the title compound as an oil (3.4 g). 1H NMR δ ($CDCl_3$) 1.31-1.40 (2H, m), 2.60 (2H, t), 2.97 (1H, dd), 3.19-3.28 (2H, m), 3.43 (1H, dd), 3.65 (1H, d), 3.83 (1H, d), 3.84 (2H, d), 4.91 (1H, dd), 6.13 (1H, br. triplet), 6.22 (1H, m), 6.31 (1H, m), 7.14-7.36 (6H, m).

Example 109 - (+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-phenylhex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide (2.9 g, 7.2 mmol). Recrystallisation of the crude product from ethyl acetate gave a sample containing about 99% of diastereomer 1 (0.2 g), m.p. 160-161°C. ^1H NMR δ ($CDCl_3$) 1.32-1.36 (4H, m) 1.50-1.63 (4H, m), 2.60 (2H, t), 3.01 (1H, dd), 3.18-3.30 (2H, m), 3.42 (1H, dd), 3.76 (1H, d), 4.00 (1H, d), 4.10-4.16 (2H, m), 4.60 (1H, dd), 6.42 (2H, m), 6.55 (1H, br. triplet), 7.16-7.19 (3H, m), 7.25-7.29 (2H, m), 7.43 (1H, m). $n_{c=o}$ 1748, 1791cm^{-1} (CCl_4)

Found: C, 63.18; H, 6.59; N, 6.77%

$C_{22}H_{28}N_2O_4S$ requires: C, 63.44; H, 6.78; N, 6.73%

Example 110 - (+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 109 were purified by chromatography (silica, 0-2% MeOH in CH_2Cl_2) and recrystallisation from ether/ethyl acetate to give a sample of diastereomer 2 containing 5% of diastereomer 1 (1.08 g), m.p. 61-62°C. ^1H NMR δ ($CDCl_3$) 1.33-1.37 (4H, m), 1.51-1.63 (4H, m), 2.60 (2H, t), 3.00 (1H, dd), 3.23-3.30 (3H, m), 3.98 (1H, d), 4.29 (1H, d), 4.12 (1H, d), 4.24 (1H, d), 4.61 (1H,dd), 6.42 (2H, m), 7.15-7.18 (3H, m), 7.25-7.31 (3H, m), 7.44-7.45 (1H, m). $\nu_{c=o}$1793cm^{-1} (CCl_4)

Found: C, 63.41; H, 6.63; N, 6.80%

$C_{22}H_{28}N_2O_4S$ requires: C, 63.44; H, 6.78; N, 6.73%

Example 111 - (+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-phenylhex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (0.10 g). Trituration with ether gave the title compound (0.065 g), m.p. 102-104°C. ^{1}H NMR δ ($CDCl_3$) 1.32-1.36 (4H, m), 1.49-1.64 (4H, m), 2.60 (2H, t), 3.12 (1H, dd), 3.22-3.29 (3H, m), 3.94 (1H, d), 4.03 (1H, d), 4.38 (1H, d), 4.45 (1H, d), 4.89 (1H, dd), 6.00 (1H, br. triplet), 6.44-6.46 (1H, m), 6.55-6.56 (1H, m), 7.16-7.19 (3H, m), 7.25-7.29 (2H, m), 7.46-7.47 (1H, m). $\nu_{C=O}$ 1797 cm^{-1} (CCl_4)

Found: C, 60.15; H, 6.32; N, 6.50%

$C_{22}H_{28}N_2O_5S$ .0.3H_2O requires: C, 60.34; H, 6.58; N, 6.40%

Example 112 - (+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(2-furylmethylthio)-azetidin-2-one (15 mmol), N-(6-(4-fluorophenyl)hex-1-yl)-2-bromoacetamide* (15 mmol), tetrabutylammonium bromide (1.5 mmol), and powdered KOH (16.5 mmol) in dry THF (100 ml). Chromatography (silica, 0-2% MeOH in CH_2Cl_2) gave the title compound as an oil (3.4 g). ^{1}H NMR δ ($CDCl_3$) 1.25-1.64 (8H, m), 2.57 (2H, t), 2.98 (1H, dd), 3.23 (2H, dt), 3.43 (1H, dd), 3.67 (1H, d), 3.76-3.91 (3H, m), 4.90 (1H, dd), 6.10 (1H, br. triplet), 6.22 (1H, d), 6.31 (1H, dd), 6.90-6.98 (2H, m), 7.08-7.18 (2H,m), 7.36 (1H, m).

*obtained by treating of 6-(4-fluorophenyl)hexylamine (2.0g) and Hunig's base (1.33g) in dry dichloromethane (25 ml) with bromoacetylbromide (2.07g) in dichloromethane (10 ml) at 0-5 °C.

Example 113 - (+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-fluorophenyl)-hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide (2.0 g, 4.8 mmol). Recrystallisation of the crude product from ethyl acetate gave a sample containing about 93% of diastereomer 1 (0.35 g), m.p. 157-8°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.35 (4H, m), 1.50-1.58 (4H, m), 2.56 (2H, t), 3.02 (1H, dd), 3.20-3.26 (2H, m), 3.42 (1H, dd), 3.74 (1H, d), 4.00 (1H, d), 4.10-4.17 (2H, m), 4.59 (1H, dd), 6.42 (2H, m), 6.65 (1H, br. triplet), 6.92-6.97 (2H, m), 7.09-7.13 (2H, m), 7.43-7.44 (1H, m). $n_{C=O}$ 1791 cm^{-1}

Found: C, 58.85; H, 6.00; N, 6.36%

$C_{22}H_{27}FN_2O_4S$ .0.68H_20 requires: C, 59.14; H, 6.40; N, 6.27%

Example 114 - (+/-)-N-[6-(4-Fluorophenyl)hexy]-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

Evaporation of the mother liquors from example 113 and crystallisation from ethyl acetate/ether gave a sample containing 97% of diasteromer 2 (0.62 g), m.p. 100-101°C. ^{1}H NMR δ ($CDCl_3$) 1.33-1.35 (4H, m), 1.50-1.60 (4H, m), 2.56 (2H, t), 3.01 (1H, dd), 3.22-3.31 (3H, m), 3.98 (1H, d), 4.11 (1H, d), 4.23 (1H, d), 4.29 (1H, d), 4.60 (1H, dd), 6.41-6.42 (2H, m), 6.92-6.96 (2H, m), 7.09-7.13 (2H, m) 7.26 (1H, br. triplet), 7.44-7.45 (1H, m). $n_{C=O}$ 1794 cm^{-1}

Found: C, 60.70; H, 6.22; N, 6.44%

$C_{22}H_{27}FN_2O_4S$ requires: C, 60.81; H, 6.26; N, 6.45%

Example 115 - (+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-(4-fluorophenyl)hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (1.0 g). Trituration of the crude product with ether and recrystallisation from ethyl acetate/pet. ether gave the title compound (0.29 g), m.p. 114-115°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.35 (4H, m), 1.49-1.60 (4H, m), 2.57 (2H, t), 3.12 (1H, dd), 3.22-3.29 (3H, m), 3.95 (1H, d), 4.03 (1H, d), 4.38 (1H, d), 4.45 (1H, d), 4.88 (1H, dd), 6.01 (1H, br. triplet), 6.44-6.45 (1H, m), 6.55-6.56 (1H, m), 6.93-6.97 (2H, m), 7.09-7.13 (2H, m), 7.46-7.47 (1H, m). $n_{c=o}$ 1797 cm^{-1}

Found: C, 58.27; H, 5.96; N, 6.20%

$C_{22}H_{27}FN_2O_5S$ requires: C, 58.65; H, 6.04; N, 6.22%

Example 116 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(2-furylmethylthio)-azetidin-2-one (12 mmol), N-(6-(4-chlorophenyl)hex-1-yl)-2-bromoacetamide (12 mmol), tetrabutylammonium bromide (1.2 mmol), and powdered KOH (13.2 mmol) in dry THF (100 ml). Chromatography (silica, 50-100% EtOAc in pet. ether) gave the title compound as an oil (3.9 g). ^{1}H NMR δ ($CDCl_3$) 1.23-1.61 (8H, m), 2.56 (2H, t), 2.97 (1H, dd), 3.23 (2H, dt), 4.05 (1H, dd), 3.62-3.91 (4H, m), 4.91 (1H, dd), 6.18 (1H, br. triplet), 6.22 (1H, d), 6.30 (1H, dd), 7.08 (2H, d), 7.20-7.26 (2H, m), 7.36 (1H, d).

Example 117 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-chlorophenyl)-hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide (3.8 g, 8.7 mmol). Trituration of the crude product with ether gave a sample of diastereomer 1 (0.49 g), m.p. 171-2°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.34 (4H, m), 1.49-1.61 (4H, m), 2.56 (2H, t), 3.02 (1H, dd), 3.20-3.26 (2H, m), 3.42 (1H, dd), 3.75 (1H, d), 4.00 (1H, d), 4.10-4.17 (2H, m), 4.60 (1H, dd), 6.42 (2H, m), 6.60 (1H, br. triplet), 7.08-7.10 (2H, m), 7.22-7.26 (2H, m), 7.43-7.44 (1H, m). $n_{c=o}$ 1791 cm^{-1}

Found: C, 58.16; H, 5.91; N, 6.25%

$C_{22}H_{27}ClN_2O_4S$ requires: C, 58.59; H, 6.03; N, 6.21%

Example 118 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 117 were evaporated and crystallised from ether to give a sample of diastereomer 2 (1.2 g), m.p. 92-3°C. ^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.50-1.59 (4H, m), 2.56 (2H, t), 3.01 (1H, dd), 3.24-3.31 (3H, m), 3.98 (1H, d), 4.11 (1H, d), 4.25 (1H, d), 4.27 (1H, d), 4.60 (1H, dd), 6.41-6.42 (2H, m), 7.08-7.10 (2H, m), 7.21-7.26 (2H, m), 7.35 (1H, br. triplet), 7.44-7.45 (1H, m). $n_{c=o}$ 1794 cm^{-1}

Found: C, 58.32; H, 5.95; N, 6.23%

$C_{22}H_{27}ClN_2O_4S$ requires: C, 58.59; H, 6.03; N, 6.21%

Example 119 - (+/-)-N-(6-[4-Chlorophenyl)hex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-(4-chlorophenyl)hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide. Trituration of the crude product with ether gave the title compound (0.6 g), m.p. 107-8°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.35 (4H, m), 1.49-1.60 (4H, m), 2.57 (2H, t), 3.12 (1H, dd), 3.22-3.29 (3H, m), 3.95 (1H, d), 4.03 (1H, d), 4.38 (1H, d), 4.45 (1H,d), 4.88 (1H, dd), 6.03 (1H, br triplet), 6.44-6.46 (1H, m), 6.55-6.56 (1H, m), 7.08-7.11 (2H, m) 7.21-7.26 (2H, m), 7.45-7.47 (1H, m). $n_{C=O}$ 1797 cm^{-1}

Found: C, 56.54; H, 5.74; N, 6.02%

$C_{22}H_{27}ClN_2O_5S$ requires: C, 56.58; H, 5.83; N, 6.00%

Example 120 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-4-(3-Furylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using 3-(acetylthiomethyl)furan (64 mmol) and 4-acetoxyazetidin-2-one (64 mmol). Cystallisation from ether/pet. ether gave the title compound (10 g), m.p. 60-61°C. ^{1}H NMR δ ($CDCl_3$) 2.90 (1H, dd), 3.35 (1H, dd), 3.68 (2H, d), 4.70 (1H, dd), 6.14 (1H, br s), 6.42 (1H, m), 7.38-7.42 (2H, m).

b) (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(3-furylmethylthio)-azetidin-2-one (13.6 mmol), N-(6-(4-chlorophenyl)hex-1-yl)-2-bromoacetamide (13.6 mmol), tetrabutylammonium bromide (1.36 mmol), and powdered KOH (14 mmol) in dry THF (100 ml). Chromatography (silica, 50-100% EtOAc in pet. ether) gave the title compound as an oil (4.0 g). ^{1}H NMR δ ($CDCl_3$) 1.25-1.36 (4H, m), 1.40-1.68 (4H, m), 2.56 (2H, t), 2.96 (1H, dd), 3.20-3.28 (2H, m), 3.41 (1H, dd), 3.61-3.73 (3H, m), 3.85 (1H, d), 4.84 (1H, dd), 6.12 (1H, dd), 6.39 (1H, m), 7.06-7.10 (2H, m), 7.21-7.26 (2H, m), 7.37-7.39 (2H, m).

Example 121 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-chlorophenyl)-hex-1-yl)-4-(3-furylmethylthio)-2-oxoazetidin-1-ylacetamide (2.5 g, 5.7 mmol). Crystallisation of the crude product from ethyl acetate gave a sample containing 98% of diastereomer 1 (0.6 g), m.p. 162-163°C. ^{1}H NMR δ ($CDCl_3$) 1.30-1.34 (4H, m), 1.49-1.59 (4H, m), 2.55 (2H, t), 3.04 (1H, dd), 3.20-3.26 (2H, m), 3.55 (1H, dd), 3.74-3.78 (2H, m), 3.86 (1H, d), 4.13 (1H, d), 4.59 (1H, dd), 6.37-6.38 (1H, m), 6.60 (1H, br. triplet), 7.08-7.10 (1H, m), 7.21-7.26 (2H, m), 7.46-7.47 (2H, m). $n_{C=O}$ 1792 cm^{-1}

Found: C, 58.52; H, 5.94; N, 6.20%

$C_{22}H_{27}ClN_2O_4S$ requires: C, 58.59; H, 6.03; N, 6.21%

Example 122 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 121 were evaporated, triturated with ether, and recrystallised from ethyl acetate to give a sample containing 98% of diastereomer 2

(0.7 g), m.p. 95-96°C. ^{1}H NMR δ ($CDCl_3$) 1.32-1.34 (4H, m), 1.50-1.60 (4H, m), 2.56 (2H, t), 3.03 (1H, dd), 3.20-3.32 (3H, m), 3.86-3.98 (3H, m), 4.24 (1H, d), 4.66 (1H, dd), 6.38-6.39 (1H, m), 7.08-7.10 (2H, m), 7.14 (1H, br. triplet), 7.21-7.26 (2H, m), 7.46-7.48 (2H, m). $n_{C=O}$ 1794 cm^{-1}

Found: C, 58.53; H, 5.94; N, 6.20%

$C_{22}H_{27}ClN_2O_4S$ requires: C, 58.59; H, 6.03; N, 6.21%

Example 123 - (+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-(4-chlorophenyl)hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide. Trituration of the crude product with ether gave the title compound, m.p. 95-96°C. ^{1}H NMR δ ($CDCl_3$) 1.31-1.35 (4H, m), 1.48-1.61 (4H, m), 2.56 (2H, t), 3.20-3.27 (4H, m), 3.87 (1H, d), 4.02 (1H, d), 4.18 (1H, d), 4.25 (1H, d), 4.91 (1H, dd), 5.98 (1H, br. triplet), 6.53-6.54 (1H, m), 7.08-7.11 (2H, m), 7.21-7.26 (2H, m), 7.47-7.48 (1H, m), 7.57 (1H, d). $n_{C=O}$ 1795 cm^{-1}

Found: C, 55.41; H, 5.61; N, 5.83%

$C_{22}H_{27}ClN_2O_5S$ .0.5H_2O requires: C, 55.51; H, 5.93; N, 5.89%

Example 124 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-4-(2-Thienylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using 2-(acetylthiomethyl)thiophene (71 mmol) and 4-acetoxyazetidin-2-one (71 mmol). Chromatography (silica, 50-70% EtOAc in pet. ether) gave the title compound as an oil (9.1 g). ^{1}H NMR δ ($CDCl_3$) 2.88 (1H, m), 3.35 (1H, m), 4.06 (2H, m), 4.75 (1H, m), 5.82 (1H, m), 6.96 (2H, m), 7.24 (1H, m)

b) (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(2-thienylmethylthio)-azetidin-2-one (5 mmol), N-(6-(4-chlorophenyl)hex-1-yl)-2-bromoacetamide (5.5 mmol), tetrabutylammonium bromide (0.5 mmol), and powdered KOH (5.25 mmol) in dry THF (25 ml). Chromatography (silica, 30-80% EtOAc in pet. ether) and trituration with ether/pet. ether gave the title compound (0.66 g), m.p. 55-7°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 2.97 (1H, dd), 3.23 (2H, m), 3.41 (1H, dd), 3.63 (1H, d), 3.79 (1H, d), 4.05 (2H, m), 4.88 (1H, m), 6.05 (1H, m), 6.89-7.26 (7H, m).

Example 125 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-chlorophenyl)-hex-1-yl)-4-(2-thienylmethylthio)-2-oxoazetidin-1-ylacetamide (3.0 g, 6.65 mmol). Crystallisation of the crude product from ethyl acetate and recrystallisation from acetonitrile gave a sample containing 97% of diastereomer 1 (0.73 g), m.p. 161-2°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.51-1.61 (4H, m), 2.56 (2H, t), 3.01 (1H, dd), 3.23 (2H, m), 3.48 (1H, dd), 3.74 (1H, d), 4.13 (1H, d), 4.13 (1H, dd), 4.25 (1H, dd), 4.57 (1H, dd), 6.59 (1H, m), 7.03-7.35 (7H, m). $n_{C=O}$ 1791 cm^{-1}

Found: C, 56.51; H, 5.71; N, 6.06%

$C_{22}H_{27}ClN_2O_3S_2$ requires: C, 56.58; H, 5.83; N, 6.00%

Example 126 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The ethyl acetate mother liquors from example 125 gave further crystals on standing, which contained 98% of diastereomer 2 (0.57 g), m.p. 93-5°C. ^{1}H NMR δ ($CDCl_3$) 1.34 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 2.98 (1H, dd), 3.25 (3H, m), 3.89 (1H, d), 4.25 (1H, d), 4.25 (1H, d), 4.33 (1H, d), 4.65 (1H, dd), 7.04-7.35 (7H, m). $n_{C=O}$ 1793 cm^{-1}

Found: C, 56.41; H, 5.72; N, 5.99%

$C_{22}H_{27}ClN_2O_3S_2$ requires: C, 56.58; H, 5.83; N, 6.00%

Example 127 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-(4-chlorophenyl)hex-1-yl)-4-(2-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (1.1 g). Cystallisation from ethyl acetate/pet. ether gave the title compound (0.9 g), m.p. 108-110°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.57 (2H, t), 3.09-3.28 (4H, m), 3.88 (1H, d), 3.97 (1H, d), 4.53 (1H, d), 4.60 (1H, d), 4.91 (1H, dd), 5.98 (1H, m), 7.05-7.41 (7H, m). $n_{C=O}$ 1795 cm^{-1}

Found: C, 54.59; H, 5.52; N, 5.80%

$C_{22}H_{27}ClN_2O_4S_2$ requires: C, 54.70; H, 5.63; N, 5.80%

Example 128 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-4-(3-thienylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using 3-(acetylthiomethyl)thiophene (85 mmol) and 4-acetoxyazetidin-2-one (85 mmol). Chromatography (silica, 50-70% EtOAc in pet. ether) and trituration with pet. ether gave the title compound (8.65 g), m.p. 41-45°C. ^{1}H NMR δ ($CDCl_3$) 2.85 (1H, m), 3.32 (1H, m), 3.88 (2H, m), 4.68 (1H, m), 5.72 (1H, s), 7.01-7.15 (2H, m), 7.33 (1H, m)

b) (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(3-thienylmethylthio)-azetidin-2-one (5 mmol), N-(6-(4-chlorophenyl)hex-1-yl)-2-bromoacetamide (5.5 mmol), tetrabutylammonium bromide (0.5 mmol), and powdered KOH (5.25 mmol) in dry THF (25 ml). Chromatography (silica, 40-90% EtOAc in pet. ether) and trituration with pet. ether gave the title compound (0.85 g), m.p.54-57°C. ^{1}H NMR δ ($CDCl_3$) 1.32 (4H, m), 1.53 (4H, m), 2.56 (2H, t), 2.93 (1H, dd), 3.22 (2H, m), 3.38 (1H, dd), 3.56 (1H, d), 3.76 (1H, d), 3.84 (2H, m), 4.81 (1H, m), 6.07 (1 H, m), 7.04-7.82 (7 H, m)

Example 129 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-chlorophenyl)-hex-1-yl)-4-(3-thienylmethylthio)-2-oxoazetidin-1-ylacetamide (4.12 g, 9.1 mmol). Crystallisation of the crude product from ethyl acetate and recrystallisation from acetonitrile gave a sample of diastereomer 1 (0.57 g), m.p. 158-9°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 2.94 (1H, dd), 3.23 (2H, m), 3.44

(1H, dd), 3.73 (1H, d), 3.98 (1H, d), 4.11 (1H, d), 4.06 (1H, d), 4.51 (1H, dd), 6.61 (1H, m), 7.01-7.41 (7H, m). $n_{c=o}$ 1791 cm^{-1}

Found: C, 56.45; H, 5.62; N, 6.02%

$C_{22}H_{27}ClN_2O_3S_2$ requires: C, 56.58; H, 5.83; N, 6.00%

Example 130 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 129 were recrystallised successively from ethyl acetate, acetonitrile and ethyl acetate to obtain a sample containing 80% of diastereomer 2 (1.42 g), m.p. 109-111°C. ^1H NMR δ ($CDCl_3$) 1.34 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 2.93 (1H, dd), 3.24 (3H, m), 3.89 (1H, d), 4.09 (1H, d), 4.18 (1H, d), 4.23 (1H, d), 4.59 (1H, dd), 7.02-7.42 (7H, m). $n_{c=o}$ 1793 cm^{-1}

Found: C, 56.55; H, 5.65; N, 6.03%

$C_{22}H_{27}ClN_2O_3S_2$ requires: C, 56.58; H, 5.83; N, 6.00%

Example 131 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 107, using N-(6-(4-chlorophenyl)hex-1-yl)-4-(3-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (0.81 g). Cystallisation from ethyl acetate/pet. ether gave the title compound (0.67 g), m.p. 114-116°C. ^1H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.57 (2H, t), 3.05 (1H, dd), 3.15 (1H, dd), 3.25 (2H, m), 3.84 (1H, d), 3.94 (1H, d), 4.38 (1H, d), 4.43 (1H, d), 4.83 (1H, dd), 5.96 (1H, m), 7.08-7.43 (7H, m). $n_{c=o}$ 1794 cm^{-1}

Found: C, 54.62; H, 5.44; N, 5.83%

$C_{22}H_{27}ClN_2O_4S_2$ requires: C, 54.70; H, 5.63; N, 5.80%

Example132 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylthio)-2-oxoazetidin-1-ylacetamide

a) (+/-)-4-(2-Thiazolylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using 2-(acetylthiomethyl)thiazole (23 mmol) and 4-acetoxyazetidin-2-one (23 mmol). Trituration with ether gave the title compound (1.48 g), m.p. 89-92°C. ^1H NMR δ ($CDCl_3$) 2.76 (1H, m), 2.30 (1H, m), 4.26 (2H, s), 4.85 (1H, m), 7.68 (1H, d), 7.73 (1H, d), 8.63 (1H, br s).

b) (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(2-thiazolylmethylthio)azetidin-2-one (6.9 mmol), N-(6-(4-chlorophenyl)hex-1-yl)-2-bromoacetamide (6.9 mmol), tetrabutylammonium bromide (0.69 mmol), and powdered KOH (6.9 mmol) in dry THF (40 ml). Repeated chromatography (silica, 2-6% MeOH in CH2Cl2; silica, t-BuOMe) gave the title compound as an oil (0.04 g). ^1H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 2.99 (1H, dd), 3.23 (2H, m), 3.44 (1H, dd), 3.73 (1H, d), 3.90 (1H, d), 4.12 (1H, d), 4.21 (1H, d), 5.02 (1H, dd), 6.19 (1H, m), 7.07-7.26 (4H, m), 7.31 (1H, d), 7.69 (1H, d).

Example 133 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-(4-chlorophenyl)-hex-1-yl)-4-(2-thiazolylmethylthio)-2-oxoazetidin-1-ylacetamide (1.03 g, 2.28 mmol). Trituration of the crude product with ethyl acetate gave a sample containing 96% of

diastereomer 1 (0.35 g), m.p. 154-157°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.56 (2H, t), 3.02 (1H, dd), 3.23 (2H, m), 3.36 (1H, dd), 3.80 (1H, d), 4.14 (1H, d), 4.35 (1H, d), 4.42 (1H, d), 4.92 (1H, dd), 6.46 (1H, m), 7.09 (2H, m), 7.23 (2H, m), 7.43 (1H, d), 7.84 (1H, d). $n_{C=O}$ 1760, 1791 cm^{-1}

Found: C, 53.91; H, 5.55; N, 8.94%

$C_{21}H_{26}ClN_3O_3S_2$ requires: C, 53.89; H, 5.60; N, 8.98%

Example 134 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 133 were concentrated and diluted with pet. ether to induce crystallisation of a sample containing 94% of diastereomer 2 (0.49 g), m.p. 103-104°C. ^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.55 (4H, m), 2.57 (2H, t), 3.11 (1H, dd), 3.25 (2H, m), 3.33 (1H, dd), 4.08 (1H, d), 4.29 (1H, d), 4.44 (1H, d), 4.50 (1H, d), 4.98 (1H, dd), 7.09 (2H, m), 7.24 (2H, m), 7.34 (1H, m), 7.42 (1H, d), 7.84 (1H, d). $n_{C=O}$ 1793 cm^{-1}

Found: C, 54.12; H, 5.56; N, 8.87%

$C_{21}H_{26}ClN_3O_3S_2$ requires: C, 53.89; H, 5.60; N, 8.98%

Example 135 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

a) Methyl 5-(acetylthiomethyl)furan-5-carboxylate

A solution of potassium thioacetate (45.7 g, 0.4 mol) in dry DMF (100 ml) was added to an ice-cooled solution of methyl 5-(chloromethyl)furan-2-carboxylate (68 g, 0.39 mol) in dry DMF (300 ml). Cooling was removed, and the mixture stirred for a further 30 min, then poured into water and extracted with ether. Chromatography (silica, 0-30% ether in pet. ether) of the organic extracts gave the title compound as an oil (42.7 g). ^{1}H NMR δ ($CDCl_3$) 2.36 (3H, s), 3.88 (3H, s), 4.16 (2H, s), 6.35 (1H, d), 7.08 (1H, d).

b) 4-(5-(Methoxycarbonyl)2-furylmethylthio)azetidin-2-one

The synthesis was carried out as in example 101a, using methyl 5-(acetylthiomethyl)furan-5-carboxylate (47 mmol), 4-acetoxyazetidin-2-one (47 mmol), and sodium methoxide (47 mmol) in place of sodium ethoxide. The crude product was triturated with ether to give the title compound (8.7 g), m.p. 102-103°C. ^{1}H NMR δ ($CDCl_3$) 2.85 (1H, dd), 3.43 (1H, dd), 3.88-3.92 (5H, m), 4.92 (1H, dd), 6.33 (1H, m), 6.78 (1H, br. singlet), 7.09-7.11 (1H, m).

c) (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylthio)-2-oxoazetidin-1-ylacetamide

The synthesis was carried out as in example 101b, using (+/-)-4-(5-(methoxycarbonyl)2-furylmethylthio)azetidin-2-one (21 mmol), N-(6-phenylhex-1-yl)-2-bromoacetamide (21 mmol), tetrabutylammonium bromide (3 mmol), and powdered KOH (211 mmol) in dry THF. Chromatography (silica, EtOAc/pet. ether) gave the title compound as an oil (5.0 g). ^{1}H NMR δ ($CDCl_3$) 1.29-1.35 (4H, m), 1.43-1.63 (4H, m), 2.55 (2H, t), 2.94 (1H, dd), 3.19-3.27 (2H, m), 3.24 (1H, dd), 3.78 (1H, d), 3.88-3.90 (3H, m), 3.95-3.97 (1H, m), 4.04-4.17 (2H, m), 5.01 (1H, dd), 6.25 (1H, br triplet), 6.33-6.35 (1H, m), 7.06-7.10 (3H, m), 7.20-7.26 (3H, m).

Example 136 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1)

The synthesis was carried out as in example 102, using (+/-)-N-(6-phenylhex-1-yl)-4-(5-methoxycarbonyl-2-furylmethylthio)-2-oxoazetidin-1-ylacetamide (4.0 g, 8 mmol). Recrystallisation of the crude product from ethyl acetate gave a sample of diastereomer 1 (0.8 g), m.p. 141-142°C. ^{1}H NMR δ ($CDCl_3$) 1.20-1.35 (4H, m), 1.40-1.65 (4H, m), 2.55 (2H, t), 3.05 (1H, dd), 3.19-3.33 (3H, m), 3.83 (1H, d), 3.90 (3H, s), 4.09-4.16 (3H, m), 4.71 (1H, dd), 6.46 (1H, br. triplet), 6.55-6.56 (1H, m), 7.07-7.26 (5H, m). $n_{c=o}$ 1792 cm^{-1}

Found: C, 56.65; H, 5.68; N, 5.55%

$C_{24}H_{29}ClN_2O_6S$ requires: C, 56.63; H, 5.74; N, 5.50%

Example 137 - (+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2)

The mother liquors from example 136 were evaporated and recrystallised from ethyl acetate to give a sample of diastereomer 2 (1.5 g), m.p. 113-114°C. ^{1}H NMR δ ($CDCl_3$) 1.29-1.40 (4H, m), 1.50-1.64 (4H, m), 2.56 (2H, t), 3.00 (1H, dd), 3.23-3.40 (3H, m), 3.90 (3H, s), 4.03 (1H, d), 4.19-4.29 (3H, m), 4.72 (1H, dd), 6.53-6.55 (1H, m), 7.00 (1H, br. triplet), 7.07-7.26 (5H, m). $n_{c=o}$ 1795 cm^{-1}

Found: C, 56.73; H, 5.69; N, 5.57%

$C_{24}H_{29}ClN_2O_6S$ requires: C, 56.63; H, 5.74; N, 5.50%

Example 138 - (+/-)-4-(2-furylmethylthio)-1-(9-phenylnonyl)azetidin-2-one

A suspension of sodium hydride (3.65 mmol) in dry THF (10 ml) was cooled in ice/salt, and a solution of (+/-)-4-(2-furylmethylthio)azetidin-2-one (0.61 g, 3.32 mmol) in THF (10 ml) was added dropwise below 5°C. The resulting solution was further cooled to -10°C, and a solution of 9-phenylnonyl-1-triflate (1.17 g, 3.32 mmol) in THF (10 ml) was added gradually over 1 min. After stirring for a further 5 min at 0°C, the reaction mixture was poured into brine and extracted with ether. Chromatography of the organic extracts (silica, 10-25% EtOAc in pet. ether) gave the title compound as an oil (0.38 g). ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (14H, m), 2.60 (2H, t, J=8 Hz), 2.9 (2H,m), 3.3 (2H, m), 4.78 (2H, s), 4.68 (1H, m), 6.20, 6.32 (each 1H, m), 7.15 - 7.3 (5H, m), 7.36 (1H, m).

Example 139 - (+/-)-4-(2-furylmethylsulphinyl)-1-(9-phenylnonyl)azetidin-2-one

The synthesis was carried out as in example 102, using (+/-)-4-(2-furylmethylthio)-1-(9-phenylnonyl)azetidin-2-one (0.37 g, 0.97 mmol). Chromatography (silica, 50-70% EtOAc in pet. ether) gave the title compound as an oil (0.28 g), containing about 63% of diastereomer 1, 37% of diastereomer 2. ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (14H, m), 2.55 (3H, m), 2.90, (1H, dd, J=5, 15 Hz), 3.10 (1H, dd, J=5, 15 Hz), 3.15-3.5 (3H, m), 3.95-4.15 (2H, m), 4.42 (1H, m), 6.42 (2H, m), 7.1-7.3 (5H, m), 7.43 (1H, m). $n_{c=o}$ 1776 cm^{-1}

Found: C, 68.5; H, 7.8; N, 3.3%

$C_{23}H_{31}NO_3S$ requires: C, 68.8; H, 7.8; N, 3.5%

Example 140 - (+/-)-4-(2-furylmethylthio)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one

The synthesis was carried out as in example 138, using (+/-)-4-(2-furylmethylthio)azetidin-2-one (1.5 g, 8.2 mmol) and 9-(4-fluorophenyl)nonyl-1-triflate (2.9 g, 7.8 mmol). Chromatography (silica, 10-25% EtOAc in pet. ether) gave the title compound

as an oil (0.56 g). ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (14H, m), 2.56 (2H, t, J=7.7Hz), 2.90 (2H, m), 3.29 (2H, m), 3.77 (2H, s), 4.68 (1H, m), 6.20 (1H, m), 6.31 (1H, m), 6.95 (2H, m), 7.10 (2H, m), 7.36 (1H, m).

Example 141 - (+/-)-4-(2-furylmethylsulphinyl)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one

The synthesis was carried out as in example 102, using (+/-)-4-(2-furylmethylthio)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one (0.52 g, 1.28 mmol). Chromatography (silica, 50-70% EtOAc in pet. ether) gave the title compound as an oil (0.42 g), containing about 65% of diastereomer 1, 35% of diastereomer 2. ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (14H, m), 2.55 (3H, m), 2.90, (1H, dd, J=5, 15 Hz), 3.10 (1H, dd, J=5, 15 Hz), 3.15-3.5 (2H, m) 3.95-4.15 (2H, m), 4.42 (1H, m), 6.42 (2H, m), 6.95, 7.10 (each 2H, m), 7.43 (1H, m). $n_{C=O}$ 1776 cm^{-1}

Found:	C, 65.7; H, 7.2; N, 3.2%
$C_{23}H_{30}FNO_3S$ requires:	C, 65.8; H, 7.2; N, 3.3%

Example 142 - (+/-)-4-(2-furylmethylsulphonyl)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one

The synthesis was carried out as in example 107, using (+/-)-4-(2-furylmethylsulphinyl)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one (88 mg). Chromatography (silica, EtOAc/pet. ether 2:1) gave the title compound as an oil (56 mg). ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (14H, m), 2.56 (2H, t, J=8 Hz), 2.99 (1H, dd, J=2, 15 Hz), 3.15 (2H, m), 3.45 (1H, m), 4.37 (2H, s), 4.57 (1H, m), 6.45, 6.55 (each 1H, m), 6.95, 7.10 (each 2H, m), 7.47 (1H, m).

Example 143. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide

A solution of 4-(5-allyloxycarbonylfuran-2-methyl)thioazetidin-2-one (4 g, 0.015 mol) and N-(4-fluorophenylhex-1-yl)bromoacetamide (4.73 g, 0.015 mol) in dry tetrahydrofuran (150 ml) was cooled to -30°C and a solution of potassium t-butoxide (1.85 g, 0.0165 mol) in dry tetrahydrofuran (80 ml) added dropwise over 15 min. The temperature was allowed to rise to 10°C over 2 hr, then the mixture diluted with water and extracted with ethyl acetate, filtering off and discarding any insoluble solids. the extracts were dried ($MgSO_4$), evaporated, and the product purified by flash chromatography (silica, ethyl acetate/petrol), to give the title compound as a yellow oil (2.54g, 33% yield). ^{1}H NMR δ ($CDCl_3$) 1.32 (4H, m, $N(CH_2)_2(C\underline{H}_2)_2$), 1.52 (4H, m, $NCH_2C\underline{H}_2$ + $FPhCH_2C\underline{H}_2$), 2.55 (2H, t, $FPhC\underline{H}_2$), 2.96 (1H, dd, H_{3a}), 3.24 (2H, m, $NC\underline{H}_2$), 3.49 (1H, dd, H_{3b}), 3.76-4.06 (4H, $C\underline{H}_2CO$ + $C\underline{H}_2S$), 4.79 (2H, m, $OC\underline{H}_2$), 5.03 (1H, dd, $\underline{H}_4$), 5.36 (2H, m, $C\underline{H}_2CH$), 5.99 (1H, m, $C\underline{H}CH_2$), 6.30 (1H, m, $N\underline{H}$), 6.35, 7.12 (each 1H, d, furan-$\underline{H}$), 6.92-7.12 (4H, m, FPh-$\underline{H}$)

Example 144. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 1)

Treatment of N-[6-(4-fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide with mCPBA in dichloromethane at low temperature gave, after work-up and recrystallisation as described for Example 102, the title compound as white crystals, m.p. 122-5°C, 16% yield. ^{1}H NMR δ ($CDCl_3$) 1.32 (4H, m, $N(CH_2)_2(C\underline{H}_2)_2$), 1.54 (4H, m, $NCH_2C\underline{H}_2$ + $FPhCH_2C\underline{H}_2$), 2.56 (2H, t, $FPhC\underline{H}_2$), 3.08 (1H, dd, H_{3a}), 3.23 (2H, m, $NC\underline{H}_2$), 3.30 (1H, dd, H_{3b}), 3.55, 3.73

(each 1H, d, SCH_2), 3.84, 4.13 (each 1H, d, CH_2CO), 4.73 (1H, dd, H_4), 4.80 (2H, m, OCH_2), 5.38 (2H, m, CH_2CH), 5.97 (1H, m, $CHCH_2$), 6.56, 7.18 (each 1H, d, furan-H), 6.91-7.14 (4H, m, FPh-H)

Example 145. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)

Recrystallisation of the mother liquors from Example 144 gave the title compound (diastereoisomer 2:1 ca. 83:17) as white crystals, m.p. 79-82°C, 29% . $\nu_{C=O}$ 1793 cm^{-1} Found: C, 59.82; H, 5.93; N, 5.40%. $C_{26}H_{31}FN_2O_6S$ requires: C, 60.22; H, 6.03; N, 5.40%

Example 146. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-carboxyfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)

A solution of triphenylphosphine (0.81 g, 0.31 mmol), pyrrolidine (0.027 ml, 0.31 mmol) and N-[6-(4-fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2, 0.16 g, 0.31 mmol) in dichloromethane (10 ml) was treated with tetrakis triphenylphosphinepalladium(0) (10.7 mg, 0.0093 mmol) and the mixture stirred for 2 hr. The solvent was evaporated and the residue purified by flash chromatography (silica, dichloromethane /acetone /acetic acid). The crude product was dissolved in dichloromethane (10 ml), washed with brine, dried ($MgSO_4$), and evaporated to an oil which was treated with dichloromethane and ether to give the title compound as a solid (46mg, 31% yield), m.p.124-7°C. ^1H NMR δ ($CDCl_3$)1.31 (4H, m, $N(CH_2)_2(CH_2)_2$),) 1.53 (4H, m, NCH_2CH_2 + $FPhCH_2CH_2$), 2.56 (2H, t, $FPhCH_2$), 3.07 (1H, dd, H_{3a}), 3.26 (2H, m, NCH_2), 3.40 (1H, dd, H_{3b}), 4.21-4.34 (4H, m, SCH_2 + CH_2CO), 4.76 (1H, dd, H_4), 6.55, 7.10 (each 1H, d, furan-H), 6.92-7.16 (4H, m, FPh-H), 7.60 (1H, NH)

Example 147. N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylthio-2-oxoazetidin-1-yl)acetamide

Treatment of 4-(5-allyloxycarbonylfuran-2-methyl)thioazetidin-2-one (2.4 g) and N-(4-chlorophenylhex-1-yl)bromoacetamide* (2.99 g) in dry tetrahydrofuran (175 ml) with a solution of potassium t-butoxide (1.03 g) in dry tetrahydrofuran (50 ml) at -40°C, followed by work-up as described for Example 143 gave the title compound as a yellow oil, 37% yield. ^1H NMR δ ($CDCl_3$) 1.30-1.60 (8H, m, $4xCH_2$), 2.55 (2H, t, J=7.6 Hz, CH_2Ph), 2.92, 2.98 (1H, dd, J=2.2, 15.4 Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.46, 3.52 (1H, dd, J=5.2, 15.4 Hz, H_3), 3.94 (4H, m, NCH_2, SCH_2), 4.79 (2H, m, CO_2CH_2), 5.02 (1H, m, H_4) 5.35 (2H, m, CH_2=CH), 6.0 (1H, m, CH_2=CH), 6.26 (1H, m, NH), 6.34 (1H, d, J=3.4Hz, furan-H), 7.06-7.26 (5H, m, furan-H, Ph-H)

*obtained by treating of 6-(4-chlorophenyl)hexylamine (2.0g) and Hunig's base (1.33g) in dry dichloromethane (25 ml) with bromoacetylbromide (2.07g) in dichloromethane (10 ml) at 0-5 °C.

Example 148. N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 1).

Colourless solid, m.p. 135-136°C, 15% yield. ^1H NMR δ ($CDCl_3$) 1.3023-1.60 (8H, m, $4xCH_2$), 2.56 (2H, t, J=7.6 Hz, CH_2Ph), 3.03, 3.09 (1H, dd, J=4.7, 15 Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.28, 3.34 (1H, dd, J=5.4, 15 Hz, H_3), 3.81, 4.13 (each 1H, d, J=17.2 Hz, NCH_2), 4.09 (2H, s, $SOCH_2$), 4.70 (1H, m, H_4), 4.80 (2H, d, J=5.8 Hz, CO_2CH_2), 5.37 (2H, m, CH_2=CH), 6.0 (1H, m, CH_2=CH), 6.44 (1H, m, NH), 6.56

(1H, d, J=3.5 Hz, furan-H), 7.07-7.26 (5H, m, furan-H, Ph-H). $\nu_{c=o}$ 1792 cm^{-1}. Found: C, 58.2; H, 5.8; N, 5.3%. $C_{26}H_{31}ClN_2O_6S$ requires: C, 58.4; H, 5.8; N, 5.2%

Example 149. N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2).

Colourless solid, m.p. 89-92°C, 13% yield. ^1H NMR δ ($CDCl_3$) 1.30-1.60 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.6 Hz, CH_2Ph), 2.99, 3.05 (1H, dd, J=2.4, 15.4 Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.32, 3.39 (1H, dd, J=5.4, 15.4 Hz, H_3), 4.03, 4.25 (each 1H, d, J=17.2 Hz, NCH_2), 4.20 (2H, m, $SOCH_2$), 4.72 (1H, m, H_4), 4.79 (2H, d, J=5.8 Hz, CO_2CH_2), 5.37 (2H, m, CH_2=CH), 6.0 (1H, m, CH_2=CH), 6.55 (1H, d, J=3.5 Hz, furan-H), 7.02 (1H, m, NH), 7.07-7.26 (5H,m, furan-H, Ph-H). $\nu_{c=o}$ 1795 cm^{-1}. Found: C, 58.2; H, 5.8; N, 5.3%. $C_{26}H_{31}ClN_2O_6S$ requires: C, 58.4; H, 5.8; N, 5.2%

Example 150. N-(6-{4-Chlorophenyl}hexyl)-4-(5-carboxyfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2).

Treatment of a solution of triphenylphosphine (53.3 mg), pyrrolidine (14.3 mg) and N-[6-(4-chlorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2, 105 mg) in dichloromethane (4 ml) with with tetrakis triphenylphosphinepalladium(0) (6.5 mg) and work-up as described for Example 146 gave the title compound as a cream solid, m.p. 166-167°C, 49% yield. ^1H NMR δ (DMSO) 1.26 (4H, m, 2xCH_2), 1.37 (2H, m, CH_2), 1.52 (2H, m, CH_2), 2.50 (2H, m, CH_2Ph), 2.95, 2.99 (1H, dd, H_3), 3.05 (2H, m, $NHCH_2$), 3.83, 4.07 (each 1H, d, J=17.2 Hz, NCH_2), 4.29, 4.42 (each 1H, d, J=14 Hz, $SOCH_2$), 4.86 (1H, m, H_4), 6.60 (1H, d, J=3.2 Hz, furan-H), 7.15-7.32 (5H,m, furan-H, Ph-H), 8.08 (1H, m, NH). Found: C, 54.5; H, 5.3; N, 5.6%. $C_{23}H_{27}ClN_2O_6S$ requires: C, 55.8; H, 5.5; N, 5.7%

Example 151. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide

Treatment of 4-(5-methoxycarbonylfuran-2-methyl)thioazetidin-2-one (Example 135b) and N-(4-fluorophenylhex-1-yl)bromoacetamide in dry tetrahydrofuran with a solution of potassium t-butoxide in dry tetrahydrofuran at -30°C, followed by work-up as described for Example 143 gave the title compound as a pale yellow oil, 55% yield. ^1H NMR δ ($CDCl_3$) 1.32 (4H, m, $N(CH_2)_2(CH_2)_2$), 1.54 (4H, m, NCH_2CH_2 + $FPhCH_2CH_2$), 2.56 (2H, t, $FPhCH_2$), 2.95 (1H, dd, H_{3a}), 3.24 (2H, m, NCH_2), 3.48 (1H, dd, H_{3b}), 3.88 (3H, s, OCH_3), 3.75-4.05 (4H, m, SCH_2 + CH_2CO), 5.02 (1H, dd, H_4), 6.30 (1H, m, NH), 6.35, 7.12 (each 1H, d, furan-H), 6.90-7.13 (4H, m, FPh-H)

Treatment of N-(6-{4-fluorophenyl}hexyl)-4-(5-methoxycarbonylfuran-2-methylthio-2-oxoazetidin-1-yl)acetamide with mCPBA under the conditions described for Examples 102 and 103 gave Examples 152 and 153 after recrystallisation as described for Examples 102 and 103.

Example 152. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 1)

White crystals, m.p. 137-8°C, 16% yield. ^1H NMR δ (DMSO) 1.27 (4H, m, $N(CH_2)_2(CH_2)_2$) 1.39 (2H, m, $FPhCH_2CH_2$), 1.53, (2H, m, NCH_2CH_2), 2.55 (2H, t, $FPhCH_2$), 3.04 (4H, m, NCH_2 + H_{3a} + H_{3b}), 3.68, 4.03 (each 1H, d, SCH_2), 4.13, 4.39

(each 1H, d, $C\underline{H}_2CO$), 4.99 (1H, m, $\underline{H}_4$), 6.64, 7.30 (each 1H, d, furan-$\underline{H}$), 7.04-7.24 (4H, m, FPh-$\underline{H}$)

Example 153. N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)

White crystals, m.p. 100-2°C, 16% yield. $\nu_{C=O}$ 1795 cm^{-1}. Found: C, 58.53; H, 5.90; N, 5.68%. $C_{24}H_{29}FN_2O_6S$ requires: C, 58.52; H, 5.93; N, 5.69%

Example 201 N-(6-(Phenyl)hexyl)-(4-(2-fluorophenoxy)-2-oxoazetidin-1-yl)acetamide

A solution of 4-(2-fluorophenoxy)azetidin-2-one (0.5g, 3 mmole), N-(6-phenylhexyl)bromoacetamide (0.9g, 3 mmol) and 18-crown-6 (5 mg) in dry THF (20 ml) was cooled to -30°C and treated with potassium t-butoxide (0.3g, 3 mmol). The resulting mixture was stirred for 90 min, warmed to 0°C, quenched with aqueous citric acid and ethyl acetate. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography to give the title compound as a colourless oil (0.33g, 28%)

Found: C, 59.8; H, 5.9; N, 5.5%; $C_{23}H_{27}FN_2O_3.0.97CH_2Cl_2$ requires: C, 59.9; H, 6.1; N, 5.8%

The following compounds were prepared by the method described for Example 201 using the required azetidinone and bromoacetamide.

Example 202 N-[6-(4-Chlorophenyl)hexyl]-[4-(2-fluorophenoxy 2-oxo azetidin-1 yl) acetamide

Colourless solid, m.p. 79-80°C, 31% yieldFound: C, 63.6; H, 6.0; N, 6.5%; $C_{23}H_{26}ClFN_2O_3$. requires C, 63.8; H, 6.1; N, 6.5%

Example 203 N-(6-(4-Phenyl)hexyl)-(4-(2-methylphenoxy)-2-oxoazetidin-1-yl)acetamide

White solid, m.p. 53-4°C, 55% yield

Found: C, 72.6; H, 7.5; N, 7.2% $C_{24}H_{30}N_2O_3.0.04CH_2Cl_2$ requires C, 72.5; H, 7.5; N, 7.1%

Example 204 N-(6-(4-Phenyl)hexyl)-(4-(2-benzyloxyphenoxy-2-oxoazetidin-1-yl)acetamide

White solid, m.p. 87-8°C, 38%yield

Found: C, 74.0; H, 7.1; N, 5.8% $C_{30}H_{34}N_2O_3$ requires C, 74.1; H, 7.1; N, 5.8%

Example 205 N-(6-(4-Phenyl)hexyl)-(4-(2-methylthiophenoxy)-2-oxoazetidin-1-yl) acetamide

White solid, m.p. 79-80°C, 32% yield

Found: C, 67.0; H, 7.0; N, 6.8% $C_{24}H_{30}N_2O_3S$ requires C, 67.6; H, 7.1; N, 6.6%

Example 206 N-(6-(4-Phenyl)hexyl)-(4-(4-chlorophenoxy)-2-oxoazetidin-1-yl) acetamide

Colourless oil, 32.0% yield

Found: C, 64.5; H, 6.4; N, 6.5%; $C_{23}H_{27}ClN_2O_3$ $0.21CH_2Cl_2$ .requires: C, 64.4; H, 6.4; N, 6.5%

Example 207 (N-(6-(4-Phenyl)hexyl)-4-(4-methoxy-phenoxy)-2-oxoazetidin-1-yl)acetamide

Pale yellow solid, m.p. 43-45°C, 30% yield

Found: C,70.3; H, 7.5; N, 7.1 %; $C_{24}H_{30}N_2O_4$ .requires C, 70.2; H, 7.4; N, 6.8%

Example 208 N-(-(4-Phenyl)hexyl)(-(4-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide

Colourless oil, 15.5% yield

Found: C, 67.0; H, 6.9; N, 6.6%; $C_{24}H_{30}N_2O_3S$ requires: C, 67.0; H, 7.0; N, 6.5%

Example 209 N-(6-(4-Chlorophenyl)hexyl)-(4-(4-allyloxycarbonyl-methylphenoxy)-2-oxoazetidin-1-yl)acetamide

^{1}H NMR δ ($CDCl_3$) 1.37 (m, 4H), 1.53 (m, 4H), 2.55 (t, 2H,7.6Hz), 3.21 (dd,1H,J=16.1Hz), 3.24 (m, 2H), 3.39 (dd, 1H, J=1.6Hz), 3.59 (s,2H), 3.99, 3.94,3.99 (each 1H, d, J=17.1Hz), 5.59 (m, 2H), 5.25 (m, 1H), 5.72 (m, 1H), 5.86 (m, 1H), 6.34 (bm, 1H), 6.81-7.26 (m, 8H)

Example 210 N-(6-(4-Phenyl)hexyl)-(4-phenoxy-2-oxoazetidin-1-yl)acetamide

Pale yellow solid, m.p. 45-48°C, 41% yield,

Found: C, 72.3; H, 7.3; N, 7.7 %; $C_{23}H_{28}N_2O_3$ requires: C, 72.6; H, 7.4; N, 7.4 %

Example 211 N-(6-(4-Phenyl)hexyl)-(4-benzyloxy-2-oxoazetidin-1-yl)acetamide

Pale yellow oil, 46% yield,

Found: C, 71.5; H, 7.9; N, 6.7 %; $C_{24}H_{30}N_2O_3\,0.5C_4H_8O_2$ requires: C, 71.4; H, 7.7; N, 6.4 %

Example 212 N-(6-(4-Phenyl)hexyl)-(4-(4-methylsulphinylphenoxy)-2-oxoazetidin-1-yl)acetamide

Treatment of N-(6-(4-phenyl)hexyl)-(4-(4-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide with *meta*-chloroperbenzoic acid (*m*-CPBA) (1.1equivalent) in dichloromethane at -70°C gave the title compound as a colourless oil in 92% yield after chromatography.

Found: C, 61.6; H, 6.5; N, 6.0%; $C_{24}H_{30}N_2O_4S.0.4CH_2Cl_2$ requires: C, 61.5; H, 6.5; N, 5.90%**Example 213 N-[6-(4-Phenyl)hexyl]-[4-(4-methylsulphonylphenoxy- 2-oxo azetidin-1-yl) acetamide**

Treatment of N-(6-(4-phenyl)hexyl)-(4-(4-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide with *meta*-chloroperbenzoic acid (*m*-CPBA) (4 equivalents) in dichloromethane at 20°C gave the title compound as a colourless solid, m.p. 101-2°C, in 85% yield after chromatography.

Found: C, 62.3; H, 6.5; N, 6.1%; $C_{24}H_{30}N_2O_5S$ requires: C, 62.8; H, 6.6; N, 6.1%

Example 214 N-(6-(4-Phenyl)hexyl)-(4-(2-methylsulphinylphenoxy)-2-oxoazetidin-1-yl)acetamide

Treatment of N-(6-(4-phenyl)hexyl)-(4-(2-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide with *meta*-chloroperbenzoic acid (*m*-CPBA) (1.2 equivalent) in dichloromethane at -30°C gave the title compound as a colourless oil in 75% yield after chromatography.

Found: C, 62.9; H, 6.5; N, 6.1%; $C_{24}H_{30}N_2O_4S.0.25CH_2Cl_2$ requires: C, 62.8; H, 6.6; N, 6.0%

Example 215 N-(6-(4-Phenyl)hexyl)-(4-(2-methylsulphonylphenoxy)-2-oxoazetidin-1-yl)acetamide

Treatment of N-(6-(4-phenyl)hexyl)-(4-(2-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide with *meta*-chloroperbenzoic acid (*m*-CPBA) (3 equivalents) in dichloromethane at 20°C gave the title compound as a colourless solid, m.p. 127-128°C, in 82% yield after chromatography.

Found: C, 62.6; H, 6.5; N, 6.1%; $C_{24}H_{30}N_2O_5S$ requires: C, 62.8; H, 6.6; N, 6.1%

Example 216 N-(6-(4-Phenyl)hexyl)-(4-(2-hydroxyphenoxy)-2-oxoazetidin-1-yl)acetamide

Treatment of N-(6-(4-phenyl)hexyl)-(4-(2-benzyloxyphenoxy)-2-oxoazetidin-1-yl)acetamide with hydrogen/10% palladium on charcoal in THF at room temperature for 1 h gave the title compound as a colourless oil in 71% yield after chromatography.

Found: C, 64.4; H, 6.6; N, 6.4%; $C_{23}H_{28}N_2O_4.0.5CH_2Cl_2$ requires: C, 64.3; H, 6.7; N, 6.4%

Example 217 N-[6-(4-chlorophenyl)hexyl]-[4-(4-carboxymethylphenoxy)-2-oxo-azetidin-1-yl]- acetamide

Treatment of N-(6-(4-chlorophenyl)hexyl)-(4-(4-allyloxycarbonylmethylphenoxy)-2-oxoazetidin-1-yl)acetamide with tetrakis(triphenylphosphino)palladium, triphenylphosphine and pyrrolidine in dichloromethane at room temperature overnight and subsequent work-up followed by flash chromatography gave the title compound as a gum (38%)

^{1}H NMR δ ($CDCl_3$) 1.13 (4H, bm), 1.53 (4H, m), 2.55 (2H, t, J=7.5Hz), 3.07 (1H, d, J=15Hz), 3.23 (2H, m), 3.39 (1H, dd, J=15,3Hz), 3.59 (2H, s), 3.91 and 4.05 (1H each, d, J=17Hz), 5.71 (m, 1H), 6.36 (1H, bs), 6.83 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.24 (4H, m)

Example 218 N-(6-(4-Phenyl)hexyl)-(3-methyl-4-phenoxy-2-oxoazetidin-1-yl) acetamide

3-methyl-4-phenoxyazetidin-2-one was prepared from 3-methyl-4-acetoxyazetidin-2-one as described in Prep 1 above and subsequently treated with N-(6-phenylhexyl)bromoacetamide as for Example 201 to give the title compound as a pale yellow oil, 52.3% yield.

Found: C, 71.8; H, 7.4; N, 7.1%; $C_{24}H_{30}N_2O_3.0.1\ CH_2Cl_2$ requires C, 71.8; H, 7.6; N, 6.9%

Example 219 4-Benzyloxy-1-(4-phenyl-2-oxo-butyl)-azetidin-2-one

To a solution of 4-benzyloxyazetidin-2-one (2g, 11.0mmol), 1-bromo-2-oxo-4-phenylbutane (2.9g, 12.0mmol), tetrabutyl ammonium bromide (TBAB) (0.4g, 1.2mmol) was added pottassium hydroxide (0.68g,12.0mmol). The mixture was stirred for 2 hr. It was quenched with water and extracted with ethyl acetate. The organic extract was dried and evaporated and the residue purified using flash chromatography to give the title compound a pale yellow oil (1.7g, 47% yield).

Found: C, 73.7; H, 6.6; N, 4.4%; $C_{20}H_{21}NO_3\ 0.15H_2O$ requires C, 73.7; H, 6.6; N, 4.3%

Example 220 4-Phenoxy-1-(4-phenyl-2-oxo-butyl)-azetidin-2-one

4-phenoxyazetidin-2-one (1g ,6.2mmol), 1-bromo-2-oxo-4-phenylbutane (1.55g, 6.7mmol), TBAB (0.2g, 0.7mmol) and potassium hydroxide (0.4g,6.7mmol) were reacted as described above to give the title compound (0.65g, 31% yield) as a pale yellow solid, m.p. 59-60°C, after flash chromatography and recrystallisation from ether/n-hexane.

Found: C, 73.0; H, 6.2; N, 4.6%. $C_{19}H_{19}NO_3\ 0.2H_2O$ requires C, 72.9; H, 6.2; N, 4.5%

Example 301 N-[6-(naphth-1-yl)-5-hexyn-1-yl]-4-benzylthio-2-oxoazetidin-1-yl acetamide

A mixture of 4-benzylthio-2-oxoazetidin-1-yl acetic acid (3.4g), 6-(naphth-1yl)-5-hexyn-1-ylamine (3.0g), 1-hydroxybenzotriazole hydrate (1.82g) and dicyclohexylcarbodiimide (2.77g) were stirred together in dry dimethylformamide (100ml) overnight. The solvent was evaporated and the residue was taken up in ethyl acetate, filtered, and extracted with water. The aqueous solution was extracted with ethyl acetate and the combined organic solutions were washed with brine, dried and evaporated. Flash chromatography (silica gel, ethyl acetate-hexane) afforded the title compound (4.65g) as an oil, 75% yield

^{1}H NMR δ ($CDCl_3$) 1.66-1.82 (4H, m), 2.58-2.63 (4H, m), 2.91 (1H, dd), 3.29-3.40 (3H, m), 3.55, 3.72 (1H each, d), 3.78 (2H, s), 4.78 (1H, dd), 6.21 (1H, br. singlet), 7.22-7.85 (11H, m), 8.28-8.32 (1H, m)

Example 302 N-[6-(Naphth-1-yl)-5-hexyn-1-yl]-4-benzylsulphinyl-2-oxoazetidin-1-yl acetamide (diastereoisomer 1)

A solution of m-CPBA (1.2g) in dichloromethane was added dropwise to a solution of N-[6-(naphth-1-yl)-5-hexyn-1-yl]-4-benzylthio-2-oxoazetidin-1-yl acetamide (2.6g) in dichloromethane (100ml) cooled to -60C. The mixture was stirred at this temperature for 1 hour, poured into a mixed solution of sodium hydrogen carbonate and sodium sulphite, and the layers separated. The aqueous solution was extracted with dichloromethane and the combined organic solutions washed with brine. The solution was dried and evaporated to give an oil which gave the title compound as white crystals from ethyl acetate, m.p. 138-139°C, 22% yield

Found: C, 70.7; H, 6.0; N, 6.0%; $C_{28}H_{28}N_2O_3S$ +0.3H_2O requires: C, 70.4; H, 6.0; N, 5.9%

Example 303 N-[6-(Naphth-1-yl)-5-hexyn-1-yl]-4-benzylsulphinyl-2-oxoazetidin-1-yl acetamide (diastereoisomer 2)

The mother liquors were evaporated and triturated with ether to give the title compound (diastereomer 2) as white crystals, m.p. 95-97°C, 56% yield

Found: C, 70.8; H, 6.0; N, 6.0%; $C_{28}H_{28}N_2O_3S$ requires:C, 71.2; H, 6.0; N, 5.9%

The following compounds (Examples 304-8) were prepared from (4-benzylthio-2-oxoazetidin-1-yl)acetic acid and the required amine by the method described for Example 301.

Example 304 N-[6-(3-Chlorophenyl)hexyn-5-yl]-(4-benzylthio-2-oxo-azetidin-1-yl)acetamide

Colourless oil, 67.8% yield ^{1}H NMR δ ($CDCl_3$) 1.34-1.67 (4H, m, 2xCH_2), 2.44 (2H, t, J=6.51Hz, ArCCCH_2), 2.94 (1H, dd, 2.43Hz, 15.34Hz, H_{3a}), 3.31 (2H, m, NHCH_2), 3.37 (1H, dd, J=5.22Hz, 15.43Hz, H_{3b}), 3.63 & 3.78 (1H each, J=16.49Hz, NCH_2), 3.87 (2H, s, SCH_2Ph), 4.80 (1H, dd, J=2.46Hz, 5.11Hz, H_4), 6.36 (1H, m, NHC=O), 7.15-7.46 (9H, m, 9xArH)

Example 305 N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylthio-2-oxo-azetidin-1yl acetamide

Colourless oil, 76.2% yield ^{1}H NMR δ ($CDCl_3$) 1.47-1.81 (4H, m, 2xCH_2), 2.51 (2H, t, J=6.48Hz, ArCCCH_2), 2.94 (1H, dd, 2.43Hz, 15.38Hz, H_{3a}), 3.22 (2H, m, NHCH_2), 3.35 (1H, dd, J=5.13Hz,1 5.38Hz, H_{3b}), 3.54 & 3.76 (1Heach, J=16.79Hz,

NCH_2), 3.81 (2H, s, SCH_2Ph), 4.80 (1H, dd, J=2.45Hz, 5.13Hz, H_4), 6.10 (1H, m, NHC=O), 7.17-7.44 (9H, m, 9xArH)

Example 306 N-(6-Phenyl-3-hexynyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide

Colourless solid, m.p. 96-97°C, 78% yield

^1H NMR δ ($CDCl_3$) 2.34 (2H, m, $CCCH_2$), 2.46 (2H, m, $CCCH_2$), 2.80 (2H, t, J=7.4Hz, $PhCH_2$), 2.91, 2.95 (1H, dd, J=2.4, 15.3Hz, H_3), 3.34 (3H, m, $NHCH_2$, H_3), 3.44, 3.73 (each 1H, d, J=16.8Hz, NCH_2), 3.80 (2H, s, SCH_2), 4.83 (1H, m, H_4), 6.0 (1H, m, NH), 7.20-7.33 (10H, m, 2Ph-H); $\nu_{c=o}$ 1771 cm^{-1}

Found: C, 70.9; H, 6.5; N, 7.0%; $C_{24}H_{26}N_2O_2S$ requires: C, 70.9; H, 6.5; N, 6.9%

Example 307 Z-N-(6-phenyl-3-hexenyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide

Colourless oil, 65% yield

^1H NMR δ ($CDCl_3$) 2.18 (2H, m, $C=CCH_2$), 2.35 (2H, m, $C=CCH_2$), 2.66 (2H, t, J=7.6Hz, $PhCH_2$), 2.89, 2.93 (1H, dd, J=2.4, 15.3Hz, H_3), 3.20 (2H, m, $NHCH_2$), 3.31, 3.37 (1H, dd, J=5.2, 15.3Hz, H_3), 3.47, 3.65 (each 1H, d, J=15.1Hz, NCH_2), 3.75 (2H, s, SCH_2), 4.80 (1H, m, H_4), 5.35 (1H, m, CH=), 5.51 (1H, m, CH=), 5.93 (1H, m, NH), 7.16-7.41 (10H, m, 2Ph-H)

Example 308 *E*-N-(6-phenyl-3-hexenyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide

Colourless solid, m.p. 96-97°C, 78% yield

^1H NMR δ ($CDCl_3$) 2.18 (2H, m, $C=CCH_2$), 2.33 (2H, m, $C=CCH_2$), 2.68 (2H, t, J=7.7Hz, $PhCH_2$), 2.90, 2.96 (1H, dd, J=2.4, 15.3Hz, H_3), 3.24 (2H, m, $NHCH_2$), 3.33, 3.39 (1H, dd, J=5.2, 15.3Hz, H_3), 3.48, 3.71 (each 1H, d, J=16.8Hz, NCH_2), 3.81 (2H, s, SCH_2), 4.81 (1H, m, H_4), 5.34 (1H, m, CH=), 5.53 (1H, m, CH=), 5.87 (1H, m, NH), 7.15-7.36 (10H, m, 2Ph-H); $\nu_{c=o}$ 1771 cm^{-1}

Found: C, 70.5; H, 6.9; N, 7.0%; $C_{24}H_{28}N_2O_2S$ requires:C, 70.6; H, 6.9; N, 6.9%

Example 309 N-(5-Phenoxypentyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide

Yellow oil, 74% yield

^1H NMR δ ($CDCl_3$) 1.4-1.9 (6H, m, 3 x CH_2), 2.93 (1H, dd, J=2, 15 Hz, H_3), 3.3 (2H, m, $NHCH_2$), 3.36 (1H, dd, J=5, 15 Hz, H_3), 3.55, 3.72 (each 1H, d, J=17 Hz, NCH_2), 3.81 (2H, s, SCH_2), 3.95 (2H, t, J=6 Hz, CH_2O), 4.81 (1H, m, H_4), 6.13 (1H, br s, NH), 6.9 (3H, m, Ph-H), 7.3 (7H, m, Ph-H)

Example 310 N-(2-(2-Phenoxyethoxy)ethyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide

Yellow oil, 84% yield

^1H NMR δ ($CDCl_3$) 2.89 (1H, dd, J=2, 15 Hz, H_3), 3.31 (1H, dd, J=5, 15 Hz, H_3), 3.50 (3H, m, $NHCH_2$ + NCH_2), 3.63 (2H, m, CH_2O), 3.80 (5H, m, CH_2O + SCH_2 + NCH_2), 4.10 (2H, m, CH_2OPh), 4.82 (1H, m, H_4), 6.38 (1H, br s, NH), 6.9 (3H, m, Ph-H), 7.3 (7H, m, Ph-H)

Example 311 N-(2-(3-Phenylpropyloxy)ethyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide

Yellow oil, 77% yield

^1H NMR δ ($CDCl_3$) 1.90 (2H, m, CH_2), 2.68 (2H, t, J=8 Hz, CH_2Ph), 2.93 (1H, dd, J=2, 15 Hz, H_3), 3.36 (1H, dd, J=5, 15 Hz, H_3), 3.45 (7H, m, $NHCH_2$ + CH_2O +

NCH_2), 3.80 (3H, m, SCH_2 + NCH_2), 4.85 (1H, m, H_4), 6.25 (1H, br s, NH), 7.3 (10H, m, Ph-H)

The following sulfoxides (Examples 312 - 327) were prepared in the same way as described for Examples 2 and 3.

Example 312 N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide

White solid, m.p. 133-134°C, 15.5% yieldFound: C, 62.8; H, 5.4; N, 6.13%; $C_{24}H_{25}ClN_2O_3S$ requires: C, 63.1; H, 5.5; N, 6.1%

Example 313 N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide

White solid, m.p. 68-70°C, 18.0% yieldFound: C, 62.8; H, 5.5; N, 6.2%; $C_{24}H_{25}ClN_2O_3S$ requires: C, 63.1; H, 5.5; N, 6.1%

Example 314 N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide

White solid, m.p. 132-134°C, 48.1% yieldFound: C, 62.8; H, 5.5; N, 6.1%; $C_{24}H_{25}ClN_2O_3S$ requires: C, 63.1; H, 5.5; N, 6.1 %

Example 315 N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide

White solid, m.p. 91-92°C, 48.1% yieldFound: C, 62.9; H, 5.6; N, 6.2%; $C_{24}H_{25}ClN_2O_3S$ requires:C, 63.1; H, 5.5 ; N, 6.1 %

Example 316 N-(6-Phenyl-3-hexynyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1)

Colourless solid, m.p. 186°C, 14% yield

^{1}H NMR δ ($CDCl_3$) 2.34 (2H, m, $CCCH_2$), 2.46 (2H, m, $CCCH_2$), 2.80 (2H, t, J=7.4Hz, $PhCH_2$), 2.91, 2.95 (1H, dd, J=4.4, 14.8Hz, H_3), 3.31 (2H, m, $NHCH_2$), 3.41, 3.44 (1H, dd, J=2.0, 14.8Hz, H_3), 3.78-4.01 (4H, m, NCH_2, $SOCH_2$), 4.59 (1H, m, H_4), 6.38 (1H, m, NH), 7.20-7.40 (10H, m, 2Ph-H); $\nu_{C=O}$ 1791 cm^{-1}

Found: C, 68.0; H, 6.1; N, 6.6%; $C_{24}H_{26}N_2O_3S$ requires: C, 68.2; H, 6.2; N, 6.6%

Example 317 N-(6-Phenyl-3-hexynyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2)

Colourless solid, m.p. 127-128°C, 48% yield

^{1}H NMR δ ($CDCl_3$) 2.34 (2H, m, $CCCH_2$), 2.46 (2H, m, $CCCH_2$), 2.72-2.81 (3H, m, $PhCH_2$, H_3), 3.09, 3.13 (1H, dd, J=5.6, 15.2Hz, H_3), 3.34 (2H, m, $NHCH_2$), 3.93-4.19 (4H, m, NCH_2, $SOCH_2$), 4.65 (1H, m, H_4), 6.74 (1H, m, NH), 7.20-7.40 (10H, m, 2Ph-H)

Example 318 Z-N-(6-Phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1)

Colourless soild, m.p. 145-146°C, 19% yield

^{1}H NMR δ ($CDCl_3$) 2.21 (2H, m, $C{=}CCH_2$), 2.35 (2H, m, $C{=}CCH_2$), 2.66 (2H, t, J=7.6Hz, $PhCH_2$), 2.91, 2.95 (1H, dd, J=4.8, 14.8Hz, H_3), 3.19 (2H, m, $NHCH_2$), 3.42, 3.45 (1H, dd, J=2.0, 14.8Hz, H_3), 3.73, 4.02 (each 1H, d, J=17.6Hz, NCH_2), 3.87, 4.01 (each 1H, d, J= 13.2Hz, $SOCH_2$), 4.53 (1H, m, H_4), 6.47 (1H, m, NH), 7.16-7.41 (10H, m, 2Ph-H); $\nu_{C=O}$ 1791 cm^{-1}

Found: C, 67.6; H, 6.6; N, 6.7%; $C_{24}H_{28}N_2O_3S$ requires: C, 67.9; H, 6.7; N, 6.6%

Example 319 ***Z*-N-(6-phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2)**

Colourless solid, m.p. 104-105°C, 14% yield

^{1}H NMR δ ($CDCl_3$) 2.21 (2H, m, C=CC$\underline{H}_2$), 2.37 (2H, m, C=CC$\underline{H}_2$), 2.67 (2H, t, J=7.6Hz, PhC$\underline{H}_2$), 2.79, 2.83 (1H, dd, J=2.4, 15.6Hz, $\underline{H}_3$), 3.12, 3.16 (1H, dd, J=5.6, 15.6Hz, $\underline{H}_3$), 3.22 (2H, m, NHC$\underline{H}_2$), 3.90, 4.18 (each 1H, d, J=16.8Hz, NC$\underline{H}_2$), 3.97, 4.16 (each 1H, d, J= 12.8Hz, SOC$\underline{H}_2$), 4.61 (1H, m, $\underline{H}_4$), 5.35 (1H, m, C$\underline{H}$=), 5.51 (1H, m, C$\underline{H}$=), 6.95 (1H, m, N$\underline{H}$), 7.16-7.41 (10H, m, 2Ph-$\underline{H}$); $\nu_{c=o}$ 1793 cm^{-1}

Found: C, 67.4; H, 6.6; N, 6.7%; $C_{24}H_{28}N_2O_3S$ requires: C, 67.9; H, 6.7; N, 6.6%

Example 320 ***E*-N-(6-Phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1)**

Colourless soild, m.p.182-183°C, 18% yield

^{1}H NMR δ ($CDCl_3$) 2.19 (2H, m, C=CC$\underline{H}_2$), 2.31 (2H, m, C=CC$\underline{H}_2$), 2.67 (2H, t, J=7.7Hz, PhC$\underline{H}_2$), 2.91, 2.96 (1H, dd, J=4.7, 14.8Hz, $\underline{H}_3$), 3.24 (2H, m, NHC$\underline{H}_2$), 3.41, 3.47 (1H, dd, J=2.2, 14.8Hz, $\underline{H}_3$), 3.73, 4.02 (each 1H, d, J=17.3Hz, NC$\underline{H}_2$), 3.88, 4.01 (each 1H, d, J= 13.1Hz, SOC$\underline{H}_2$), 4.55 (1H, m, $\underline{H}_4$), 6.44 (1H, m, N$\underline{H}$), 7.16-7.40 (10H, m, 2Ph-$\underline{H}$); $\nu_{c=o}$ 1790cm^{-1}

Found: C, 67.5; H, 6.6; N, 6.6%; $C_{24}H_{28}N_2O_3S$ requires: C, 67.9; H, 6.7; N, 6.6%

Example 321 ***E*-N-(6-phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2)**

Colourless solid, m.p.111-112°C, 13% yield

^{1}H NMR δ ($CDCl_3$) 2.21 (2H, m, C=CC$\underline{H}_2$), 2.34 (2H, m, C=CC$\underline{H}_2$), 2.67 (2H, t, J=7.6Hz, PhC$\underline{H}_2$), 2.78, 2.84 (1H, dd, J=2.5, 15.3Hz, $\underline{H}_3$), 3.11, 3.17 (1H, dd, J=5.3, 15.3Hz, $\underline{H}_3$), 3.28 (2H, m, NHC$\underline{H}_2$), 3.90, 4.18 (each 1H, d, J=17.1Hz, NC$\underline{H}_2$), 3.97, 4.16 (each 1H, d, J= 12.9Hz, SOC$\underline{H}_2$), 4.62 (1H, m, $\underline{H}_4$), 5.38 (1H, m, =C$\underline{H}$), 5.53 (1H, m, =C$\underline{H}$), 6.86 (1H, m, N$\underline{H}$), 7.16-7.42 (10H, m, 2Ph-$\underline{H}$); $\nu_{c=o}$ 1793cm^{-1}

Found: C, 67.8; H, 6.6; N, 6.6%; $C_{24}H_{28}N_2O_3S$ requires: C, 67.9; H, 6.7; N, 6.6%

Example 322 N-(5-phenoxypentyl)-(4-benzylsulfinyl-2-oxoazetidin-1-yl)acetamide

White solid, 18% yield, m.p. 132-135°C

^{1}H nmr δ (CDCl3) 1.17-1.54 (6H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 2.94 (1H,dd, J=15.0, 4.75Hz, $\underline{H}_{3b}$), 3.25 (2H, m, NH-C$\underline{H}_2$), 2.44 (1H, dd, J=15.0, 2.25Hz, $\underline{H}_{3a}$), 3.68-4.16 (6H, m, C$\underline{H}_2$-OPh, N-C$\underline{H}_2$, SOC$\underline{H}_2$Ph), 4.52 (1H, m, $\underline{H}_4$), 6.74 (1H, m, NH), 6.86-6.95, 7.22-7.35, 7.37-7.40 (3H, 4H, 3H, m, O-Ph-$\underline{H}$, SOCH$_2$Ph-$\underline{H}$).

Example 323 N-(5-phenoxypentyl)-(4-benzylsulfinyl-2-oxoazetidin-1-yl)acetamide

White solid, 21% yield, m.p. 116-118°C

^{1}H nmr δ ($CDCl_3$) 1.46-1.86 (6H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 2.87 (1H, dd, J=15.5, 2.0Hz, $\underline{H}_{3a}$), 3.17 (1H, dd, J=15.5, 5.0Hz, $\underline{H}_{3b}$), 3.26-3.39 (2H, m, NH-C$\underline{H}_2$), 3.85-4.29 (6H, m, N-C$\underline{H}_2$, C$\underline{H}_2$-OPh, SOC$\underline{H}_2$Ph), 4.60 (1H, m, $\underline{H}_4$), 6.86-6.94,7.22-7.43 (3H, 8H, m, CH$_2$Ph-H, O-Ph-$\underline{H}$, N$\underline{H}$).

Found: C, 64.2; H, 6.4; N, 6.5%; $C_{23}H_{28}N_2O_4S$ requires: C, 64.5; H, 6.6; N, 6.5%

Example 324 N-(2-(2-Phenoxyethoxy)ethyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1)

Colourless solid, m.p. 133-5°C, 40% yield

^{1}H NMR δ ($CDCl_3$) 2.89 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.39 (1H, dd, J=2, 15 Hz, $\underline{H}_3$) 3.45 (2H, m, $NC\underline{H}_2$), 3.64 (2H, m,$OC\underline{H}_2$), 3.80 (2H, m, $OC\underline{H}_2$), 3.90 (4H, m, $NC\underline{H}_2$ + $SOC\underline{H}_2$), 4.12 (2H, m, $C\underline{H}_2OPh$), 4.60 (1H, m, $\underline{H}_4$), 6.65 (1H, br s, N$\underline{H}$), 6.95 (3H, m, Ph-$\underline{H}$), 7.3 (7H, m, Ph-$\underline{H}$); $\nu_{c=o}$ 1789 cm^{-1}

Found: C, 61.1; H, 6.0; N, 6.6%; $C_{22}H_{26}N_2O_5S$ requires: C, 61.4; H, 6.1; N, 6.5%

Example 325 N-(2-(2-Phenoxyethoxy)ethyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2)

Colourless solid, m.p. 109-12°C, 47% yield

^{1}H NMR δ ($CDCl_3$) 2.67 (1H, dd, J=2, 15 Hz, $\underline{H}_3$), 3.06 (1H, dd, J=5, 15 Hz, $\underline{H}_3$) 3.5 (2H, m, $NC\underline{H}_2$), 3.65 (2H, m,$OC\underline{H}_2$), 3.82 (2H, m, $OC\underline{H}_2$), 4.0 (6H, m, $NC\underline{H}_2$ + $SOC\underline{H}_2$ + $C\underline{H}_2OPh$), 4.65 (1H, m, $\underline{H}_4$), 7.06 (1H, br s, N$\underline{H}$), 6.9 (3H, m, Ph-$\underline{H}$), 7.3 (7H, m, Ph-$\underline{H}$); $\nu_{c=o}$ 1790 cm^{-1}

Found: C, 61.0; H, 6.0; N, 6.5%; $C_{22}H_{26}N_2O_5S$ requires: C, 61.4; H, 6.1; N, 6.5%

Example 326 N-2-(3-Phenylpropyloxy)ethyl-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1)

Colourless solid, m.p. 124-5°C, 27% yield

^{1}H NMR δ ($CDCl_3$) 1.90 (2H, m, $C\underline{H}_2$), 2.68 (2H, t, J=8 Hz, $C\underline{H}_2Ar$), 2.91 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.4 (7H, m, $NC\underline{H}_2$ + $\underline{H}_3$ + 2 x $OC\underline{H}_2$), 3.85 - 4.0 (4H, m, $SOC\underline{H}_2$ + $NC\underline{H}_2$), 4.62 (1H, m, $\underline{H}_4$), 6.61 (1H, br s, N$\underline{H}$), 7.15 - 7.45 (10H, m, 2 x Ph-$\underline{H}$); $\nu_{c=o}$ 1789 cm^{-1}

Found: C, 64.2; H, 6.5; N, 6.6%; $C_{23}H_{28}N_2O_4S$ requires: C, 64.5; H, 6.6; N, 6.5%

Example 327 N-2-(3-Phenylpropyloxy)ethyl-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2)

Colourless solid, m.p. 82-4°C, 24% yield

^{1}H NMR δ ($CDCl_3$) 1.85 (2H, m, $C\underline{H}_2$), 2.7 (3H, m, $C\underline{H}_2Ar$ + $\underline{H}_3$), 3.09 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.45 (6H, m, $NC\underline{H}_2$ + 2 x $OC\underline{H}_2$), 3.9 - 4.2 (4H, m, $SOC\underline{H}_2$ + $NC\underline{H}_2$), 4.67 (1H, m, $\underline{H}_4$), 6.97 (1H, br s, N$\underline{H}$), 7.15 - 7.4 (10H, m, 2 x Ph-$\underline{H}$); $\nu_{c=o}$ 1790 cm^{-1}

Found: C, 64.3; H, 6.5; N, 6.6%; $C_{23}H_{28}N_2O_4S$ requires: C, 64.5; H, 6.6; N, 6.5%

Example 328 N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphonyl-2-oxo-azetidin-1-yl acetamide

Treatment of N-[6-(2-chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide (diastereoisomer 1) with mCPBA (1 equivalent) in dichloromethane at room temperature gave the title compound as a white solid, m.p. 114-117°C, 86.7% yield;

Found:C, 60.4; H, 5.4; N, 5.8%; $C_{24}H_{25}ClN_2O_4S$ requires:C, 60.9; H, 5.3; N, 5.8%

The following sulfones (Examples 329-331) were prepared in an analogous way, or were isolated from the mixture formed when the corresponding sulfides were treated with *m*CPBA.

Example 329 N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphonyl-2-oxo-azetidin-1-yl acetamide

White solid, m.p. 122-124°C, 5.6% yield

Found: C, 60.7; H, 5.3; N, 6.0%; $C_{24}H_{25}ClN_2O_3S$ requires: C, 60.9; H, 5.3; N, 5.9%

Example 330 N-(6-Phenyl-3-hexynyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide

Colourless solid, m.p. 135-136°C, 88% yield
^{1}H NMR δ ($CDCl_3$) 2.33 (2H, m, CCC$\underline{H}_2$), 2.47 (2H, m, CCC$\underline{H}_2$), 2.81 (2H, t, J=7.4Hz, PhC$\underline{H}_2$), 2.94, 3.00 (1H, dd, J=2.4, 15.3Hz, $\underline{H}_3$), 3.07, 3.13 (1H, dd, J=5.1, 15.3Hz, $\underline{H}_3$), 3.30 (2H, m, NHC$\underline{H}_2$), 3.69, 3.97 (each 1H, d, J=18.9Hz, NC$\underline{H}_2$), 4.30, 4.37 (each 1H, d, J=14.2Hz, $SO_2C\underline{H}_2$), 4.89 (1H, m, $\underline{H}_4$), 5.77 (1H, m, N$\underline{H}$), 7.20-7.40 (10H, m, 2Ph-$\underline{H}$); $\nu_{c=o}$ 1792 cm^{-1}
Found: C, 65.4; H, 6.0; N, 6.4%; $C_{24}H_{26}N_2O_4S$ requires: C, 65.7; H, 6.0; N, 6.4%

Example 331 ***E*-N-(6-phenyl-3-hexenyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide**

Colourless solid, m.p. 115-116°C, 39% yield
^{1}H NMR δ ($CDCl_3$) 2.17 (2H, m, C=CC$\underline{H}_2$), 2.35 (2H, m, CCC$\underline{H}_2$), 2.69 (2H, t, J=7.6Hz, PhC$\underline{H}_2$), 2.94, 3.00 (1H, dd, J=2.4, 15.4Hz, $\underline{H}_3$), 3.07, 3.13 (1H, dd, J=5.1, 15.4Hz, $\underline{H}_3$), 3.24 (2H, m, NHC$\underline{H}_2$), 3.74, 3.95 (each 1H, d, J=16.9Hz, NC$\underline{H}_2$), 4.30, 4.37 (each 1H, d, J=14.2Hz, $SO_2C\underline{H}_2$), 4.87 (1H, m, $\underline{H}_4$), 5.33 (1H, m, =C$\underline{H}$), 5.53 (1H, m, =C$\underline{H}$), 5.70 (1H, m, N$\underline{H}$), 7.16-7.44 (10H, m, 2Ph-$\underline{H}$); $\nu_{c=o}$ 1794 cm^{-1}
Found: C, 65.1; H, 6.3; N, 6.4%; $C_{24}H_{28}N_2O_4S$ requires: C, 65.4 H, 6.4; N, 6.4%

Example 332 1-(2-(6-Phenylhexyloxy)ethyl-4-benzylthio-2-oxoazetidine

A 60% dispersion of sodium hydride in mineral oil (0.30 g, 7.5mmoles) was suspended in dry THF (15 ml) at -10°C under nitrogen and a solution of 4-(benzylthio)-2-azetidinone (1.35g) in THF (10 ml) was added over 10 mins keeping temp <0°C. The mixture was stirred at 0°C for 15 mins, cooled to -10°C and 2-(6-phenylhexyloxy)ethyl triflate(3.54g,) in THF(10 ml) was added over 3 mins keeping temp <0°C. The mixture was stirred at RT for 30mins then poured into brine (50 ml), separated and the aqueous extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated to a red oil. This was purified by chromatography on silica gel (40-60 petroleum ether/ethyl acetate) to give 1-(2-(6-phenylhexyloxy)ethyl-4-benzylthio-2-oxoazetidine as a colourless oil (1.71g, 62%)
^{1}H NMR δ ($CDCl_3$) 1.3-1.7 (8H, m, 4 x C$\underline{H}_2$), 2.59 (2H, t, J=8 Hz, C$\underline{H}_2$Ph), 2.88 (1H, dd, J=2, 15 Hz, $\underline{H}_3$), 3.0 (1H, m, NC$\underline{H}_2$), 3.27 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.4 (5H, m, NC$\underline{H}_2$ + C$\underline{H}_2$OC$\underline{H}_2$), 3.81 (2H, s, SC$\underline{H}_2$), 4.75 (1H, m, $\underline{H}_4$), 7.15-7.35 (10H, m, Ph-$\underline{H}$).

The following Examples (333-336) were prepared from 4-benzylthio-azetidin-2-one and the corresponding triflate in an analogous manner to Example 332.

Example 333 1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylthio-2-oxoazetidine

Colourless oil, 62% yield
1H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x C$\underline{H}_2$), 2.55 (2H, t, J=8 Hz, C$\underline{H}_2$Ph), 2.88 (1H, dd, J=2, 15 Hz, $\underline{H}_3$), 3.0 (1H, m, NC$\underline{H}_2$), 3.28 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.4 (5H, m, NC$\underline{H}_2$ + C$\underline{H}_2$OC$\underline{H}_2$), 3.81 (2H, s, SC$\underline{H}_2$), 4.75 (1H, m, $\underline{H}_4$), 7.07 (2H, m, ClPh-$\underline{H}$), 7.35 (7H, m, Ph-$\underline{H}$ + ClPh-$\underline{H}$)

Example 334 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylthio-2-oxoazetidine

Colourless oil, 22% yield
1H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x C$\underline{H}_2$), 2.55 (2H, t, J=8 Hz, C$\underline{H}_2$Ph), 2.88 (1H, dd, J=2, 15 Hz, $\underline{H}_3$), 3.05 (1H, m, NC$\underline{H}_2$), 3.27 (1H, dd, J=5, 15 Hz, $\underline{H}_3$), 3.4

(5H, m, NCH_2 + CH_2OCH_2), 3.81 (2H, s, SCH_2), 4.75 (1H, m, H_4), 6.95, 7.10 (each 2H, m, FPh-H), 7.25 (5H, m, Ph-H)

Example 335 N-3-(Phenoxypropyl)-4-benzylthio-2-oxoazetidine

Yellow oil, 82% yield

^{1}H NMR δ ($CDCl_3$) 2.0 (2H, m, CH_2), 2.89 (1H, dd, J=2, 15 Hz, H_3), 3.08, 3.41 (each 1H, m, NCH_2), 3.26 (1H, dd, J=5, 15 Hz, H_3), 3.78 (2H, s, SCH_2), 3.95 (2H, m, CH_2OPh), 4.63 (1H, m, H_4), 6.9 (3H, m, Ph-H), 7.3 (7H, m, Ph-H)

Example 336 1-(2-Benzyloxyethyl)-4-benzylthio-azetidin-2-one

Colourless oil, 74% yield

^{1}H NMR δ ($CDCl_3$) 2.7 (1H, dd, J=2, 15 Hz, H_3), 3.0 (1H, m, NCH_2), 3.26 (1H, dd, J=5, 15 Hz, H_3), 3.5 (3H, m, NCH_2 + CH_2CH_2O), 3.76 (2H, m, SCH_2Ph), 4.50 (2H, m, OCH_2Ph), 4.7 (1H, m, H_4), 7.2-7.4 (10H, m, 2xPh-H).

The following sulfoxides (Examples 337-345) were prepared by treating the corresponding sulfides with *m*CPBA, as described in Examples 302 & 303.

Example 337 1-(2-(6-Phenylhexyloxy)ethyl-4-benzylsulphinyl-2-oxoazetidine (80% Diastereoisomer 2)

Colourless solid, m.p. 47-9°C, 37% yield

^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x CH_2), 2.6 (3H, m CH_2Ph + H_3), 2.98 (1H, dd, J=5, 15 Hz, H_3), 3.3-3.8 (6H, m, NCH_2 + CH_2OCH_2), 4.05 (2H, d, J=13 Hz, SCH_2), 4.52 (1H, m, H_4), 7.14-7.4 (10H, m, Ph-H); $\nu_{c=o}$ 1776 cm^{-1}

Found: C, 69.7; H, 7.4; N, 3.5%; $C_{24}H_{31}NO_3S$ requires: C, 69.7; H, 7.6; N, 3.4%

Example 338 1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 1)

Colourless oil, 27% yield

^{1}H NMR δ ($CDCl_3$) 1.2-1.65 (8H, m, 4 x CH_2), 2.58 (2H, t, J=8Hz, CH_2Ph), 2.87 (1H, dd, J=5, 15 Hz, H_3), 3.25 - 3.7 (7H, m, NCH_2 + CH_2OCH_2 + H_3), 3.84,3.98 (2H, 2 x d, J=13Hz, $SOCH_2$), 4.51 (1H, m, H_4), 7.09 (2H, m, ClPh-H), 7.3 (7H, m, Ph-H + ClPh-H); $\nu_{c=o}$ 1777 cm^{-1}

Found: C, 64.1; H, 6.6; N, 3.1%; $C_{24}H_{30}ClNO_3S$ requires:C, 64.3; H, 6.8; N, 3.1%

Example 339 1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2)

Colourless solid, m.p. 86-8°C, 37% yield

^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (8H, m, 4 x CH_2), 2.55 (3H, m, CH_2Ph + H_3), 2.99 (1H, dd, J=5, 15 Hz, H_3), 3.3 - 3.8 (6H, m, NCH_2 + CH_2OCH_2), 4.01,4.09 (2H, 2 x d, J=13Hz, $SOCH_2$), 4.52 (1H, m, H_4), 7.09 (2H, m, ClPh-H), 7.3 (7H, m, Ph-H + ClPh-H); $\nu_{c=o}$ 1777 cm^{-1}

Found: C, 64.2; H, 6.6; N, 3.3%; $C_{24}H_{30}ClNO_3S$ requires: C, 64.3; H, 6.7; N, 3.1%

Example 340 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 1)

Colourless oil, 12% yield

^{1}H NMR δ ($CDCl_3$) 1.25-1.65 (8H, m, 4 x CH_2), 2.58 (2H, t, CH_2Ph), 2.87 (1H, dd, J=5, 15 Hz, H_3), 3.25 - 3.7 (7H, m, NCH_2 + CH_2OCH_2 + H_3), 3.84,3.98 (2H, 2 x d, J=13Hz, $SOCH_2$), 4.52 (1H, m, H_4), 6.95, 7.10 (each 2H, m, FPh-H), 7.3 (5H, m, Ph-H); $\nu_{c=o}$ 1777 cm^{-1}

Example 341 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2)

Colourless solid, m.p. 77-8°C, 37% yield

^{1}H NMR δ ($CDCl_3$) 1.25-1.65 (8H, m, 4 x CH_2), 2.55 (3H, m, CH_2Ph + H_3), 2.98 (1H, dd, J=5, 15 Hz, H_3), 3.4 - 3.75 (6H, m, NCH_2 + CH_2OCH_2), 4.02,4.09 (2H, 2 x d, J=13Hz, $SOCH_2$), 4.52 (1H, m, H_4), 6.95, 7.10 (each 2H, m, FPh-H), 7.3 (5H, m, Ph-H); $\nu_{c=o}$ 1777 cm^{-1}

Found: C, 66.5; H, 6.9; N, 3.2%; $C_{24}H_{30}FNO_3S$ requires: C, 66.8; H, 7.0; N, 3.3%

Example 342 4-Benzylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one (Diastereoisomer 1)

Colourless solid, m.p. 93-97°C

^{1}H nmr δ ($CDCl_3$) 2.05-2.17 (2H, m, $CH_2CH_2CH_2$), 2.78(1H, dd, J=14.75, 4.75Hz, H_{3b}), 3.34-3.57 (3H, m, H_{3a}, NCH_2), 3.82, 3.92 (2H, dd, J=13.00, 13.00Hz, $SOCH_2Ph$), 3.95-4.06 (2H, m, CH_2-OPh), 4.37 (1H, m, H_4), 6.83-6.98 (5H, m, OPh-H), 7.19-7.37 (5H, m, CH_2Ph-H).

Found: C, 66.5; H, 6.2; N, 4.1%; $C_{19}H_{21}NO_3S$ requires: C, 66.3; H, 6.2; N, 4.4%

Example 343 4-Benzylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one (Diastereoisomer 2)

Colourless solid, m.p. 62-65°C

^{1}H nmr δ ($CDCl_3$) 2.12-2.19 (2H, m, $CH_2CH_2CH_2$), 2.47 (1H, dd, J=15.0, 2.25Hz, H_{3a}), 2.91 (1H, dd, J=15.0, 5.0Hz, H_{3b}), 3.51-3.67 (2H, m, NCH_2), 3.95-4.07 (4H, m, CH_2O, $SOCH_2Ph$), 4.42 (1H, m, H_4), 6.83-6.97 (5H, m, OPh-H), 7.22-7.39 (5H, m, $SOCH_2Ph$-H).

Found: C, 66,5; H, 6.2; N, 4.1%; $C_{19}H_{21}NO_3S$ requires: C, 66.4; H, 6.3; N, 4.4%

Example 344 1-(2-Benzyloxyethyl)-4-benzylsulphinyl-azetidin-2-one (57% Diastereoisomer 1)

Colourless oil, 49% yield

^{1}H NMR δ ($CDCl_3$) 2.78 (1H, dd, J=5, 15 Hz, H_3), 3.35 (1H, d, J=13 Hz, H_3), 3.4-3.8 (4H, m, NCH_2CH_2), 3.95, 4.07 (each 1H, d, J=15 Hz, $SOCH_2$), 4.5 (3H, m, OCH_2Ph + H_4), 7.2-7.4 (10H, m, Ph-H); $\nu_{c=o}$ 1777 cm^{-1}

Example 345 1-(2-Benzyloxyethyl)-4-benzylsulphinyl-azetidin-2-one (80% Diastereoisomer 2)

Colourless oil, 26% yield

^{1}H NMR δ ($CDCl_3$) 2.49 (1H, d, J=15 Hz, H_3), 2.93 (1H, dd, J=5, 15 Hz, H_3), 3.4-3.8 (4H, m, NCH_2CH_2), 3.95, 4.07 (each 1H, d, J=13 Hz, $SOCH_2$), 4.4-4.6 (3H, m, OCH_2Ph + H_4), 7.2-7.4 (10H, m, Ph-H); $\nu_{c=o}$ 1777 cm^{-1}

Found: C, 66.4; H, 6.2; N, 4.3%; $C_{19}H_{21}NO_3S$ requires: C, 66.5; H, 6.2; N, 4.1%

Example 346 4-Methylthio-1-(3-phenoxypropyl)azetidin-2-one

A solution of 4-methylthioazetidin-2-one (0.7g, 5.97mmol) in dry THF (10ml) was added dropwise over 10 minutes to a suspension of NaH (0.24g, 6.07mmol) in dry THF (5ml) at -20°C under a N_2 atmosphere. A solution of 3-iodo-1-phenoxypropane (1.56g, 5.97mmol) in dry THF (10ml) was added dropwise over 10 minutes at -55°C. This mixture was stirred for 18 hours overnight, then poured onto ice/water (50g), filtered and partially evaporated. The residue was dtreated with ethyl acetate and the organic layer was washed with brine (x2), dried ($MgSO_4$) and evaporated under

reduced pressure to a yellow oil. The oil was purified by flash chromatography on silica gel to give 4-methylthio-1-(3-phenoxypropyl)azetidin-2-one a colourless solid (0.64g, 42%), m.p. 41-2°C.

^{1}H NMR δ ($CDCl_3$) 2.04 (3H, s, SCH_3), 2.10 (2H, m, CH_2), 2.95 (1H, dd, J=2, 15 Hz, H_3), 3.25 (2H, m, H_3 +NCH_2), 3.56 (1H, m, NCH_2), 4.02 (2H, m, CH_2OPh), 4.66 (1H, m, H_4), 6.9 (3H, m, Ph-H), 7.3 (2H, m, Ph-H)

Example 347 4-Methylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one

Treatment of 4-methylthio-1-(3-phenoxypropyl)azetidin-2-one (0.59g, 2.34mmol) with mCPBA as in Example 302 gave 4-Methylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one as a waxy white solid (0.39g, 62%).

^{1}H nmr δ ($CDCl_3$) 2.12-2.23 (4H, m, 2x$CH_2CH_2CH_2$), 2.43(3H, s, $SOCH_3$), 2.56 (3H, s, $SOCH_3$), 2.78 (1H, dd, J=15.00, 2.50Hz, H_{3a}), 3.07 (1H, dd, J=14.5, 4.75Hz, H_{3b}), 3.24 (1H, dd, J=15.00, 5.25Hz, H_{3b}), 3.47-3.71 (5H, m, 2xN-CH_2, H_{3a}), 4.05-4.20 (4H, m, 2xCH_2O), 4.40 (1H, m, H_4), 4.50 (1H, m, H_4), 6.8-7.0, 7.2-7.33 (6H, 4H, m, 2xAr-H).

Found: C, 58.4; H, 6.4; N, 5.2%; $C_{13}H_{17}NO_3S$ requires: C, 58.1; H, 6.5; N, 5.3%

Example 348 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylthio)-2-oxoazetidine

A solution of 4-(4-(ethoxycarbonyl)benzylthio)azetidin-2-one (1.85g, 0.00697 moles), 2-(6-(4-Fluorophenyl)hexyloxy)ethyl triflate (2.62g, 0.00704 moles), terabutylammonium bromide (0.22g, 0.00068 moles) in dry tetrahydrofuran (40ml), cooled to 10°C, was treated with powdered potassium hydroxide (0.47g, 0.00838 moles). The cooling bath was removed and the reaction was stirred at room temperature for 2 hours, partitioned between brine (70ml) and ethyl acetate (75ml). The organic layer was dried ($MgSO_4$) and evaporated to an oil (3.7g). Purified by flash column chromatography on silica gel eluted with 2:1 P.E. 40-60°C:ethyl acetate to give 1-(2-(6-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylthio)-2-oxoazetidine as a colourless oil (1.15g, 34%).

^{1}H nmr δ ($CDCl_3$) 1.42 (11H, m, CH_2x4, CH_3), 2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.84, 2.90 (1H, dd, J=1.9, 15.2Hz, H_3), 3.03 (1H, m, 1 of NCH_2), 3.26, 3.32 (1H, dd, J= 5, 15.2Hz, H_3), 3.40 (5H, m, CH_2OCH_2,1 of NCH_2), 3.85 (2H, s, CH_2S), 4.36 (2H, q, CH_2O), 4.75 (1H, m, H_4), 6.91-7.11 (4H, m, p-F-Ar-H), 7.39, 8.01 (4H, 2xd, J=8.3Hz, Ar-H)

Example 349 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine

Treatment of 1-(2-(6-fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzyl-sulphinyl)-2-oxoazetidine (1.05g) with mCPBA (0.67g) following the method of Example 302 gave, after chromatography and re-crystallisations, the title compound as a 96:4 ratio of diastereoisomers 2:1 as a colourless solid, m.p. 75-75°C, 25% yield

^{1}H nmr δ ($CDCl_3$) 1.42 (11H, m, CH_2x4, CH_3), 2.56 (2H, t, J=7.7Hz, CH_2Ph), 2.63, 2.69 (1H, dd, J=2.2, 15.1Hz, H_3), 3.05, 3.10 (1H, dd, J= 5, 15.1Hz, H_3), 3.37-3.73 (6H, m, CH_2OCH_2, NCH_2), 4.08 (2H, s, CH_2SO), 4.36 (2H, q, CH_2O), 4.54 (1H, m, H_4), 6.91-7.11 (4H, m, p-F-Ar-H), 7.38, 8.05 (4H, 2xd, J=8.3Hz, Ar-H)

Example 350 1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (predominantly diastereoisomer 1)

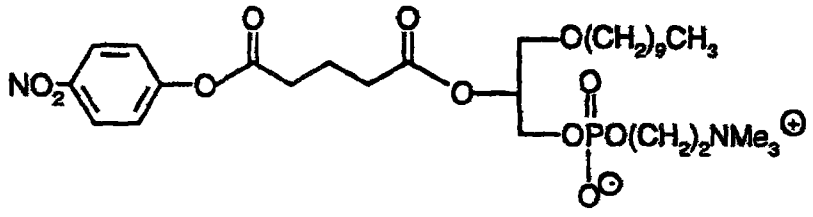
The recrystallisations of Example 349 also gave the title compound as a 68:32 mixture of diastereoisomers as a colourless solid, m.p. 53-55°C, 12.5%yield

^{1}H nmr (diastereoisomer 1)δ ($CDCl_3$) 1.42 (11H, m, CH_2x4, CH_3), 2.56 (2H, t, J=7.7Hz, CH_2Ph), 2.85, 2.90 (1H, dd, J=4.6, 14.6Hz, H_3), 3.30-3.7 (7H, m, H_3, CH_2OCH_2, NCH_2), 3.93 (2H, m, CH_2SO), 4.36 (2H, q, CH_2O), 4.53 (1H, m, H_4), 6.91-7.11 (4H, m, p-F-Ar-H), 7.33, 8.05 (4H, 2xd, J=8.2Hz, Ar-H)

Biological Data

1. 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.

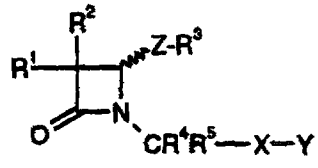
Lp-PLA$_2$ was partially purified by density gradient centrifugation of human plasma. Active fractions were pooled and used as the source of Lp-PLA$_2$. The enzyme was pre-incubated at 37 °C with vehicle or test compound for 10 min in a total volume of 180 µl. The reaction was then initiated by the addition 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 according to the present invention are found to have IC$_{50}$ values in the range 0.7-100,000 nM.

Claims

1. A compound of formula (I):



(I)

in which:

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

R^4 and R^5 which may be the same or different is each selected from hydrogen, $C_{(1-6)}$alkyl, $C_{(2-6)}$alkenyl, aryl, aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl each of which may be optionally substituted or R^4 and R^5 may be linked together to form the remainder of a (C_{3-7})cycloalkyl ring;

X is a linker group;

Y is an optionally substituted aryl group;

Z is oxygen and R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl, $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, aryl, or aryl(C_{1-4})alkyl, 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, heteroaryl, or heteroaryl(C_{1-4})alkyl, each of which may be optionally substituted; and

excluding compounds in which:

X is a direct bond; a group $X^1(CH_2)_m$ in which X^1 is CO, $CONR^6$, COO, $CONR^6CO$, or CONHO in which R^6 is hydrogen or $C_{(1-6)}$alkyl and m is 0 or an integer from 1 to 12; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;

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, or aryl(C_{1-4})alkyl, each of which may be optionally substituted; and

R^4 and R^5 is each hydrogen.

2. A compound as claimed in claim 1 in which X is:

direct bond;

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

a group $(X^1)_aX^2$ in which a is 0 or 1 and X^2 is a $C_{(1-12)}$alkylene chain interupted and/or terminated at the end adjacent to Y by one or more groups X^3 selected from O, $S(O)_x$, NR^6, alkene or alkyne, in which x is 0, 1 or 2; or

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

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3. A compound as claimed in claim 1 or 2 in which:
X is a direct bond; a group $X^1(CH_2)_m$ as defined in claim 2; a group $(X^1)_aX^2$ as defined in claim 2; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;
Z is oxygen and R^3 is $C_{(1-8)}$alkyl, $C_{(3-8)}$cycloalkyl, $C_{(3-8)}$cycloalkyl$C_{(1-6)}$alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, aryl, or aryl(C_{1-4})alkyl, 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 heteroaryl or heteroaryl(C_{1-4})alkyl, each of which may be optionally substituted.

4. A compound as claimed in claim 3 in which R^4 and R^5 is each hydrogen or one is hydrogen and the other is methyl.

5. A compound as claimed in claim 3 or 4 in which Z is oxygen and R^3 is optionally substituted aryl; or $S(O)_n$ in which n is 0, 1 or 2 and R^3 is optionally substituted heteroaryl(C_{1-4})alkyl.

6. A compound as claimed in claim 5 in which Z is oxygen and R^3 is optionally substituted phenyl.

7. A compound as claimed in claim 5 in which Z is $S(O)_n$ and R^3 is optionally substituted heteroarylmethyl.

8. A compound as claimed in claim 7 in which which ZR^3 is optionally substituted fur-2-ylmethyl.

9. A compound as claimed in claim 7 in which which ZR^3 is 5-carboxyfur-2-ylmethyl.

10. A compound as claimed in claim 1 or 2 in which:
X is a direct bond; a group $X^1(CH_2)_m$ as defined in claim 2; a group $(X^1)_aX^2$ as defined in claim 2; or a $C_{(1-12)}$alkylene chain optionally interupted by X^1;
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 or aryl(C_{1-4})alkyl, each of which may be optionally substituted;
R^4 and R^5 which may be the same or different is each selected from hydrogen, $C_{(1-6)}$alkyl, $C_{(2-6)}$alkenyl, aryl, aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl each of which may be optionally substituted or R^4 and R^5 may be linked together to form the remainder of a (C_{3-7})cycloalkyl ring, with the proviso that R^4 and R^5 are not both hydrogen.

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11. A compound as claimed in claim 10 in which one of R^4 and R^5 is hydrogen and the other is methyl.

12. A compound as claimed in any one of the preceding claims in which, when one of one of R^4 and R^5 is hydrogen and the other is methyl, the absolute configuration at the carbon to which R^4 and R^5 are attached is S.

13. A compound as claimed in any one of claims 3 to 12 in which X is $CONH(CH_2)_6$, $CONR^6(CH_2)_4C{\equiv}C$ or $(CH_2)O(CH_2)_6$.

14. A compound as claimed in claim 1 or 2 in which:
X is a group $(X^1)_aX^2$ as defined in claim 2;
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 or aryl(C_{1-4})alkyl, each of which may be optionally substituted; and
R^4 and R^5 is each hydrogen.

15. A compound as claimed in claim 14 in which X is $CONR^6(CH_2)_4C{\equiv}C$ or $(CH_2)O(CH_2)_6$.

16. A compound as claimed in any one of claims 10 to 15 in which ZR^3 is optionally substituted benzylsulfinyl.

17. A compound as claimed in claim 16 in which ZR^3 is 4- carboxybenzylsulfinyl or a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenylester thereof.

18. A compound as claimed in any one of claims 1 to 5 and 7 to 15 in which, when Z is $S(O)_n$, n is 1.

19. A compound as claimed in claim 18 in which the absolute configurations at C-4 and the SO moiety are R and S respectively.

20. A compound as claimed in any one of the preceding claims in which Y is a benzene ring, optionally substituted by up to three further substituents.

21. A compound as claimed in claim 20 in which Y is phenyl optionally substituted by halo.

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

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N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomers b1 &b2);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (-)b2);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (+)b2);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (+)b1);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (isomer (-)b1);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulfinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1);
N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulfinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomers b1+b2);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer (-)b2);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer (+)b2);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2);
N-[6-(4-fluorophenylhexyl)]-2-[4-benzylsulphonyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a);
N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphonyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer b);
N-(Benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer a);
N-(Benzyl)-2-[4-benzylthio-2-oxoazetidin-1-yl]propionamide (diastereoisomer b);
N-[6-(4-Fluorophenylhexyl)]-2-[4-(allyloxycarbonylbenzylthio)-2-oxoazetidin-1-yl]propionamide (diastereoisomer a);
(+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-(allyloxycarbonyl-benzylthio)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b);
(+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)- 2-oxoazetidin-1-yl]propionamide (diastereoisomers b2+b1);

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(+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b2);
(+/-)-N-[6-(4-Fluorophenylhexyl)]- 2-[4-(4-allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer b1);
(+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(allyloxycarbonyl)benzylsulphinyl)- 2-oxoazetidin-1-yl]propionamide (diastereoisomer a1);
(+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(allyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2);
(+/-)-N-[6-(4-fluorophenylhexyl)]- 2-[4-(4-(carboxy)benzylsulphinyl)-2-oxoazetidin-1-yl]propionamide (diastereoisomers b2+b1);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomers a and b);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide;
N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-(3-furyl)propionamide (diastereoisomer a2);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer a);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer b);
N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer a2);
N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenyl)propionamide (diastereoisomer a1);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer b1);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer b2);
(+)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer (+)-b2);
(-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-3-phenylpropionamide (diastereoisomer (-)-b2);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (diastereoisomer a);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylthio)-2-oxoazetidin-1-yl-2-allylacetamide (diastereoisomer b);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-2-allylacetamide (diastereoisomers a2+a1);
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-(4-benzylsulphinyl)-2-oxoazetidin-1-yl-2-allylacetamide;
(+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butyramide;
N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide;
(+/-)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (Isomer a1);

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(+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (isomer b1 and b2);
N-[6-(4-Fluorophenyl)hexyl]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]butanamide (isomer a2);
(+/-)-N-[6-(4-Fluorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]pentanamide;
(+/-)-N-[6-(4-chlorophenylhexyl)]-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propanamide;
N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer b1&b2);
N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a1);
N-(Benzyl)-2-[4-benzylsulphinyl-2-oxoazetidin-1-yl]propionamide (diastereoisomer a2);
(α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-carboxybenzylsulphinyl]-2-oxoazetidin-1-ylpropionamide;
(α-*S*,4-*R*,*SS*)-N-[6-(4-Fluorophenyl)hexyl]-2-[4-allyloxybenzylsulphinyl]-2-oxoazetidin-1-ylpropionamide;
(+/-)-4-(Pyrid-2-ylmethylthio)-1-(4-phenyl-2-oxobutyl)azetidin-2-one;
(+/-)-4-(Pyrid-2-ylmethylsulphinyl)-1-(4-phenyl-2-oxobutyl)azetidin-2-one (diastereomer 1);
(+/-)-4-(Pyrid-2-ylmethylsulphinyl)-1-(4-phenyl-2-oxobutyl)azetidin-2-one (diastereomer 2);
(+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-(6-Phenylhex-1-yl)-4-(pyrid-4-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-(6-Phenylhex-1-yl)-4-(1-oxopyrid-4-ylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-(6-Phenylhex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-[6-(4-Fluorophenyl)hexy]-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;

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(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-(6-[4-Chlorophenyl)hex-1-yl)-4-(2-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-(6-[4-Chlorophenyl]hex-1-yl)-4-(3-furylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(2-thienylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(3-thienylmethylsulphonyl)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylthio)-2-oxoazetidin-1-yl-acetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(thiazol-2-ylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylthio)-2-oxoazetidin-1-ylacetamide;
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 1);
(+/-)-N-[6-(4-Chlorophenylhexyl)]-4-(5-methoxycarbonyl-2-furylmethylsulphinyl)-2-oxoazetidin-1-ylacetamide (diastereomer 2);
(+/-)-4-(2-furylmethylthio)-1-(9-phenylnonyl)azetidin-2-one;

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(+/-)-4-(2-furylmethylsulphinyl)-1-(9-phenylnonyl)azetidin-2-one;
(+/-)-4-(2-furylmethylthio)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one;
(+/-)-4-(2-furylmethylsulphinyl)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one;
(+/-)-4-(2-furylmethylsulphonyl)-1-(9-(4-fluorophenyl)nonyl)azetidin-2-one;
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide;
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 1);
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-allyloxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-carboxyfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylthio-2-oxoazetidin-1-yl)acetamide;
N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 1);
N-(6-{4-Chlorophenyl}hexyl)-4-(5-allyloxycarbonylfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2);
N-(6-{4-Chlorophenyl}hexyl)-4-(5-carboxyfuran-2-methylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereomer 2);
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylthio)-2-oxoazetidin-1-ylacetamide;
N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 1)N-[6-(4-Fluorophenyl)hex-1-yl]-4-(5-methoxycarbonylfuran-2-methylsulphinyl)-2-oxoazetidin-1-ylacetamide (Diastereomer 2)N-[6-(4-Chlorophenyl)hexyl]-[4-(2-fluorophenoxy 2-oxo azetidin-1 yl) acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(2-methylphenoxy)-2-oxoazetidin-1--yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(2-benzyloxyphenoxy-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(2-methylthiophenoxy)-2-oxoazetidin-1-yl) acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(4-chlorophenoxy)-2-oxoazetidin-1-yl) acetamide;
(N-(6-(4-Phenyl)hexyl)-4-(4-methoxy-phenoxy)-2-oxoazetidin-1-yl)acetamide;
N-(-(4-Phenyl)hexyl)(-(4-methylthiophenoxy)-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Chlorophenyl)hexyl)-(4-(4-allyloxycarbonyl-methylphenoxy)-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-phenoxy-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-benzyloxy-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(4-methylsulphinylphenoxy)-2-oxoazetidin-1-yl)acetamide;
N-[6-(4-Phenyl)hexyl]-[4-(4-methylsulphonylphenoxy- 2-oxo azetidin-1-yl) acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(2-methylsulphinylphenoxy)-2-oxoazetidin-1-yl)acetamide
N-(6-(4-Phenyl)hexyl)-(4-(2-methylsulphonylphenoxy)-2-oxoazetidin-1-yl)acetamide;
N-(6-(4-Phenyl)hexyl)-(4-(2-hydroxyphenoxy)-2-oxoazetidin-1-yl)acetamide;
N-[6-(4-chlorophenyl)hexyl]-[4-(4-carboxymethylphenoxy)-2-oxo-azetidin-1-yl]-acetamide;
N-(6-(4-Phenyl)hexyl)-(3-methyl-4-phenoxy-2-oxoazetidin-1-yl) acetamide;
4-Benzyloxy-1-(4-phenyl-2-oxo-butyl)-azetidin-2-one;
4-Phenoxy-1-(4-phenyl-2-oxo-butyl)-azetidin-2-one;

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N-[6-(naphth-1-yl)-5-hexyn-1-yl]-4-benzylthio-2-oxoazetidin-1-yl acetamide;
N-[6-(Naphth-1-yl)-5-hexyn-1-yl]-4-benzylsulphinyl-2-oxoazetidin-1-yl acetamide (diastereoisomer 1);
N-[6-(Naphth-1-yl)-5-hexyn-1-yl]-4-benzylsulphinyl-2-oxoazetidin-1-yl acetamide (diastereoisomer 2);
N-[6-(3-Chlorophenyl)hexyn-5-yl]-(4-benzylthio-2-oxo-azetidin-1-yl)acetamide;
N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylthio-2-oxo-azetidin-1yl acetamide;
N-(6-Phenyl-3-hexynyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide;
Z-N-(6-phenyl-3-hexenyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide;
E-N-(6-phenyl-3-hexenyl)-(4-benzylthio-2-oxoazetidin-1-yl)acetamide;
N-(5-Phenoxypentyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide;
N-(2-(2-Phenoxyethoxy)ethyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide;
N-(2-(3-Phenylpropyloxy)ethyl)-4-benzylthio-2-oxoazetidin-1-ylacetamide;
N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide;
N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide;
N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide;
N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphinyl-2-oxo-azetidin-1-yl acetamide;
N-(6-Phenyl-3-hexynyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1);
N-(6-Phenyl-3-hexynyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2);
Z-N-(6-Phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1);
Z-N-(6-phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2);
E-N-(6-Phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 1);
E-N-(6-phenyl-3-hexenyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (diastereoisomer 2);
N-(5-phenoxypentyl)-(4-benzylsulfinyl-2-oxoazetidin-1-yl)acetamide;
N-(5-phenoxypentyl)-(4-benzylsulfinyl-2-oxoazetidin-1-yl)acetamide;
N-(2-(2-Phenoxyethoxy)ethyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1);
N-(2-(2-Phenoxyethoxy)ethyl)-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2);
N-2-(3-Phenylpropyloxy)ethyl-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 1);
N-2-(3-Phenylpropyloxy)ethyl-(4-benzylsulphinyl-2-oxoazetidin-1-yl)acetamide (Diastereoisomer 2);
N-[6-(2-Chlorophenyl)hexyn-5-yl]-4-benzylsulphonyl-2-oxo-azetidin-1-yl acetamide;
N-[6-(3-Chlorophenyl)hexyn-5-yl]-4-benzylsulphonyl-2-oxo-azetidin-1-yl acetamide;
N-(6-Phenyl-3-hexynyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide;
E-N-(6-phenyl-3-hexenyl)-(4-benzylsulphonyl-2-oxoazetidin-1-yl)acetamide;
1-(2-(6-Phenylhexyloxy)ethyl-4-benzylthio-2-oxoazetidine;
1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylthio-2-oxoazetidine;

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1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylthio-2-oxoazetidine;
N-3-(Phenoxypropyl)-4-benzylthio-2-oxoazetidine; 1-(2-Benzyloxyethyl)-4-benzylthio-azetidin-2-one;
1-(2-(6-Phenylhexyloxy)ethyl-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2);
1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 1);
1-(2-(6-(4-Chlorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2);
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 1);
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-benzylsulphinyl-2-oxoazetidine (Diastereoisomer 2);
4-Benzylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one (Diastereoisomer 1);
4-Benzylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one (Diastereoisomer 2);
1-(2-Benzyloxyethyl)-4-benzylsulphinyl-azetidin-2-one (Diastereoisomer 1);
1-(2-Benzyloxyethyl)-4-benzylsulphinyl-azetidin-2-one (Diastereoisomer 2);
4-Methylthio-1-(3-phenoxypropyl)azetidin-2-one;
4-Methylsulphinyl-1-(3-phenoxypropyl)azetidin-2-one;
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylthio)-2-oxoazetidine;
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (Diastereoisomer 1); and
1-(2-(6-(4-Fluorophenyl)hexyloxy)ethyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (Diastereoisomer 2).

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

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

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

26. 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.

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27. 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.

28. A method as claimed in claim 27 in which the disease state is associated with the increased involvement of monocytes, macrophages or lymphocytes.

29. A method as claimed in claim 27 in which the disease state is associated with the formation of lysophosphatidylcholine and oxidised free fatty acids.

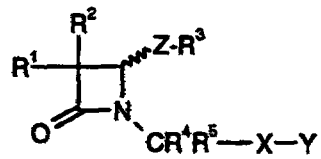
30. A method as claimed in claim 27 in which the disease state is associated with lipid peroxidation in conjunction with Lp PLA2 activity.

31. A method as claimed in claim 27 in which the disease state is associated with endothelial dysfunction.

32. A compound of formula (I) as defined in claim 1 in combination with a further therapeutically active agent selected from an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory or anti-hypertension agents for use in therapy.

33. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

(A) treating an azetidone of formula (II):



(II)

in which:

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

with an alkylating agent of the formula (III):

$$L^1CR^4R^5XY$$

(III)

in which Z is a suitable leaving group such as halogen;

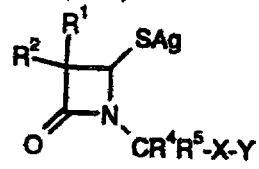
one of R^4 and R^5 is hydrogen; and

X and Y are as hereinbefore defined;

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in the presence of a suitable base such as sodium hydride or potassium hydroxide, in a suitable alkylating solvent such as tetrahydrofuran (THF), and at a temperature in the range -10 to 0°C;

(B) treating a compound of formula (VIII):



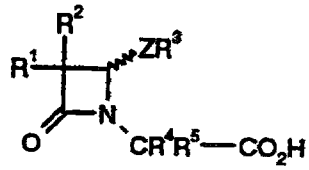
(VIII)

in which R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined;
with an alkylating agent of the formula (IX):

$$R^3Z \qquad \text{(IX)}$$

in which R^3 and Z are as hereinbefore defined;
under suitable alkylating conditions, at a temperature in the region 25°C;

(C) when X denotes a group $CONR^6(CH_2)_m$, $CONR^6X^2$, $CONR^6O(CH_2)_m$ or $CONR^6OX^2$, treating an acid of the formula (IV):



(IV)

in which:
Z, R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined;
with an amine of the formula (V):

$$NHR^6X^5Y \qquad \text{(V)}$$

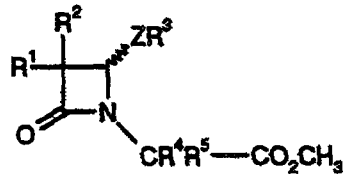
or a hydroxylamine of the formula (VI):

$$NH_2OX^5Y \qquad \text{(VI)}$$

in which X^5 is $(CH_2)_m$ or X^2 and m, R^6, Y and X^2 are as 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;

(D) when X denotes a group $COO(CH_2)_m$ or $COOX^2$, effecting a transesterification reaction with the methyl ester of formula (VII):

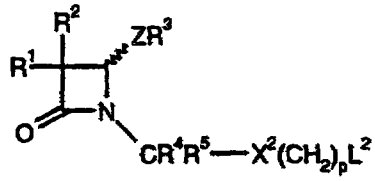


(VII)

in which:
Z, R^1, R^2, R^3, R^4 and R^5 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.

(E) when X denotes a group $COO(CH_2)_m$ or $COOX^2$, treating a compound of formula (IV) with an alcohol YX^5OH or an activated derivative thereof, for instance a tosylate; and

(F) when the linker group X contains an ether function, treating a compound of formula (VIII):



(VIII)

in which Z, R^1, R^2, R^3, R^4, R^5 and X^2 are as hereinbefore defined;
with a compound of formula (IX):

$$L^3(CH_2)_qY$$

(IX)

in which:
one of L^2 and L^3 is a halogen or other suitable leaving group such as triflate or tosylate and the other is OH or a suitable salt therof, and p and q are as hereinbefore defined;

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under standard ether forming conditions.

34. A compound of formula (I) substantially as herein before described in any one of Examples 1 to 350.

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