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(71) Applicant(s)
Avexxin AS

(72) Inventor(s)
Kokotos, George;Johansen, Berit;Magrioti, Victoria;Tsakos, Michael

(74) Agent / Attorney
Fisher Adams Kelly Pty Ltd, L 6 175 Eagle St, BRISBANE, QLD, 4000

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University of Athens, Panepistimiopolis, GR-15771 Athens (GR).

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(74) Agent: CAMPBELL, Neil; St Bride's House, 10 Salisbury Square, London EC4Y 8JD (GB).

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(71) Applicant (for all designated States except US):
AVEXXIN AS [NO/NO]; Nordahl Bruns vei 2A, N-7052 Trondheim (NO).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KOKOTOS, George [GR/GR]; Department of Chemistry, University of Athens, Panepistimiopolis, GR-15771 Athens (GR). JOHANSEN, Berit [NO/NO]; Department of Biology, Norwegian University of Science and Technology, N-7491 Trondheim (NO). MAGRIOTI, Victoria [GR/GR]; Department of Chemistry, University of Athens, Panepistimiopolis, GR-15771 Athens (GR). TSAKOS, Michael [GR/GR]; Department of Chemistry,

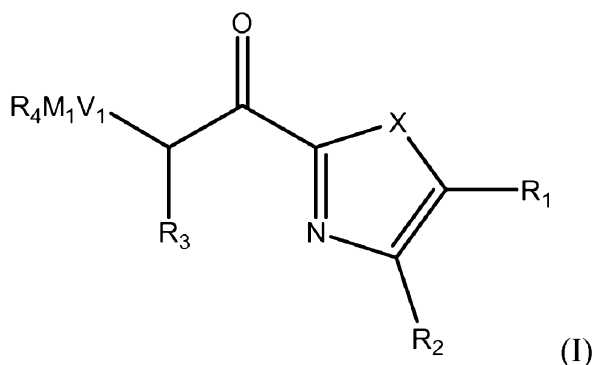
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(54) Title: ANTI INFLAMMATORY 2-OXOTHIAZOLES AND 2 -OXOOXAZOLES



(57) Abstract: A compound of formula (I) wherein X is O or S; R₁ is H, OH, SH, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, halo, haloC₁₋₆alkyl, CN, C₁₋₆-alkyl, OC₁₋₆alkyl, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl, C₂₋₆-alkenyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, C₁₋₆alkyl-C₆₋₁₀aryl, heterocyclyl, heteroaryl, CONH₂, CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, OCOC₁₋₆alkyl, or is an acidic group, such as a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group; R₂ is as defined for R₁ or R₁ and R₂ taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R₅; R₃ is H, halo (preferably fluoro), or CHaI₃ (preferably CF₃); each R₅ is defined as for R₁; V₁ is a covalent bond or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆alkyl), S, SO, or SO₂; M₁ is absent or is a C₅₋₁₀ cyclic group or a C₅₋₁₅ aromatic group; and R₄ is H, halo, OH, CN, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, haloC₁₋₆alkyl, a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group, said C₁₋₂₀alkyl or C₂₋₂₀alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆alkyl), S, SO, or SO₂; with the proviso that the group V₁M₁R₄ as a whole provides at least 4 backbone atoms from the C(R₃) group; or a salt, ester, solvate, N-oxide, or prodrug thereof; for use in the treatment of a chronic inflammatory condition.



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ANTI INFLAMMATORY 2-OXOTHIAZOLES AND 2 -OXOOXAZOLES

This invention relates to the use of various 2-oxothiazole or 2-oxooxazole compounds for use in the prevention or treatment of chronic inflammatory disorders such as glomerulonephritis, rheumatoid arthritis and psoriasis. The invention also relates to certain new 2-oxothiazole or 2-oxo-oxazole compounds, pharmaceutical compositions comprising said compounds and to new processes for the manufacture thereof.

Mammalian cells contain a large number of phospholipases that hydrolyse phospholipids in a structurally specific manner for production of a myriad of products, many of which have potent biological activity. There has been considerable interest in characterising these enzymes because of their role in production of lipid mediators of inflammation. Since the first studies 20 years ago showing that mammalian cells contain a cytosolic calcium dependent phospholipase specific for arachidonic acid, an extensive amount of evidence has substantiated a primary role for cPLA₂ as the key enzyme that mediates the release of arachidonic acid for the production of eicosanoids.

The enzyme cPLA₂ contributes to the pathogenesis of a variety of diseases particularly those in which inflammation plays a primary role implicating a role for inflammatory lipid mediators in disease pathogenesis. The inhibition therefore of such lipase enzymes offers a potential therapy for inflammatory conditions in particular chronic inflammatory conditions such as those above, psoriasis and glomerulonephritis.

The phospholipases are a group of enzymes that release unsaturated fatty acids from the sn2 position of membrane phospholipids. Once released, the fatty acids are converted by various enzymes into biologically very important signalling molecules. Release of arachidonate initiates the arachidonate cascade leading to the synthesis of eicosanoids such as prostaglandins.

Eicosanoids are important in a variety of physiological processes and play a central role in inflammation. In *Inflammation*, Vol. 18, No. 1 1994, Andersen et al identify the presence of certain phospholipases in psoriatic human skin.

It is therefore believed that inhibition of phospholipase enzymes should have potential in curing some of the inflammatory symptoms, including epidermal hyperproliferation due to increased leukotriene production, related to eicosanoid production and cell activation in both epidermis and dermis in psoriasis.

5 Psoriasis is a common, chronic, inflammatory skin disorder. Psoriatic tissue is characterised by chronic inflammation in both epidermis and dermis, the disease being further characterised by hyperplasia of epidermal keratinocytes, fibroblast activation, alteration of eicosanoid metabolism, and leukocyte infiltration.

10 Glomerulonephritis, also known as glomerular nephritis, abbreviated GN, is a renal disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria or as a nephrotic syndrome, acute renal failure, or chronic renal failure. Glomerulonephritis is categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types.

15 The glomerulus is a unique vascular network with three specialised types of cell: the endothelial cell, the mesangial cell and the visceral epithelial cell. Mesangial cells (MC) serve a number of functions in the renal glomerular capillary including structural support of the capillary tuft, modulation of the glomerular hemodynamics and a phagocytic function allowing removal of macromolecules and immune complexes. The proliferation of MC is a prominent feature of glomerular disease including IgA nephropathy, membranoproliferative glomerulonephritis, 20 lupus nephritis, and diabetic nephropathy.

25 Reduction of MC proliferation in glomerular disease models by treatment with, for example, a low protein diet has been shown to produce extracellular matrix expansion and glomerulosclerotic changes. MC proliferation inhibitors may therefore offer therapeutic opportunities for the treatment of proliferative glomerular disease.

30 Mesangial proliferative glomerulonephritis is a form of glomerulonephritis which involves inflammation at the kidney glomeruli. The mesangial cells which are a part of the glomerular capillaries increase in size giving the glomeruli a lumpy appearance. The disorder usually causes nephritic syndrome which represents

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protein loss in the urine. It may be present as acute, chronic or rapidly progressive glomerulonephritis and may progress to chronic renal failure.

The present inventors seek new treatments for, *inter alia*, chronic inflammatory conditions such as GN and psoriasis.

5 The present inventors have surprisingly found that certain 2-oxo-thiazoles or 2-oxo-oxazoles are ideal cPLA₂ inhibitors and offer new therapeutic routes to the treatment of chronic inflammatory disorders.

2-oxothiazole type structures are not new. In Bioorganic and Medicinal Chemistry 16 (2008) 1562-1595, there is a review of chemistry in this field. 2-oxo
10 (benz)thiazoles carrying peptides or amino acids on the 2-position (i.e. where the 2-oxo group forms part of the backbone of an amino acid) are known in the art as thrombin inhibitors.

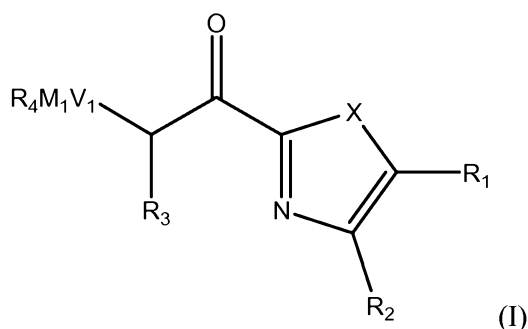
Also reported are certain hydrolase and transferase inhibitors in particular having a 2-oxo-oleyl side chain. Similar compounds as fatty acid amide hydrolase
15 inhibitors are reported in J Med Chem Vol. 51, No. 237329-7343. Their potential as inhibitors of cPLA₂ is not discussed.

A wider variety of 2-oxo-oxazole compounds are known from these papers. The majority of these compounds are either unsubstituted oxazole rings or they carry substituents in the position adjacent the oxygen atom. Their potential as inhibitors
20 of cPLA₂ is not discussed.

Never before therefore, have the compounds claimed herein been identified as potential inhibitors of phospholipase enzymes and hence no link with chronic inflammatory conditions has been made.

Thus, viewed from one aspect the invention provides a compound of formula
25 (I)

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wherein X is O or S;

R₁ is H, OH, SH, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, halo, haloC₁₋₆alkyl, CN, C₁₋₆-alkyl, OC₁₋₆alkyl, C₂₋₆-alkenyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, C₁₋₆alkylC₆₋₁₀aryl, heterocyclyl, heteroaryl, CONH₂, CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, OCOC₁₋₆alkyl, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl or is an acidic group, such as a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R₂ is as defined for R₁ or R₁ and R₂ taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R₅;

R₃ is H, halo (preferably fluoro), or CHal₃ (preferably CF₃);

each R₅ is defined as for R₁;

V₁ is a covalent bond or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆ alkyl), S, SO, or SO₂;

M₁ is absent or is a C₅₋₁₀ cyclic group or a C₅₋₁₅ aromatic group (e.g. C₆₋₁₄ aromatic group); and

R₄ is H, halo, OH, CN, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, haloC₁₋₆alkyl, a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group, said C₁₋₂₀alkyl or C₂₋₂₀alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆ alkyl), S, SO, or SO₂;

with the proviso that the group V₁M₁R₄ as a whole provides at least 4 backbone atoms from the C(R₃) group;

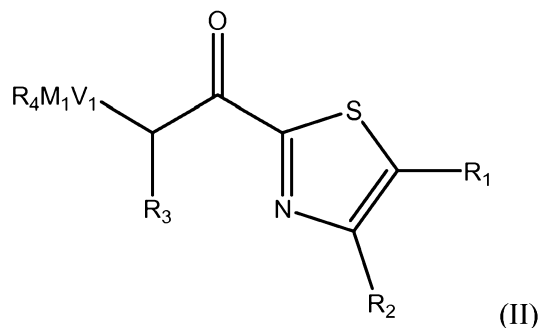
or a salt, ester, solvate, N-oxide, or prodrug thereof;

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for use in the treatment of a chronic inflammatory condition.

Viewed from another aspect the invention provides a compound of formula

(II)



5

wherein R₁, R₂, R₃, R₅ and R₄M₁V₁ are as hereinbefore defined;

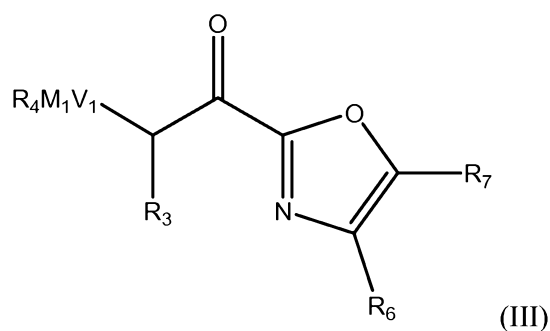
or a salt, ester, solvate, N-oxide, or prodrug thereof;

with the proviso that R₄M₁V₁C(R₃) is not oleyl.

10

Viewed from another aspect the invention provides a compound of formula

(III)



15

wherein R₆ is H, C₁₋₆alkyl, COOH, COOC₁₋₆alkyl, CONH₂, CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl;

R₇ is H;

wherein R₃ is as hereinbefore defined;

V₁ is a covalent bond or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group;

20

M₁ is a covalent bond or is a C₅₋₁₀ cyclic group or a C₅₋₁₀ aromatic group;

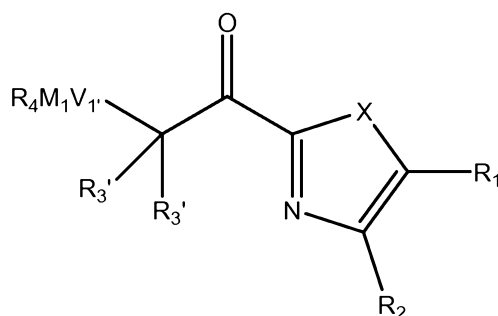
and

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R_4 is H, halo, OH, CN, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, $haloC_{1-6}alkyl$, a $C_{1-20}alkyl$ group, or C_{2-20} -mono or multiply unsaturated alkenyl group, said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6}alkyl)$, S, SO, or SO_2 ;

5 or a salt, ester, solvate, N-oxide, or prodrug thereof
with the proviso that $R_4M_1V_1C(R_3)$ is not oleyl or $-(CH_2)_6Ph$.

Viewed from another aspect the invention provides a compound of formula (I')



10

wherein X is O or S;

R_1 is H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$, $CONHC_{1-6}alkyl$, $CON(C_{1-6}alkyl)_2$, $OCOC_{1-6}alkyl$, $C_{1-6}alkylCOOH$, $C_{1-6}alkylCOOC_{1-6}alkyl$ or is an acidic group, such as a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

15

R_2 is as defined for R_1 or R_1 and R_2 taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R_5 ;

20 each $R_{3'}$ is the same or different and is H, $C_{1-6}alkylCOOR_a$ where R_a is H or $C_{1-6}alkyl$, halo (preferably fluoro), or $CHal_3$ (preferably CF_3);

each R_5 is defined as for R_1 ;

V_1 is a covalent bond, $-NHCOC_{0-6}alkyl-$ (i.e. where NH is adjacent the $CR_{3'}$ group), a $C_{1-20}alkyl$ group, or C_{2-20} -mono or multiply unsaturated alkenyl group; said
25 alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6}alkyl)$, S, SO, or SO_2 ;

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M_1 is absent or is a C_{5-10} cyclic group or a C_{5-15} aromatic group (e.g. C_{6-14} aromatic group); and

R_4 is H, halo, OH, CN, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, $haloC_{1-6}alkyl$, a $C_{1-20}alkyl$ group, or C_{2-20} -mono or multiply unsaturated alkenyl group, said $C_{1-20}alkyl$ or $C_{2-20}alkenyl$ groups being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6}alkyl)$, S, SO, or SO_2 ;

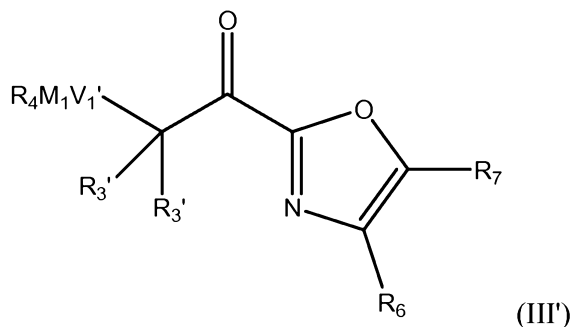
with the proviso that the group $V_1M_1R_4$ as a whole provides at least 4 backbone atoms from the $C(R_3')_2$ group;

or a salt, ester, solvate, N-oxide, or prodrug thereof

with the proviso that $R_4M_1V_1C(R_3')_2$ is not oleyl. It is also preferred if $R_4M_1V_1C(R_3')_2$ is not CH_2Ph .

The invention also concerns a compound of formula (I') as hereinbefore defined but without the disclaimer for use in the treatment of a chronic inflammatory condition.

Viewed from another aspect the invention provides a compound of formula (III')



wherein R_6 , R_7 , R_3' , V_1 , M_1 , R_4 are as hereinbefore defined;

with the proviso that $R_4M_1V_1C(R_3')$ is not oleyl or $-(CH_2)_6Ph$.

Viewed from another aspect the invention provides a pharmaceutical composition claim comprising a compound of formula (I'), (II), (III) or (III') as hereinbefore defined.

Viewed from another aspect the invention provides a compound of formula (I'), (II), (III) or (III') as hereinbefore defined for use in therapy.

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Viewed from another aspect the invention provides use of the a compound of formula (I) or (I') as hereinbefore defined in the manufacture of a medicament for the treatment of a chronic inflammatory condition.

Viewed from another aspect the invention provides a method of treating a
5 chronically inflammatory disorder comprising administering to a patient an effective amount of a compound of formula (I) or (I') as hereinbefore defined.

Definitions

10 In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl radicals and may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl.

The term "cycloalkyl" refers to an optionally substituted carbocycle
15 containing no heteroatoms, including mono-, and multicyclic saturated carbocycles, as well as fused ring systems. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "alkenyl" includes both straight and branched chain alkenyl
20 radicals. The term alkenyl refers to an alkenyl radicals one or more double bonds and may be, but is not limited to vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-pentenyl and hexenyl.

The term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring.
25 Examples and suitable values of the term "aryl" are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl, indenyl and the like.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted monocyclic or bicyclic unsaturated, aromatic ring system containing at least one heteroatom selected independently from N, O or S. Examples
30 of "heteroaryl" may be, but are not limited to thiophene, thienyl, pyridyl, thiazolyl, isothiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolonyl, oxazolonyl, thiazolonyl, tetrazolyl and thiadiazolyl,

benzoimidazolyl, benzooxazolyl, benzothiazolyl, tetrahydrotriazolopyridyl, tetrahydrotriazolopyrimidinyl, benzofuryl, thionaphthyl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolyl, , phtalazinyl, naphthyridinyl, quinoxalinyl, quinazolyl, imidazopyridyl, oxazolopyridyl, 5 thiazolopyridyl, pyridyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, cynnolyl, pteridinyl, furazanyl, benzotriazolyl, pyrazolopyridinyl, purinyl and the like.

In this specification, unless stated otherwise, the term "heterocycle" refers to an optionally substituted, monocyclic or bicyclic saturated, partially saturated or 10 unsaturated ring system containing at least one heteroatom selected independently from N, O and S, e.g. piperidinyl, morpholino, or piperazinyl.

Any cyclic group can be a cycloalkyl group, cycloalkenyl group or heterocyclic group.

Any aromatic group can be aryl or heteroaryl in nature, e.g. phenyl, naphthyl 15 or pyridyl.

An acidic group is one comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group, e.g. an C₁₋₆alkyl linked to a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group. Highly preferred acidic groups are COOH, COOC₁₋₆alkyl, or C₁₋₆alkyl substituted by COOH, COOC₁₋₆alkyl or C₆₋₁₀aryl group substituted by COOH, COOC₁₋₆alkyl. 20

Detailed Description of Invention

It is preferred if X is S and the ring system is a thiazole system. 25

It is preferred if R₁ is hydrogen.

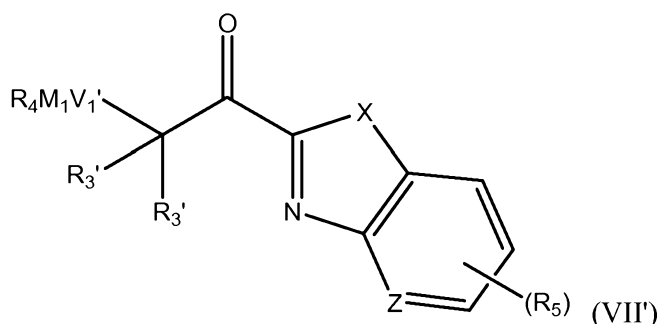
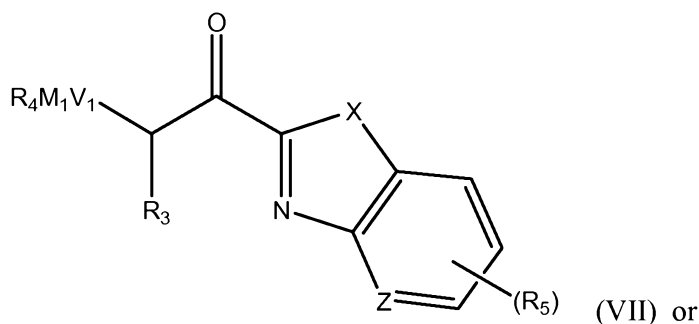
It is preferred if R₂ is hydrogen or is an acidic group, e.g. a group comprising a carboxylic group or derivative thereof (i.e. a COO group). Thus, R₂ may be COOH, or an ester, e.g. alkyl ester thereof. The acid group may also be spaced apart from the ring by some form of linking chain such as an alkylene chain or an 30 aromatic group. Highly preferred groups are COOH, COOC₁₋₆alkyl and C₁₋₆alkylCOOH.

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It is believed that the presence of a carboxyl functional group attached to the heterocyclic ring enhances interaction of the compound with the active site of the phospholipase enzyme, in particular, the side chain of arginine 200. This arginine is believed to carry a free guanidine group so any substituent which can favourably interact with this guanidine is preferred at the R₁ and/or R₂ position.

In one embodiment R₁ and R₂ can be taken together to form a ring system such as a phenyl ring or pyridine ring. Where a pyridine ring system forms the N atom is preferably in the 4-position of the ring (S=1 position, N=3, N=4). Preferably the ring system will be a carbon ring system, e.g. forming a benzothiazole type structure. If such a ring system is formed, it may be substituted preferably by 1 or 2 groups R₅. Preferences for R₅ are the same as those for R₂. Preferably the R₅ group is positioned on the 5-position of the ring (where S is the 1-position and N is the 3-position). Ideally however such a ring system is unsubstituted.

Preferred compounds in this regard are of formula (VII)



where the substituents are as hereinbefore defined and Z is C or N.

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It is especially preferred if at least one of R_1 and R_2 (especially R_1) is hydrogen. The heterocyclic ring is ideally only monosubstituted. In a further preferred embodiment both R_1 and R_2 are hydrogen.

5 R_3 is preferably hydrogen or, in a highly preferred embodiment, R_3 is halo, especially fluoro. It is believed that the presence of the F atom adjacent the carbonyl enhances the activity of the carbonyl group and may also interact favourably with the active site in the cPLA₂ enzyme, in particular IVa PLA₂.

It is preferred if one $R_{3'}$ is H. It is also preferable if one $R_{3'}$ is halo, especially fluoro. The presence of two fluoro atoms as $R_{3'}$ is also preferred. It is
10 believed that the presence of the F atom adjacent the carbonyl enhances the activity of the carbonyl group and may also interact favourably with the active site in the cPLA₂ enzyme, in particular IVa PLA₂.

The discussion of the group $V_1M_1R_4$ which follows also applies to $V_1M_1R_4$. The group $V_1M_1R_4$ as a whole provides at least 4 backbone atoms from the $C(R_3)$
15 group. Preferably, $V_1M_1R_4$ provides at least 5 backbone atoms, more preferably at least 7 backbone atoms especially at least 10 backbone atoms from the $C(R_3)$ group. For the avoidance of doubt, where there is an aromatic group in the backbone, the backbone is considered to follow the shortest route around the ring. Thus, for a 1,4-phenyl group, that would constitute 4 backbone atoms. A 1,3 linked 5 membered
20 ring in the backbone would constitute 3 backbone atoms and so on.

V_1 (or $V_{1'}$) is preferably an C_{1-15} -alkyl group, C_{2-20} -alkenyl group or is a $-C_{1-6}$ alkylO- group (i.e. where the O atom bonds to M_1). Any alkenyl group can have one or more than one double bond. Where more than one double bond is present, it is preferred if these are non conjugated. Double bonds will preferably take the cis
25 form. Preferred alkyl groups for V_1 (or $V_{1'}$) include C_{1-6} -alkyl.

It is especially preferred if any alkyl or alkenyl group in V_1 (or $V_{1'}$) is linear.

$V_{1'}$ may also represent an amide linkage NHCO which may then optionally carry an alkyl chain of up to 6 carbon atoms. That chain is preferably linear. The NH part of the linkage is adjacent the $CR_{3'}$ group.

30 Preferably M_1 is either absent or is an C_{6-10} aryl group, especially a phenyl group. Alternatively, M_1 may be a bicyclic aromatic group such as decalin. A further preferred embodiment is where M_1 represents a biphenyl group, i.e. a C_{5-15}

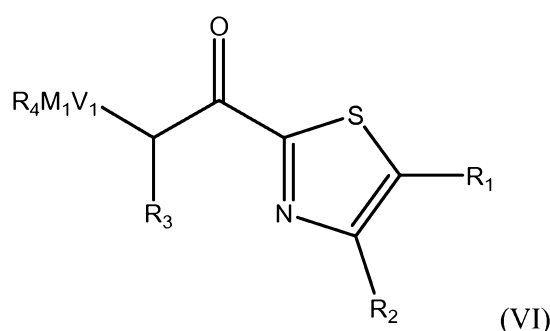
- 12 -

aromatic group in which two phenyl groups are directly linked. Where M_1 is a phenyl group, V_1 or V_1' and R_4 are preferably attached in the 1 and 4 positions of the ring, i.e. they are para to each other.

R_4 is preferably an H atom, C_{1-10} alkyl group or an C_{1-10} alkoxy group.

5 In one embodiment it is preferred in any compound of the invention that $R_4M_1V_1C(R_3)$ or $R_4M_1V_1C(R_3)_2$ is not oleyl or $-(CH_2)_6Ph$.

Thus, a still more preferred compound of the invention is of formula (VI)



10

wherein R_1 is H;

R_2 is H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, or C₁₋₆alkylCOOC₁₋₆alkyl;

R_3 is H or F;

V_1 is C₁₋₁₅-alkyl group, C₂₋₂₀-alkenyl group or is a -C₁₋₆-alkylO- group;

15 M_1 is absent or is a phenyl group;

R_4 is H, C₁₋₁₀alkyl group or an C₁₋₁₀alkoxy group.

In further highly preferred combinations:

- 20
1. V_1 is C₁₋₁₅-alkyl group or C₂₋₂₀-alkenyl group, M_1 is absent and R_4 is H.
 2. V_1 is C₁₋₆-alkyl group or is a -C₁₋₆-alkylO group, M_1 is a phenyl group, and R_4 is H or C₁₋₆ alkoxy (where the O atom is adjacent the M_1 group);
 3. $R_4V_1M_1$ represents a C₁₀₋₂₀ linear alkyl group.

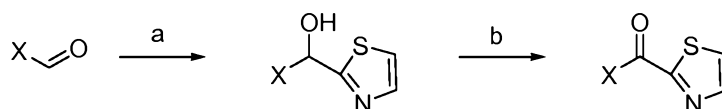
Also preferred are options 1-3 above in which V_1 is V_1' .

25 In a highly preferred embodiment, the invention provides the compounds in the examples.

Synthesis

The manufacture of the compounds of the invention typically involves known literature reactions. For example, the formation of an 2-oxothiazole, the precursor to many of the claimed compounds, can be achieved by reaction of an aldehyde XCOH with thiazole in the presence of a base and subsequent oxidation of the hydroxyl to a ketone. The X group is obviously selected to form the desired $R_4M_1V_1$ or $R_4M_1V_{1'}$ group or a precursor thereof.

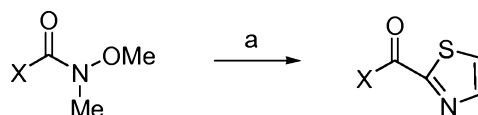
These reactions are summarised in Scheme 1 below.



Scheme 1. (a) thiazole, *base*; (b) oxidation, e.g. Dess-Martin periodinane.

It will be appreciated that in the scheme above and many of those below, specific reagents and solvents may be mentioned to aid the skilled man in carrying out the reactions described. The skilled man will appreciate however that a variety of different conditions, reagents, solvents, reactions etc could be used to effect the chemistry described and the conditions quoted are not intended to be limiting on the reactions described.

An alternative strategy involves the reaction of an alkoxy amide $XCON(Oalkyl)$ with thiazole in base which affords 2-oxothiazoles directly. This reaction is summarised in scheme 2.

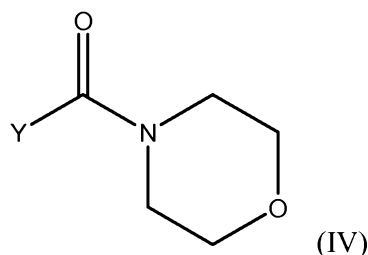


Scheme 2. (a) thiazole, *base*.

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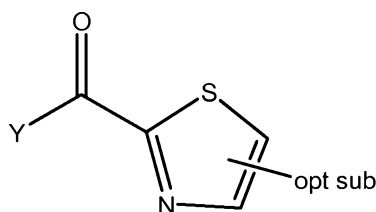
The inventors have however found a new and preferred way of forming 2-oxothiazoles and this forms a still yet further aspect of the invention. The new process involves the reaction of an oxo-morpholino structure with thiazole, typically in the presence of a base. This reaction affords 2-oxo thiazoles directly and is a new reaction.

Thus viewed from another aspect the invention provides a process for the formation of a 2-oxothiazole comprising reacting a compound of formula (IV)



wherein Y is an organic group, e.g. a group $R_4M_1V_1CH(R_3)$,

with an optionally substituted thiazole in the presence of a base so as to form an optionally substituted compound of formula (V)



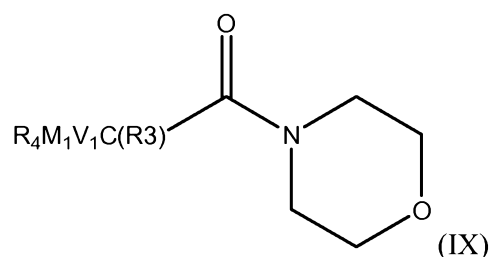
This reaction is effected in the presence of a base, e.g. nBuLi or the like. Ideally, the reaction is effected at low temperature, e.g. at 0°C or below so in an ice bath, or other known cooling system, e.g. liquid ammonia.

It will be appreciated that this reaction is preferably used to form compounds of formula (I) or (II) or (III) or their (I')/(III') analogues and this forms a still further aspect of the invention. It will be preferred therefore if the definition of Y reflects the group $R_4M_1V_1CH(R_3)$ or $R_4M_1V_1C(R_3)_2$ or forms a precursor thereto. It will also be preferred if the thiazole used reflects the preferred thiazole reactant required to make a compound of the invention, i.e. carrying the necessary R_1/R_2 substituents

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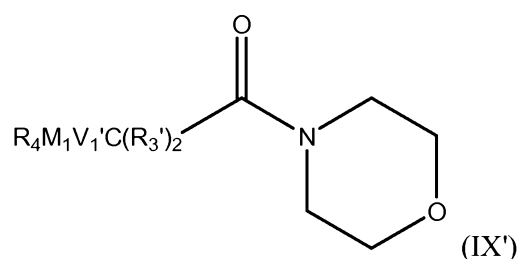
etc. The reaction is however more generally applicable so variable Y is broadly defined and the thiazole may be optionally substituted.

It is believed that the morpholino intermediates used in this reaction are new and these form a further aspect of the invention. Thus, viewed from another aspect
5 the invention provides an intermediate compound of formula (IX)



wherein $R_4M_1V_1CH(R_3)$ is as hereinbefore defined.

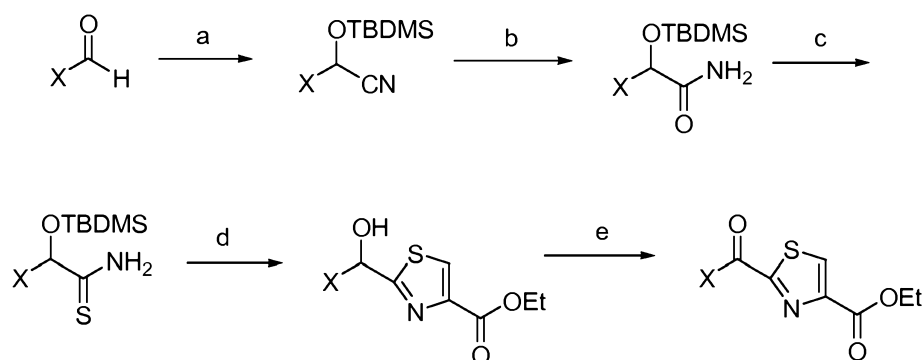
10 Viewed from another aspect the invention provides an intermediate compound of formula (IX')



15 wherein $R_4M_1V_1C(R_3)_2$ is as hereinbefore defined.

There are still further ways of developing a 2-oxo thiazole ring carrying a substituent. The ring itself can be generated from a thioamide as described in scheme 3.

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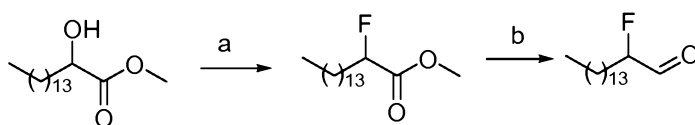


Scheme 3. (a) TBDMSCN, KCN; (b) H₂O₂, Bu₄NHSO₄; (c) Lawesson's reagent; (d) BrCH₂COCOOEt; (e) Dess Martin periodinane.

5

As noted above, an interesting class of compounds of the invention are those having a fluoro atom adjacent the carbonyl. This is conveniently introduced before attachment of the ring system by conventional chemistry. A hydroxy group may be converted to a fluoro group using Diethylaminosulfur trifluoride (DAST) for example. This chemistry is elucidated below:

10



15

Scheme 4. (a) DAST (b) i. LiAlH₄, ii. (COCl)₂,

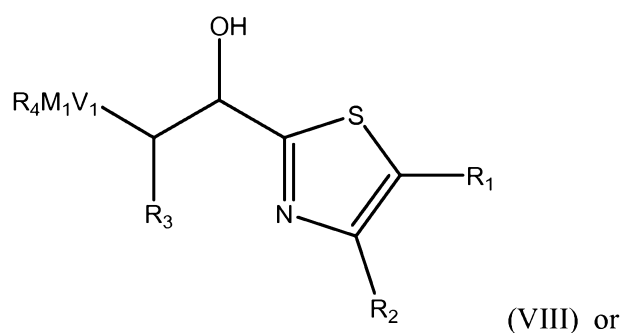
The formed compound can react with thiazole as described above. Variations of the substituents on the heterocyclic rings and manipulation of the side chain binding the carbonyl can be achieved using all manner of synthetic techniques which the skilled man will know. Guidance is offered in the examples as to how to make a wide variety of compounds and the principles described can be extended to the compounds encompassed by the claims.

20

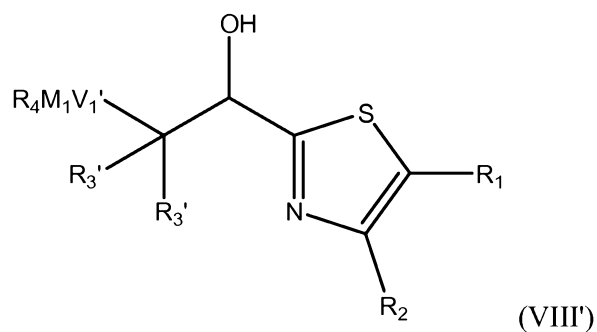
The principles described above for preparing thiazoles can be extended to the oxazole species.

Intermediates

Various intermediates are also new and form a further aspect of the invention. In particular, the invention covers the reduced analogue of the final 2-oxoheterocycle, i.e. a 2-hydroxy analogue. Thus, viewed from another aspect the invention provides a compound of formula (VIII)



10



wherein R_1 , R_2 , R_3 , R_3' , R_5 and $R_4M_1V_1$ / $R_4M_1V_1'$ are as hereinbefore defined;

or a salt, ester, solvate, N-oxide, or prodrug thereof;

preferably with the proviso that $R_4M_1V_1C(R_3)$ or $R_4M_1V_1C(R_3)_2$ is not oleyl.

Chronic Inflammatory Disorders

The compounds of the invention are used in the treatment of chronic inflammatory disorders, in particular those associated with phospholipase inhibition.

Preferably, any compound of the invention will achieve 90% inhibition against IVa PLA₂.

Preferably, compounds of the invention inhibit IVa cPLA₂ at a low μ M range such as 5 μ M or less, preferably 4 μ M or less.

5 It is further preferred that the compounds of the invention show greater inhibition of IVa cPLA₂ than iPLA₂ or sPLA₂ according to published assays for these enzymes (see, for example, Yang, H et al. (1999) *Anal. Biochem.* 269: 278). Ideally, the compounds of the invention show limited or no inhibition of iPLA₂ or sPLA₂ and they are therefore highly specific for the IVa cPLA₂ enzyme.

10 Specific diseases of interest are glomerulonephritis, inflammatory dermatoses such as psoriasis and rheumatoid arthritis.

Further conditions of interest include other inflammatory dermatoses such as atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, pityriasis rosea, lichen planus and drug eruptions.

15 Furthermore the compounds of the invention may have use in the treatment of other types of arthritis and dermatoses, inflammatory CNS diseases, multiple sclerosis, chronic obstructive pulmonary disease, chronic lung inflammatory conditions, inflammatory bowel disease such as ulcerative colitis and crohns disease and cardiovascular disease.

20 Thus viewed from a further aspect the invention provides for the treatment of any of the conditions listed above using the compounds of the invention.

Formulation

25 The compounds of the invention are preferably formulated as pharmaceutically acceptable compositions. The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when
30 administered to a mammal (e.g. human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the

Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans.

The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is
5 administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th
10 Edition, incorporated by reference. Particularly preferred for the present invention are carriers suitable for immediate-release, i.e., release of most or all of the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible.

The compounds of the invention can be administered in salt, solvate, prodrug
15 or ester form, especially salt form. Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula (I) and the resulting mixture
20 evaporated to dryness (lyophilised) to obtain the acid addition salt as a solid. Alternatively, a compound of formula (I) may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether
25 or hexane, and isolated by filtration.

Suitable addition salts are formed from inorganic or organic acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, trifluoroacetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate,
30 gluconate, succinate, pyruvate, oxalate, oxaloacetate, trifluoroacetate, saccharate, benzoate, alkyl or aryl sulphonates (eg methanesulphonate, ethanesulphonate, benzenesulphonate or p-toluenesulphonate) and isethionate. Representative

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examples include trifluoroacetate and formate salts, for example the bis or tris trifluoroacetate salts and the mono or diformate salts, in particular the tris or bis trifluoroacetate salt and the monoformate salt.

Those skilled in the art of organic chemistry will appreciate that many
5 organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compounds of the invention are within the scope of the invention. The salts of the compound of Formula (I) may form solvates (e.g. hydrates) and the invention
10 also includes all such solvates.

The term "prodrug" as used herein means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects.

The compounds of the invention are proposed for use in the treatment of,
15 inter alia, chronic inflammatory disorders. By treating or treatment is meant at least one of:

- (i). preventing or delaying the appearance of clinical symptoms of the disease developing in a mammal;
20
- (ii). inhibiting the disease i.e. arresting, reducing or delaying the development of the disease or a relapse thereof or at least one clinical or subclinical symptom thereof, or
- (iii). relieving or attenuating one or more of the clinical or subclinical symptoms of
25 the disease.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician. In general a skilled man can appreciate when "treatment" occurs.

30 The word "treatment" is also used herein to cover prophylactic treatment, i.e. treating subjects who are at risk of developing a disease in question.

The compounds of the invention can be used on any animal subject, in particular a mammal and more particularly to a human or an animal serving as a model for a disease (e.g. mouse, monkey, etc.).

5 An "effective amount" means the amount of a compound that, when administered to an animal for treating a state, disorder or condition, is sufficient to effect such treatment. The "effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated and will be ultimately at the discretion of the attendant doctor.

10 While it is possible that, for use in the methods of the invention, a compound of formula I may be administered as the bulk substance, it is preferable to present the active ingredient in a pharmaceutical formulation, for example, wherein the agent is in admixture with a pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

15 The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable
20 or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition. The choice of pharmaceutical carrier can be
25 selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, in addition to, the carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

30 It will be appreciated that pharmaceutical compositions for use in accordance with the present invention may be in the form of oral, parenteral, transdermal, inhalation, sublingual, topical, implant, nasal, or enterally administered (or other mucosally administered) suspensions, capsules or tablets, which may be formulated

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in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

There may be different composition/formulation requirements depending on the different delivery systems. Likewise, if the composition comprises more than
5 one active component, then those components may be administered by the same or different routes.

The pharmaceutical formulations of the present invention can be liquids that are suitable for oral, mucosal and/or parenteral administration, for example, drops, syrups, solutions, injectable solutions that are ready for use or are prepared by the
10 dilution of a freeze-dried product but are preferably solid or semisolid as tablets, capsules, granules, powders, pellets, pessaries, suppositories, creams, salves, gels, ointments; or solutions, suspensions, emulsions, or other forms suitable for administration by the transdermal route or by inhalation.

The compounds of the invention can be administered for immediate-,
15 delayed-, modified-, sustained-, pulsed-or controlled-release applications.

In one aspect, oral compositions are slow, delayed or positioned release (e.g., enteric especially colonic release) tablets or capsules. This release profile can be achieved without limitation by use of a coating resistant to conditions within the stomach but releasing the contents in the colon or other portion of the GI tract
20 wherein a lesion or inflammation site has been identified or a delayed release can be achieved by a coating that is simply slow to disintegrate or the two (delayed and positioned release) profiles can be combined in a single formulation by choice of one or more appropriate coatings and other excipients. Such formulations constitute a further feature of the present invention.

25 Pharmaceutical compositions can be prepared by mixing a therapeutically effective amount of the active substance with a pharmaceutically acceptable carrier that can have different forms, depending on the way of administration.

Typically composition components include one or more of binders, fillers, lubricants, odorants, dyes, sweeteners, surfactants, preservatives, stabilizers and
30 antioxidants.

The pharmaceutical compositions of the invention may contain from 0.01 to 99% weight - per volume of the active material. The therapeutic doses will generally

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be between about 10 and 2000 mg/day and preferably between about 30 and 1500 mg/day. Other ranges may be used, including, for example, 50-500 mg/day, 50-300 mg/day, 100-200 mg/day.

Administration may be once a day, twice a day, or more often, and may be
5 decreased during a maintenance phase of the disease or disorder, e.g. once every second or third day instead of every day or twice a day. The dose and the administration frequency will depend on the clinical signs, which confirm maintenance of the remission phase, with the reduction or absence of at least one or more preferably more than one clinical signs of the acute phase known to the person
10 skilled in the art.

It is within the scope of the invention for a compound as described herein to be administered in combination with another pharmaceutical, e.g. another drug with known efficacy against the disease in question. The compounds of the invention may therefore be used in combination therapy.

15 The invention will now be further described with reference to the following non limiting examples:

The chemistry described in the following schemes is used to manufacture the compounds described in the tables which follow. The starting materials in each scheme are readily available compounds. In general, molar equivalents of each
20 reactant are employed.

The chemistry described in the following schemes is used to manufacture the compounds described in the tables which follow. The starting materials in each scheme are readily available compounds. In general, molar equivalents of each reactant are employed.

25

Experimental procedures for the formation of compounds

A. To a solution of thiazole (1.1 mmol) in dry THF (2 mL) under argon atmosphere and at -78 °C, n-BuLi solution (1.1 mmol, 2.5 M in hexanes) was
30 added dropwise over a period of 5 min. After stirring at -78 °C for 30 min, a solution of the appropriate aldehyde (1 mmol) in dry THF (2 mL) was added and the mixture was stirred for additional 4 hours at -78 °C. Then, H₂O was

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added and the mixture was extracted thrice with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) afforded the desired product.

- 5 B. To a solution of the hydroxy-heterocycle (1 mmol) in dry CH_2Cl_2 (10 mL), Dess-Martin periodinane was added (1.5 mmol) and the mixture was stirred for 1 h at rt. The organic solution was washed with 10% aqueous NaHCO_3 , dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column-chromatography using the appropriate mixture of EtOAc: petroleum ether (40-60 °C) as eluent.
- 10 C. To a stirred solution of the carboxylic acid (1 mmol) in CH_2Cl_2 (7 mL), 4-dimethylaminopyridine (DMAP) (1 mmol), *N,O*-dimethyl hydroxylamine hydrochloride (1 mmol), *N*-methylmorpholine (1 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride (WSCl.HCl) (1 mmol) were added consecutively at room temperature. The reaction mixture was left stirring for 18 h. It was then washed with an aqueous solution of 10% citric acid (3 x 10 mL), brine (10 mL), an aqueous solution of NaHCO_3 5% (3 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The amide was purified by flash chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 15 20
- 25 D. To a stirred solution of acid (1 mmol) in dry CH_2Cl_2 (7 mL), DMF (0.5 eq.) was added followed by oxalyl chloride (3 mmol) at room temperature. The reaction mixture was left stirring for 3 h. The solvent was removed and dry Et_2O (7 mL) was added and cooled at 0 °C. Pyridine (5 mmol) was added drop-wise, followed by drop-wise addition of morpholine (5 mmol). The reaction mixture was left stirring for 18 h at room temperature. Then, H_2O (8 mL) was added and it was left stirring for 30 min. The layers were separated and the organic layer was washed with an aqueous solution of HCl 1N (3 x 10 mL), brine (1 x 10 mL), an aqueous solution of NaHCO_3 5% (3 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography
- 30

- 25 -

eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) afforded the desired product.

- 5 E. To a stirred solution of thiazole or benzothiazole (3 mmol) in dry Et₂O (20 mL) at -78 °C under a dry argon atmosphere was added a solution of *n*-BuLi (1.6 M in hexanes, 3 mmol) drop-wise over a period of 10 min. The resulting orange solution was stirred for 45 min. Then, a solution of the amide (1 mmol) in dry Et₂O (2 mL) was slowly added giving the mixture a dark brown color. After stirring for 30 min. at -78 °C, the mixture was allowed to warm up to room temperature over a period of 2 h. Then, saturated aqueous ammonium chloride solution was added and the mixture was extracted with ether (2 x 10 mL). The combined extracts were washed with brine and then dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) afforded the desired product.
- 10 F. To a stirred solution of the ester (1 mmol) in dry Et₂O (10 mL) was added dropwise DIBALH (1.1 mL, 1.0 M in hexane, 1.1 mmol) at 0 °C. The reaction was stirred for 10 min and then quenched with H₂O. The mixture was stirred for 30 min, dried over Na₂SO₄, and filtered through a pad of Celite. The solvent was evaporated and the crude product was purified by silica gel column chromatography.
- 15 G. To a solution of the alcohol (1 mmol) in a mixture of toluene-EtOAc (6 mL), a solution of NaBr (1.05 mmol) in water (0.5 mL) was added, followed by AcNH-TEMPO (0.01 mmol). To the resulting biphasic system, which was cooled at -5 °C, an aqueous solution of 0.35 M NaOCl (3.14 mL, 1.10 mmol) containing NaHCO₃ (3 mmol) was added dropwise while stirring vigorously at -5 °C over a period of 1 h. After the mixture had been stirred for a further 15 min at 0 °C, EtOAc (6 mL) and H₂O (2 mL) were added. The aqueous layer was separated and washed with EtOAc (4 mL). The combined organic layers were washed consecutively with 5% aqueous citric acid (6 mL) containing 5% KI, 10% aqueous Na₂S₂O₃ (6 mL), and brine and dried over Na₂SO₄. The solvents were evaporated under reduced pressure, and the residue was used immediately in the next step without any purification.
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- 25
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- 5 H. A solution of the aldehyde (1 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of *tert*-butyl dimethylsilylcyanide (1 mmol), potassium cyanide (0.17 mmol) and 18-crown-6 (0.4 mmol) under argon atmosphere. The mixture was stirred for 1 h. The solvent was evaporated and the crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 10 I. To a solution of the cyanide (1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 30% H_2O_2 (0.5 mL), tetrabutylammonium hydrogen sulfate (0.2 mmol) and an aqueous solution of 0.5 N NaOH (1.2 mmol). The reaction mixture was stirred in a sealed flask for 18 h during which additional H_2O_2 (0.5 mL) were added thrice. H_2O and CH_2Cl_2 were added and the organic layer was separated, washed with brine and dried over Na_2SO_4 . The crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 15 J. Lawesson's reagent (0.6 mmol) was added to a solution of the amide (1 mmol) in dry toluene (10 mL) under argon atmosphere. The reaction mixture was stirred for 18 h at room temperature. The solvent was evaporated and the crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 20 K. To a solution of the thioamide (1 mmol) in ethanol (3.2 mL) under argon atmosphere, was added ethyl bromopyruvate or ethyl 4-chloroacetoacetate (1 mmol) and concentrated H_2SO_4 (10 μL). The reaction mixture was stirred for 18 h. The solvent was evaporated and the crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 25 L. To a solution of the hydroxyl heterocyclic ester (1 mmol) in EtOH (25 mL), an aqueous solution of 1 N NaOH (20 mmol, 20 mL) was added. After stirring for 1 h, the solution was acidified with aqueous solution of 1N HCl and the product was extracted with Et_2O . The organic layer was separated,
- 30

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washed with brine and dried over Na_2SO_4 . The product was used in the next step without any purification.

- 5 M. To a solution of the oxo heterocyclic ester (1 mmol) in EtOH (25 mL), an aqueous solution of 20% Cs_2CO_3 (20 mmol, 20 mL) was added. After stirring for 18 h, the solution was acidified with aqueous solution of 1N HCl and the product was extracted with Et_2O . The organic layer was separated, washed with brine and dried over Na_2SO_4 . The product was purified by recrystallization.
- 10 N. To a stirred solution of LiAlH_4 (1M in THF, 2.9 mmol) in dry Et_2O (5.5 mL) under argon atmosphere and at $-20\text{ }^\circ\text{C}$ a solution of the ester (1 mmol) in dry Et_2O (5.5 mL) was added. The reaction was stirred for 20 min at $-20\text{ }^\circ\text{C}$ and for 20 min at rt. Then, it was cooled at $0\text{ }^\circ\text{C}$ and quenched with H_2O . The mixture was stirred for 30 min at rt. Then, additional H_2O was added and the mixture was acidified with 1 N HCl to pH 5. The aqueous layer was washed
- 15 twice with Et_2O , and then the combined organic layers were washed with brine, dried over Na_2SO_4 , and the solvent was evaporated. The crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether ($40\text{-}60\text{ }^\circ\text{C}$) to afford the desired product.
- 20 O. To a stirred solution of the alcohol (1 mmol) in acetone (4.2 mL), K_2CO_3 (3 mmol) was added followed by a catalytic amount of KI and the appropriate bromide (1.1 mmol). The solution was refluxed for 18 h, the solvent was evaporated, and H_2O and EtOAc were added. The aqueous layer was washed twice with EtOAc and then the combined organic layers were washed with
- 25 brine, dried over Na_2SO_4 , and the solvent was evaporated. The crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether ($40\text{-}60\text{ }^\circ\text{C}$) to afford the desired product.
- 30 P. A solution of the hydroxy compound (1 mmol) in dry CH_2Cl_2 (50 mL) was treated dropwise with a solution of DAST (3 mmol) in dry CH_2Cl_2 (2 mL) under argon atmosphere and at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred for 2 h at $-78\text{ }^\circ\text{C}$ and for additional 16 h at rt. Then, a saturated solution of

- NaHCO₃ was added until the bubbling of CO₂ stopped. The solution was stirred for 20 min and then H₂O and CH₂Cl₂ were added. The organic layer was separated, dried over Na₂SO₄, filtered and evaporated, and the crude product was purified by column chromatography on silica gel eluting with EtOAc-petroleum ether (bp 40-60 °C) to yield the desired fluoro derivative.
- 5
- Q. A solution of oxalyl chloride (4 mmol) in dry CH₂Cl₂ (3 mL) under argon atmosphere and at -60 °C was treated dropwise with a solution of dry DMSO (8 mmol) in dry CH₂Cl₂ (3.5 mL). After 5 min, a solution of the fluoro alcohol (1 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise and after
- 10
- additional 15 min, dry Et₃N (16 mmol) was added. The reaction mixture was stirred for 1 h to reach room temperature. Then, the reaction mixture was poured in ice and the aqueous layer was extracted thrice with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and the solvent was evaporated. The crude product was purified by silica gel column
- 15
- chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- R. A solution of the aldehyde (1 mmol) and methyl (triphenylphosphanylidene)acetate (1.1 mmol) in dry CH₂Cl₂ (3 mL) under argon atmosphere was refluxed for 1 h and then left stirring for 16 h at rt.
- 20
- Saturated solution of NH₄Cl was added and the aqueous layer was extracted thrice with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and the solvent was evaporated. The crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C) to afford the desired product.
- 25
- S. A mixture of the unsaturated ester (1 mmol) in dry 1,4-dioxane (10 mL) and a catalytic amount of 10% palladium on activated carbon was hydrogenated for 18 h. After filtration through a pad of celite and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography eluting with the appropriate mixture of EtOAc: petroleum
- 30
- ether (40-60 °C) to afford the desired product.
- T. A solution of the aldehyde (1 mmol) and NaHSO₃ (1.5 mmol in 1.3 mL H₂O) in CH₂Cl₂ (1.2 mL) was stirred for 30 min at room temperature. After the

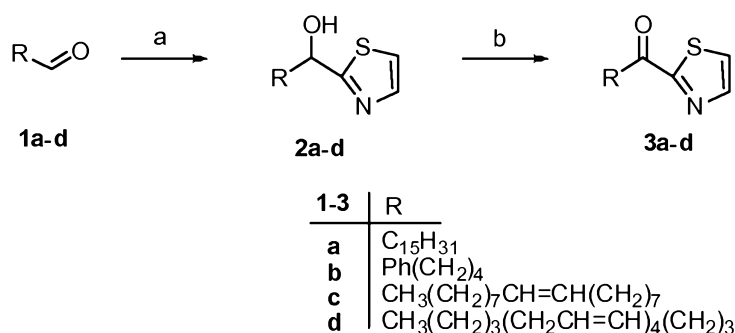
- formation of a white salt, the organic solvent was evaporated and water (1 mL) was added. The mixture was cooled to 0 °C and an aqueous solution of KCN (1.5 mmol in 1.3 mL H₂O) was added dropwise. The reaction mixture was stirred for another 18 h at room temperature and then CH₂Cl₂ and water were added. The organic layer was washed with brine and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residual oil was purified by column chromatography on silica gel eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C).
- 5
- U. The cyanhydrine (1 mmol) was treated with 6N HCl (10 mL) in MeOH for 18 h at room temperature. The organic solvent was evaporated and a saturated aqueous solution of K₂CO₃ was added to pH neutralization. After extraction with CH₂Cl₂ (3 × 15 mL), the combined organic phases were washed with brine and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residual oil was purified by column chromatography on silica gel eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C).
- 10
- 15
- V. To a stirred solution of the Z-protected amino compound (1 mmol) in MeOH (8 mL) were added successively a catalytic amount of 10% Pd/C and anhydrous ammonium formate (5 mmol). After stirring for 2 h at rt, the reaction mixture was filtered over celite. The organic layer was then concentrated under reduced pressure to yield the crude product, which was used without any further purification.
- 20
- W. To a stirred solution of phenylacetic acid (1.0 mmol) and the amino component (1.0 mmol) in dry CH₂Cl₂ (10 mL), Et₃N (1.1 mmol) and subsequently 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (WSCl) (1.1 mmol) and 1-hydroxybenzotriazole (HOBt) (1.0 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and overnight at rt. The solvent was evaporated under reduced pressure and EtOAc (20 mL) was added. The organic layer was washed consecutively with brine, 1N HCl, brine, 5% NaHCO₃, and brine, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography on
- 25
- 30

- 30 -

silica gel eluting with the appropriate mixture of EtOAc: petroleum ether (40-60 °C).

X. A solution of the *tert*-butyl ester derivative (1 mmol) in 50% TFA/CH₂Cl₂ (10 mL) was stirred for 1 h at room temperature. The organic solvent was evaporated under reduced pressure to afford the desired product.

Compounds 1-3

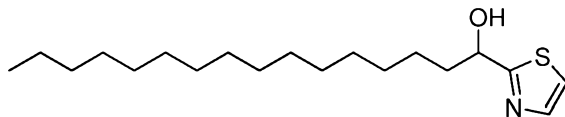


(a) thiazole, *n*-BuLi, dry THF, -78 °C; (b) Dess-Martin periodinane, dry CH₂Cl₂.

Characterising data:

1-(Thiazol-2-yl)hexadecan-1-ol (2a)

Procedure A



White solid. Yield 51%.

m.p. 69-71°C

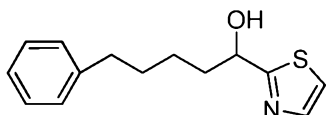
¹H NMR: δ 7.68 (d, 1H, *J* = 2.8 Hz, ArH), 7.25 (d, 1H, *J* = 2.8 Hz, ArH), 4.97 (m, 1H, CHOH), 3.14 (br s, 1H, OH), 1.86 (m, 2H, CH₂CHOH), 1.48-1.13 (m, 26H, 13 x CH₂), 0.86 (t, 3H, *J* = 6.2 Hz, CH₃).

- 31 -

^{13}C NMR: δ 175.6, 142.0, 118.8, 71.8, 38.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 25.2, 22.7, 14.1.

5-Phenyl-1-(thiazol-2-yl)pentan-1-ol (2b)

5 Procedure A



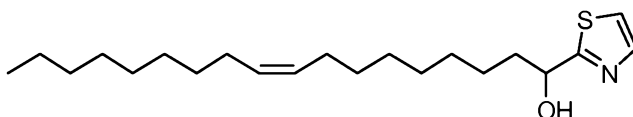
Colorless Oil. Yield 42%.

^1H NMR: δ 7.65 (d, 1H, $J = 3.4$ Hz, ArH), 7.33-7.16 (m, 6H, Ph, ArH), 4.97 (m, 1H, CHOH), 4.5 (br, 1H, OH), 2.62 (t, 2H, $J = 7.0$ Hz, CH_2Ph), 2.05-1.80 (m, 2H, CH_2CHOH), 1.74-1.45 (m, 4H, 2 x CH_2).

^{13}C NMR: δ 176.3, 142.3, 141.8, 128.3, 128.2, 125.6, 118.7, 71.4, 37.9, 35.7, 31.1, 24.9.

(Z)-1-(Thiazol-2-yl)octadec-9-en-1-ol (2c)

15 Procedure A



$\text{C}_{21}\text{H}_{37}\text{NOS}$

White oil.

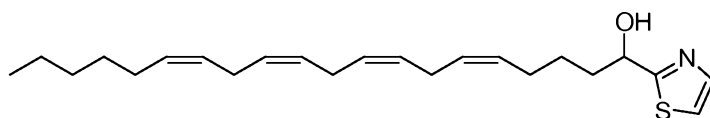
^1H NMR (CDCl_3) δ : 7.69 (d, 1H, $J = 3.4$ Hz, CHN), 7.28 (d, 1H, $J = 3.4$ Hz, CHS), 5.34 (m, 2H, $\text{CH}=\text{CH}$), 4.97 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 5.2$ Hz, CHOH), 3.47 (b, 1H, OH), 2.00 (m, 6H, 3x CH_2), 1.60-1.10 (m, 22H, 11x CH_2), 0.88 (t, 3H, $J = 6.2$ Hz, CH_3).

^{13}C NMR (CDCl_3) δ : 175.7, 142.0, 129.9, 129.8, 118.7, 71.8, 38.3, 31.9, 29.7, 29.5, 29.3, 29.2, 27.1, 25.2, 22.6, 14.1.

(5Z,8Z,11Z,14Z)-1-(Thiazol-2-yl)icosa-5,8,11,14-tetraen-1-ol (2d)

25 Procedure A

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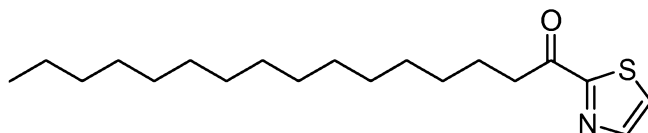
 $C_{23}H_{35}NOS$

MW: 373.60.

White oil.

5 1H NMR ($CDCl_3$) δ : 7.64 (d, 1H, $J = 3.0$ Hz, ArH), 7.23 (d, 1H, $J = 3.0$ Hz, ArH), 5.56-5.21 (m, 8H, 4 x CH=CH), 4.96 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 5.0$ Hz, CHOH), 4.20-3.90 (br, 1H, OH), 2.98-2.63 (m, 6H, 3 x CHCH₂CH), 2.18-1.79 (m, 6H, 3 x CH₂), 1.69-1.18 (m, 8H, 4 x CH₂), 0.90 (t, 3H, $J = 6.6$ Hz, CH₃).

10 ^{13}C NMR ($CDCl_3$) δ : 175.8, 141.9, 130.4, 129.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.5, 118.7, 71.5, 37.7, 31.4, 29.2, 27.1, 26.8, 25.5, 25.4, 25.1, 22.5, 14.0.

MS (ESI) m/z (%) : 373 [M^+ , 100].**1-(Thiazol-2-yl)hexadecan-1-one (3a)****Procedure B**

15

 $C_{19}H_{33}NOS$

MW: 323.54.

White solid.

m.p.: 39-41 °C

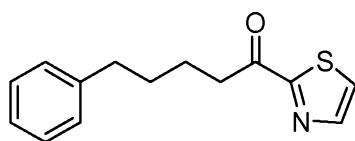
20 1H NMR (200 MHz, $CDCl_3$) δ = 7.98 (d, 1H, $J = 3.0$ Hz, ArH), 7.65 (d, 1H, $J = 3.0$ Hz, ArH), 3.14 (t, 2H, $J = 7.4$ Hz, CH₂CO), 1.81-1.68 (m, 2H, CH₂CH₂CO), 1.42-1.10 (m, 24H, 12 x CH₂), 0.86 (t, 3H, $J = 5.0$ Hz, CH₃).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 194.1, 167.3, 144.6, 126.0, 38.5, 31.9, 29.6, 29.4, 29.3, 29.2, 24.0, 22.7, 14.1.

25 MS (ESI) m/z (%) : 324 [$M+H$, 100]⁺.

5-Phenyl-1-(thiazol-2-yl)pentan-1-one (3b)**Procedure B**

- 33 -

C₁₄H₁₅NOS

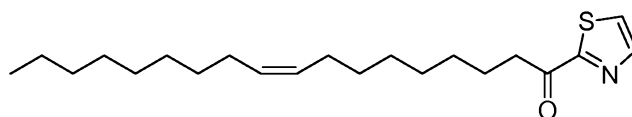
MW: 245.34.

Yellow oil.

5 ¹H NMR (200 MHz, CDCl₃) δ = 8.00 (d, 1H, J = 3.0 Hz, ArH), 7.66 (d, 1H, J = 2.8 Hz, ArH), 7.33-7.13 (m, 5H, Ph), 3.21 (t, 2H, J = 6.6 Hz, CH₂CO), 2.68 (t, 2H, J = 7.6 Hz, PhCH₂), 1.92-1.65 (m, 4H, 2 x CH₂).

¹³C NMR (50 MHz, CDCl₃) δ = 193.8, 167.1, 144.5, 142.0, 128.3, 128.2, 126.1, 125.6, 38.2, 35.6, 30.9, 23.6.

10

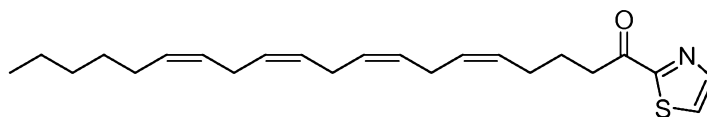
(Z)-1-(Thiazol-2-yl)octadec-9-en-1-one (3c)**Procedure B**C₂₁H₃₅NOS

15 Yellowish oil.

¹H NMR (CDCl₃) δ : 8.00 (d, 1H, J = 3.0 Hz, CHN), 7.66 (d, 1H, J = 3.0 Hz, CHS), 5.34 (m, 2H, CH=CH), 3.16 (t, 2H, J = 8.0 Hz, CH₂CO), 2.01 (m, 4H, 2xCH₂CH=), 1.80-1.60 (m, 2H, CH₂), 1.60-1.10 (m, 20H, 10xCH₂), 0.88 (t, 3H, J = 6.2 Hz, CH₃).

¹³C NMR (CDCl₃) δ : 194.1, 167.4, 144.6, 130.0, 129.7, 126.0, 38.5, 32.6, 31.9, 29.7, 29.5, 29.3, 29.2, 29.1, 27.2, 24.0, 22.7, 14.1.

20

(5Z,8Z,11Z,14Z)-1-(Thiazol-2-yl)icosa-5,8,11,14-tetraen-1-one (3d)**Procedure B**25 C₂₃H₃₃NOS

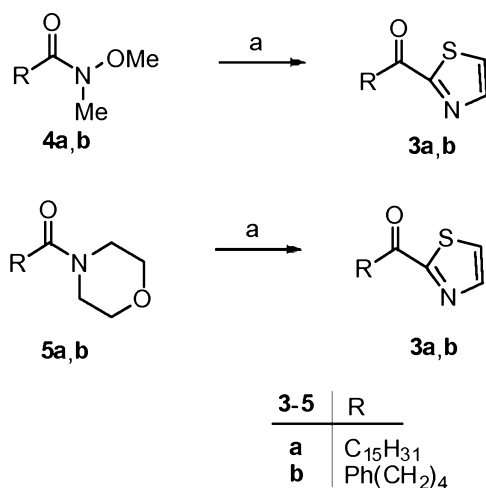
- 34 -

Yellowish oil.

^1H NMR (CDCl_3) δ : 8.00 (d, 1H, J = 2.8 Hz, ArH), 7.66 (d, 1H, J = 2.8 Hz, ArH), 5.42-5.21 (m, 8H, 4 x CH=CH), 3.19 (t, 2H, J = 7.2 Hz, CH_2CO), 2.88-2.63 (m, 6H, 3 x CHCH_2CH), 2.25-2.20 (m, 4H, 2 x CH_2), 1.45-1.17 (m, 2H, CH_2), 1.40-1.20 (m, 6H, 3 x CH_2), 0.88 (t, 3H, J = 6.4 Hz, CH_3).

^{13}C NMR (CDCl_3) δ : 193.9, 167.2, 144.6, 130.4, 129.1, 128.9, 128.5, 128.2, 128.1, 127.9, 127.5, 126.1, 37.8, 31.5, 29.3, 29.2, 27.2, 26.6, 25.6, 23.9, 22.5, 14.0.

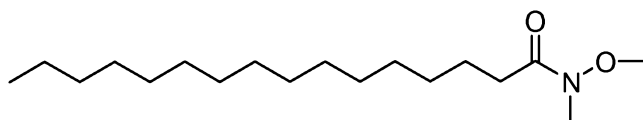
Compounds 3 to 5 (alternative strategies)



(a) thiazole, $n\text{-BuLi}$, dry Et_2O , -78°C .

15 N-Methoxy-N-methyl-palmitamide (4a)

Procedure C



$\text{C}_{18}\text{H}_{37}\text{NO}_2$

MW: 299.49.

20 colorless oil. Yield 81%.

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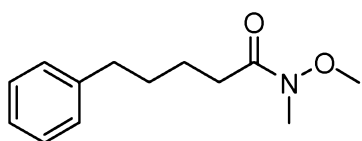
^1H NMR (200 MHz, CDCl_3) δ = 3.66 (s, 3H, OMe), 3.16 (s, 3H, NMe), 2.39 (t, 2H, J = 7.6 Hz, CH_2CO), 1.70-1.57 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 1.23-1.08 (m, 24H, 12 x CH_2), 0.86 (t, 3H, J = 3.8 Hz, CH_3).

^{13}C NMR (50 MHz, CDCl_3) δ = 174.6, 61.0, 31.8, 29.5, 29.4, 29.3, 24.8, 24.5, 22.5, 13.9.

MS (ESI) m/z (%) : 300 $[\text{M}+\text{H}, 100]^+$.

N-Methoxy-N-methyl-5-phenylpentanamide (4b) (by the Weinreb method)

Procedure C



$\text{C}_{13}\text{H}_{19}\text{NO}_2$

MW: 221.30.

Colorless oil. Yield 81%.

^1H NMR (200 MHz, CDCl_3) δ = 7.33-7.12 (m, 5H, Ph), 3.65 (s, 3H, OMe), 3.17 (s, 3H, NMe), 2.65 (t, 2H, J = 7.2 Hz, PhCH_2), 2.44 (t, 2H, J = 7.2 Hz, CH_2CO), 1.72-1.66 (m, 4H, 2 x CH_2).

^{13}C NMR (50 MHz, CDCl_3) δ = 174.6, 142.2, 128.2, 128.1, 125.6, 61.0, 35.6, 31.6, 31.1, 24.2.

MS (ESI) m/z (%) : 222 $[\text{M}+\text{H}, 100]^+$.

General procedure for the synthesis of morpholine amides

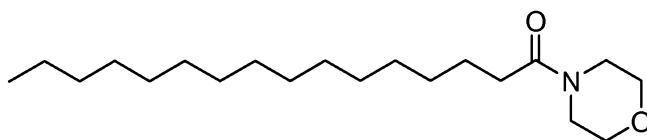
To a stirred solution of acid (1 eq.) in dry CH_2Cl_2 (7 mL), DMF (0.5 eq.) was added followed by oxalyl chloride (3 eq.) at room temperature. The reaction mixture was left stirring for 3 h. The solvent was removed and dry Et_2O (7 mL) was added and cooled at 0 °C. Pyridine (5 eq.) was added drop-wise, followed by drop-wise addition of morpholine (5 eq.). The reaction mixture was left stirring for 18 h at room temperature. Then, H_2O (8 mL) was added and it was left stirring for 30 min. The layers were separated and the organic layer was washed with an aqueous solution of HCl 1N (3 x 10 mL), brine (1 x 10 mL), an aqueous solution of NaHCO_3 5% (3 x 10

- 36 -

mL) and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography eluting with the appropriate mixture of EtOAc: pet. ether (40-60 °C) afforded the desired product.

5 **1-Morpholinohexadecan-1-one (5a)**

Procedure D



$\text{C}_{20}\text{H}_{39}\text{NO}_2$

MW: 325.53.

10 White solid. Yield 99%.

m.p.: 45-46 °C.

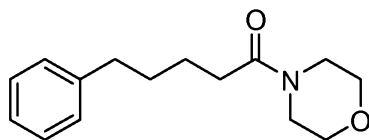
^1H NMR (200 MHz, CDCl_3) δ = 3.66-3.60 (m, 6H, CH_2OCH_2 , CHHNCHH), 3.43-3.38 (m, 2H, CHHNCHH), 2.28 (t, 2H, J = 7.2 Hz, CH_2CO), 1.63-1.52 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 1.34-1.06 (m, 24H, 12 x CH_2), 0.85 (t, 3H, J = 5.8 Hz, CH_3).

15 ^{13}C NMR (50 MHz, CDCl_3) δ = 171.8, 66.8, 66.6, 45.9, 41.7, 33.0, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.2, 22.6, 14.0.

MS (ESI) m/z (%) : 326 [$\text{M}+\text{H}$, 100] $^+$.

1-Morpholino-5-phenylpentan-1-one (5b)

20 **Procedure D**



$\text{C}_{15}\text{H}_{21}\text{NO}_2$

MW: 247.33.

Colorless oil. Yield 74% (1.025 g).

25 ^1H NMR (200 MHz, CDCl_3) δ = 7.26-7.09 (m, 5H, Ph), 3.64-3.42 (m, 6H, CH_2OCH_2 , CHHNCHH), 3.41-3.23 (m, 2H, CHHNCHH), 2.61 (t, 2H, J = 7.0 Hz, PhCH_2), 2.27 (t, 2H, J = 7.2 Hz, CH_2CO), 1.69-1.60 (m, 4H, 2 x CH_2).

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^{13}C NMR (50 MHz, CDCl_3) δ = 171.3, 141.9, 128.2, 128.1, 125.5, 66.7, 66.4, 45.7, 41.6, 35.5, 32.7, 30.9, 24.6.

MS (ESI) m/z (%) : 248 $[\text{M}+\text{H}, 100]^+$, 270 $[\text{M}+23, 23]$.

5 **Synthesis of 2-oxo-thiazoles using the Weinreb and morpholino amide method**

To a stirred solution of thiazole (3 eq.) in dry Et_2O (20 mL) at -78°C under a dry argon atmosphere was added a solution of *n*-BuLi (1.6 M in hexanes, 3 eq.) drop-wise over a period of 10 min. The resulting orange solution was stirred for 45 min.
10 Then a solution of the amide (1 eq.) in dry Et_2O (2 mL) was slowly added giving the mixture a dark brown color. After stirring for 30 min. at -78°C , the mixture was allowed to warm up to room temperature over a period of 2 h. Then, saturated aqueous ammonium chloride solution was added and the mixture was extracted with ether (2 x 10 mL). The combined extracts were washed with brine and then dried
15 over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography eluting with the appropriate mixture of EtOAc: pet. ether (40-60 $^\circ\text{C}$) afforded the desired product.

1-(Thiazol-2-yl)hexadecan-1-one (3a)

20 **Procedure E**

Yield when the Weinreb amide was used: 73%.

Yield when the morpholine amide was used: 98%.

5-Phenyl-1-(thiazol-2-yl)pentan-1-one (3b)

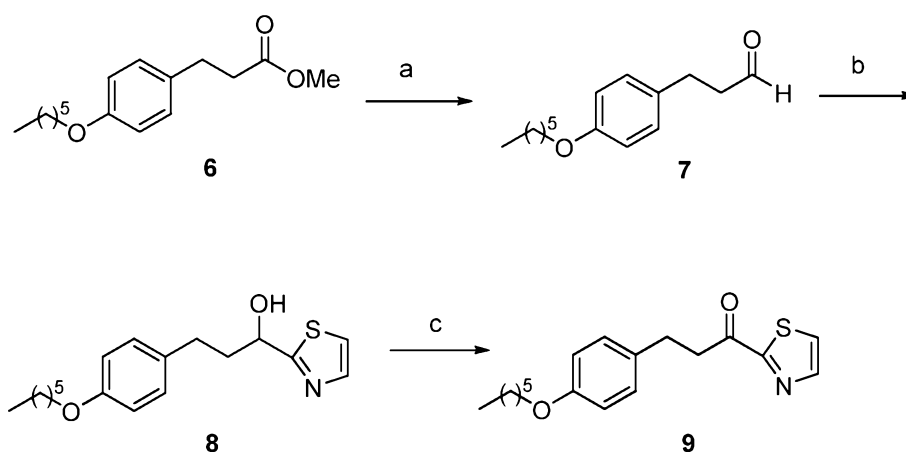
25 **Procedure E**

Yield when the Weinreb amide was used: 85%.

Yield when the morpholine amide was used: 86%.

Compounds 6 to 9

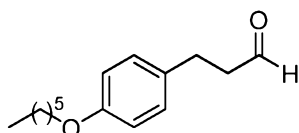
- 38 -



(a) i. DIBALH, Et₂O, 0 °C, ii. NaOCl, NaHCO₃, NaBr, 4-AcNH-TEMPO, toluene, AcOEt, H₂O, -5 °C; (b) thiazole, *n*-BuLi, dry THF, -78 °C; (c) Dess-Martin periodinane, dry CH₂Cl₂.

3-(4-(Hexyloxy)phenyl)propanal (7)

Procedure F then G



10 C₁₅H₂₂O₂

MW: 234.33

Orange oil. Yield 64%.

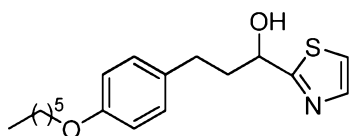
¹H NMR (200 MHz, CDCl₃) δ = 9.80 (s, 1H, CHO), 7.09 (d, 2H, *J* = 8.4 Hz, CH), 6.82 (d, 2H, *J* = 8.6 Hz, 2 x CH), 3.92 (t, 2H, *J* = 6.4 Hz, CH₂), 3.00-2.85 (m, 2H, CH₂), 2.80-2.65 (m, 2H, CH₂), 1.85-1.65 (m, 2H, CH₂), 1.50-1.20 (m, 6H, 3 x CH₂), 0.92 (m, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ = 201.7, 157.6, 132.0, 129.1, 114.5, 67.9, 45.5, 31.5, 29.2, 27.2, 25.7, 22.5, 14.0

20 3-(4-(Hexyloxy)phenyl)-1-(thiazol-2-yl)propan-1-one (8)

Procedure A

- 39 -

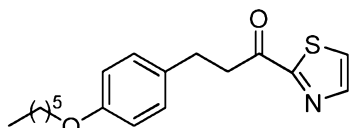
 $C_{18}H_{25}NO_2S$

MW: 319.46

Colorless oil. Yield 66%.

5 1H NMR (200 MHz, $CDCl_3$) δ = 7.65 (d, 1H, J = 3.2 Hz, ArH), 7.24 (d, 1H, J = 3.4 Hz, ArH), 7.07 (d, 2H, J = 8.8 Hz, 2 x CH), 6.79 (d, 2H, J = 8.6 Hz, 2 x CH), 4.96 (dd, 1H, J_1 = 7.6 Hz, J_2 = 5.0 Hz, CH), 3.90 (t, 2H, J = 6.4 Hz, CH_2O), 2.80-2.60 (m, 2H, CH_2), 2.25-2.05 (m, 2H, CH_2), 1.85-1.65 (m, 2H, CH_2), 1.50-1.30 (m, 6H, 3 x CH_2), 0.88 (t, 3H, J = 6.2 Hz, CH_3).

10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 175.9, 157.4, 142.0, 133.0, 129.3, 118.8, 114.4, 70.9, 67.9, 39.9, 31.5, 30.5, 29.2, 25.6, 22.5, 14.0.

3-(4-(Hexyloxy)phenyl)-1-(thiazol-2-yl)propan-1-one (9)**Procedure B**

15

 $C_{18}H_{23}NO_2S$

MW: 317.45

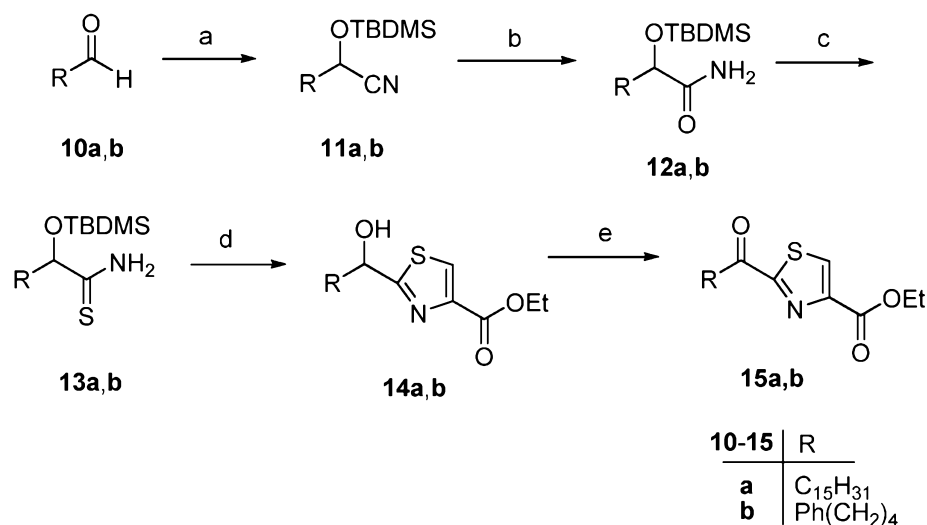
Yellowish oil. Yield 78%.

20 1H NMR (200 MHz, $CDCl_3$) δ = 7.95 (d, 1H, J = 3.2 Hz, ArH), 7.62 (d, 1H, J = 3.4 Hz, ArH), 7.15 (d, 2H, J = 8.8 Hz, CH), 6.81 (d, 2H, J = 8.4 Hz, CH), 3.90 (t, 2H, J = 6.6 Hz, CH_2O), 3.45 (t, 2H, J = 7.2 Hz, CH_2), 3.01 (t, 2H, J = 3.8 Hz, CH_2), 1.90-1.64 (m, 2H, CH_2), 1.58-1.20 (m, 6H, 3 x CH_2), 0.89 (t, 3H, J = 6.6 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 193.1, 167.1, 157.5, 144.6, 132.5, 129.3, 126.1, 114.5, 68.0, 40.3, 31.5, 29.2, 28.9, 25.7, 22.6, 14.0.

25 MS (ESI) m/z (%) : 318 $[M+H, 100]^+$.

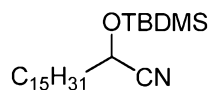
Compounds 10 to 15



- 5 (a) TBDMSCN, KCN, 18-crown-6, CH₂Cl₂; (b) 30% H₂O₂, Bu₄NHSO₄, NaOH, CH₂Cl₂; (c) Lawesson's reagent, THF; (d) BrCH₂COCOOEt, conc. H₂SO₄, EtOH, 40 °C; (e) Dess Martin periodinane, dry CH₂Cl₂.

2-(tert-Butyldimethylsilyloxy)heptadecanenitrile (11a)

10 Procedure H

C₂₃H₄₇NOSi

MW: 381.71

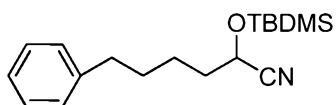
Colorless oil. Yield 85%.

- 15 ¹H NMR (200 MHz, CDCl₃) δ = 4.41 (t, 1H, *J* = 6.4 Hz, CH), 1.70-1.90 (m, 2H, CH₂), 1.40-1.55 (m, 2H, CH₂), 1.30-1.15 (m, 24H, 12 x CH₂), 1.03 – 0.82 (m, 12H, 4 x CH₃), 0.19 (s, 3H, CH₃), 0.14 (s, 3H, CH₃).
¹³C NMR (50 MHz, CDCl₃) δ = 120.1, 61.9, 36.3, 31.9, 29.6, 29.5, 29.4, 29.3, 28.9, 25.5, 24.5, 22.7, 18.0, 14.1, -5.2, -5.4.

20

2-(tert-Butyldimethylsilyloxy)-6-phenylhexanenitrile (11b)

- 41 -

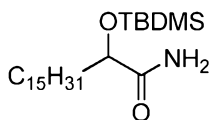
Procedure HC₁₈H₂₉NOSi

MW: 303.51

5 Colorless oil. Yield 82 %.

¹H NMR (CDCl₃): δ = 7.34-7.20 (m, 5H, Ph), 4.44 (t, 1H, *J* = 6.6 Hz, CH), 2.68 (t, 2H, *J* = 7.4 Hz, CH₂), 1.88-1.80 (m, 2H, CH₂), 1.76-1.69 (m, 2H, CH₂), 1.68-1.58 (m, 2H, CH₂), 0.97 (s, 9H, 3 × CH₃), 0.23 (s, 3H, CH₃), 0.18 (s, 3H, CH₃).

¹³C NMR (CDCl₃) δ = 142.0, 128.3, 128.0, 125.8, 120.1, 61.8, 36.1, 35.6, 30.8, 25.7, 25.5, 24.1, 18.0, -5.2, -5.4.

2-(tert-Butyldimethylsilyloxy)heptadecanamide (12a)**Procedure I**15 C₂₃H₄₉NO₂Si

MW: 399.73

Yellow oil. Yield 63%.

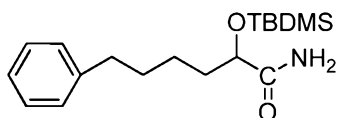
¹H NMR (200 MHz, CDCl₃) δ = 6.49 (s, 1H, *NHH*), 6.14 (s, 1H, *NHH*), 4.10 (t, 1H, *J* = 5.0 Hz, CH), 1.80-1.56 (m, 2H, CH₂), 1.40-1.10 (m, 26H, 13 × CH₂), 0.95-0.80 (m, 12H, 4 × CH₃), 0.17 (s, 3H, CH₃), 0.14 (s, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ 177.3, 73.4, 35.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 25.7, 24.1, 22.7, 18.0, 14.1, -4.9, -5.3.

MS (ESI) *m/z* (%) δ = 400 [M+H, 40]⁺, 422 [M+Na, 100]⁺.

25 **2-(tert-Butyldimethylsilyloxy)-6-phenylhexanamide (12b)****Procedure I**

- 42 -

C₁₈H₃₁NO₂Si

MW: 321.53

Colorless oil. Yield 100 %.

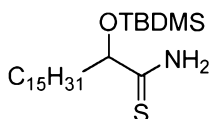
5 ¹H NMR (CDCl₃): δ = 7.28-7.15 (m, 5H, Ph), 6.51 (s, 1H, NH), 5.61 (s, 1H, NH), 4.16 (t, 1H, *J* = 6.6 Hz, CH), 2.62 (t, 2H, *J* = 7.4 Hz, CH₂), 1.77-1.32 (m, 6H, 3 × CH₂), 0.91 (s, 9H, 3 × CH₃), 0.06 (s, 6H, 2 × CH₃).

¹³C NMR (CDCl₃): δ = 177.4, 142.3, 128.2, 128.1, 125.5, 73.2, 35.6, 34.8, 31.2, 25.6, 23.8, 17.8, -5.0, -5.4.

10 MS (ESI) *m/z* (%) : 322 [M+H, 100]⁺.

2-(tert-Butyldimethylsilyloxy)heptadecanethioamide (13a)

Procedure J

C₂₃H₄₉NOSSi

15 MW: 415.79

Yellowish oil. Yield 84%.

¹H NMR (200 MHz, CDCl₃) δ = 7.96 (s, 1H, *NHH*), 7.74 (s, 1H, *NHH*), 4.56 (t, 1H, *J* = 5.0 Hz, CH), 1.90-1.70 (m, 2H, CH₂), 1.47-1.15 (m, 26H, 13 × CH₂), 1.00-0.83 (m, 12H, 4 × CH₃), 0.12 (s, 3H, CH₃), 0.09 (s, 3H, CH₃).

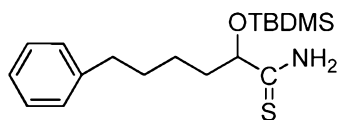
20 ¹³C NMR (50 MHz, CDCl₃) δ = 210.3, 80.1, 38.0, 32.1, 29.9, 29.8, 29.7, 29.6, 26.0, 25.7, 24.1, 22.9, 18.3, 14.3, -4.7, -4.9.

MS (ESI) *m/z* (%) : 416 [M+H, 90]⁺.

2-(tert-Butyldimethylsilyloxy)-6-phenylhexanethioamide (13b)

25 **Procedure J**

- 43 -

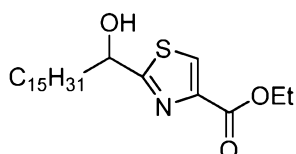
C₁₈H₃₁NOSSi

MW: 337.60

Yellowish oil. Yield 64 %.

5 ¹H NMR (CDCl₃): δ = 8.28 (s, 1H, NH), 7.98 (s, 1H, NH), 7.24-7.10 (m, 5H, Ph), 4.52 (t, 1H, *J* = 6.6 Hz, , CH), 2.57 (t, 2H, *J* = 7.4 Hz, , CH₂), 1.95-1.80 (m, 2H, CH₂), 1.62-1.45 (m, 2H, CH₂), 1.42-1.25 (m, 2H, CH₂), 0.88 (s, 9H, 3 × CH₃), 0.06 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃).

10 ¹³C NMR (CDCl₃): 209.6, 142.3, 128.3, 128.1, 125.5, 79.6, 37.4, 35.6, 31.2, 25.6, 23.5, 17.9, -5.1, -5.3.

MS (ESI) *m/z* (%) : 338 [M+H, 100]⁺.**Ethyl 2-(1-hydroxyhexadecyl)thiazole-4-carboxylate (14a)****Procedure K**

15

C₂₂H₃₉NO₃S

MW: 397.61

Yellowish solid. Yield 74%.

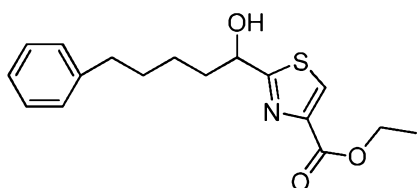
20 ¹H NMR (200 MHz, CDCl₃) δ = 8.06 (s, 1H, CH), 5.03 (dd, 1H, *J*₁ = 4.5 Hz, *J*₂ = 8.1 Hz, , CH), 4.36 (q, 2H, *J* = 7.1 Hz, , CH₂), 3.10-2.90 (br, 1H, OH), 2.00 – 1.60 (m, 2H, CH₂), 1.35 (t, 3H, *J* = 7.1 Hz, , CH₃), 1.40-1.10 (m, 26H, 13 x CH₂), 0.85 (t, 3H, *J* = 6.8 Hz, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ = 177.3, 161.4, 146.6, 127.1, 71.8, 61.3, 38.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.5, 25.1, 22.6, 14.2, 14.0.

25

Ethyl 2-(1-hydroxy-5-phenylpentyl)thiazole-4-carboxylate (14b)**Procedure K**

- 44 -

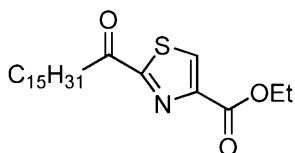
C₁₇H₂₁NO₃S

MW: 319.42

Yellowish oil. Yield 45 %.

5 ¹H NMR (CDCl₃): δ = 8.03 (s, 1H, ArH), 7.25-7.10 (m, 5H, Ph), 5.11-5.00 (m, 1H, CH), 4.33 (q, 2H, *J* = 5.8 Hz, OCH₂), 4.10-3.95 (m, 1H, OH), 2.56 (t, 2H, *J* = 7.0 Hz, CH₂), 1.85-1.78 (m, 2H, CH₂), 1.62-1.41 (m, 2H, CH₂), 1.32 (t, 3H, *J* = 5.8 Hz, CH₃), 1.24-1.20 (m, 2H, CH₂).

10 ¹³C NMR (CDCl₃): δ = 177.4, 161.3, 146.4, 142.2, 128.2, 128.1, 127.2, 125.5, 71.5, 61.3, 37.8, 35.5, 30.9, 24.7, 14.2.

Ethyl 2-palmitoylthiazole-4-carboxylate (15a)**Procedure B**15 C₂₂H₃₇NO₃S

MW: 395.60

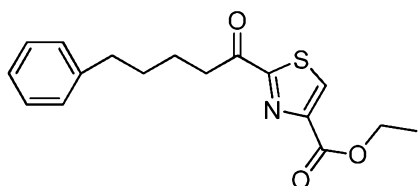
White solid. Yield 82%.

20 ¹H NMR (200 MHz, CDCl₃): δ = 8.41 (s, 1H, CH), 4.46 (q, 2H, *J* = 6.8 Hz, CH₂), 3.23 (t, 2H, *J* = 7.4 Hz, CH₂), 1.85-1.60 (m, 4H, 2 x CH₂), 1.43 (t, 3H, *J* = 6.8 Hz, CH₃), 1.42-1.00 (m, 22H, 11 x CH₂), 0.88 (t, 3H, *J* = 6.8 Hz, CH₃).

¹³C NMR (50 MHz, CDCl₃): δ = 194.3, 167.9, 161.1, 148.9, 133.2, 62.0, 38.6, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 23.8, 22.9, 14.5, 14.3.

MS (ESI) *m/z* (%) : 418 [M+Na, 100]⁺.25 **Ethyl 2-(5-phenylpentanoyl)thiazole-4-carboxylate (15b)****Procedure B**

- 45 -

C₁₇H₁₉NO₃S

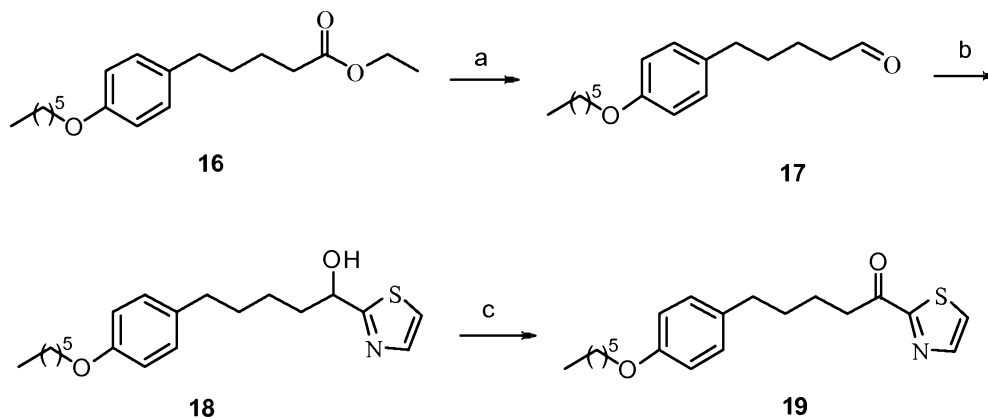
MW: 317.40

Yellowish oil. Yield 81 %

5 ¹H NMR (CDCl₃): δ = 8.38 (s, 1H, ArH), 7.24-7.13 (m, 5H, Ph), 4.42 (q, 2H, *J* = 5.8 Hz, OCH₂), 3.23 (t, 2H, *J* = 5.8 Hz, CH₂), 2.63 (t, 2H, *J* = 7.0 Hz, CH₂CO), 1.81-1.65 (m, 4H, 2 × CH₂), 1.39 (t, 3H, *J* = 5.8 Hz, CH₃).

¹³C NMR (CDCl₃): 193.8, 167.4, 160.8, 148.6, 142.0, 133.1, 128.3, 128.2, 125.7, 61.8, 38.1, 35.6, 30.7, 23.2, 14.3.

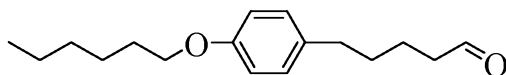
10 MS (ESI) *m/z* (%) : 318 [M+H, 100]⁺.

Compounds 16 to 19

15 (a) i. LiAlH₄, dry Et₂O, -20 °C, ii. NaOCl, NaHCO₃, NaBr, 4-AcNH-TEMPO, toluene, AcOEt, H₂O, -5 °C ; (b) thiazole, *n*-BuLi, dry THF, -78 °C ; (c) NaOCl, NaHCO₃, NaBr, 4-AcNH-TEMPO, toluene, AcOEt, H₂O, -5 °C.

5-(4-(Hexyloxy)phenyl)pentanal (17)

20 **Procedure N then G**



- 46 -

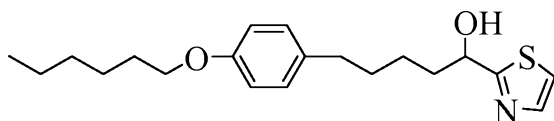
 $C_{17}H_{26}O_2$

MW : 262.39.

Yelloish oil. Yield 97%.

1H NMR (200 MHz, $CDCl_3$) δ = 9.73 (t, 1H, J = 1.8 Hz, CHO), 7.06 (d, 2H, J = 8.6 Hz, CH, Ph), 6.81 (d, 2H, J = 8.6 Hz, CH, Ph), 3.92 (t, 2H, J = 6.4 Hz, CH_2OPh), 2.56 (t, 2H, J = 7.0 Hz, $PhCH_2$), 2.47-2.35 (m, 2H, CH_2CHO), 1.81-1.67 (m, 2H, CH_2CH_2OPh), 1.65-1.57 (m, 4H, 2 x CH_2), 1.55-1.09 (m, 6H, 3 x CH_2), 0.90 (t, 3H, J = 6.8 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 202.3, 157.2, 133.6, 129.0, 114.2, 67.8, 43.6, 34.6, 31.5, 31.0, 29.2, 25.6, 22.5, 21.5, 20.8, 13.9.

5-(4-(Hexyloxy)phenyl)-1-(thiazol-2-yl)pentan-1-ol (18)**Procedure A** $C_{20}H_{29}NO_2S$

MW: 347.51.

Orange oil. Yield 74%.

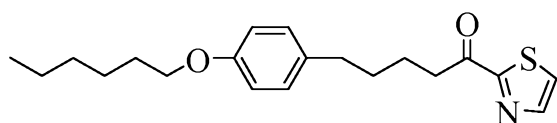
1H NMR (200 MHz, $CDCl_3$) δ = 7.62 (d, 1H, J = 3.2 Hz, ArH), 7.22 (d, 1H, J = 3.4 Hz, ArH), 7.03 (d, 2H, J = 8.8 Hz, CH, Ph), 6.77 (d, 2H, J = 8.6 Hz, CH, Ph), 4.98-4.84 (m, 1H, $CHOH$), 4.46 (d, 1H, J = 5 Hz, $CHOH$), 3.89 (t, 2H, J = 6.4 Hz, CH_2OPh), 2.52 (t, 2H, J = 7 Hz, $PhCH_2$), 2.48-1.19 (m, 14H, 7 x CH_2), 0.88 (t, 3H, J = 6.6 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 176.3, 157.0, 141.9, 134.2, 129.0, 118.5, 114.1, 71.5, 67.8, 38.0, 34.7, 31.5, 31.3, 29.2, 25.6, 24.7, 22.5, 20.9, 14.0.

MS (ESI) m/z (%) : 348 $[M+H, 100]^+$.

5-(4-(Hexyloxy)phenyl)-1-(thiazol-2-yl)pentan-1-one (19)**Procedure G**

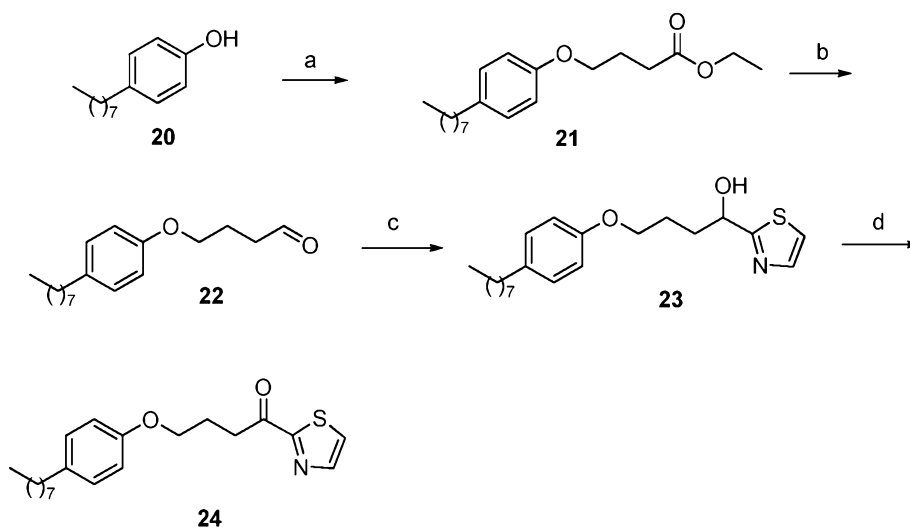
- 47 -

 $C_{20}H_{27}NO_2S$

MW: 345.50.

Yellowish oil. Yield 89%.

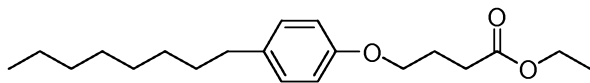
- 5 1H NMR (200 MHz, $CDCl_3$) δ = 7.98 (d, 1H, J = 3.2 Hz, ArH), 7.65 (d, 1H, J = 3.4 Hz, ArH), 7.08 (d, 2H, J = 8.8 Hz, CH, Ph), 6.81 (d, 2H, J = 8.4 Hz, CH, Ph), 3.91 (t, 2H, J = 6.6 Hz, CH_2OPh), 3.18 (t, 2H, J = 6.8 Hz, CH_2CO), 2.60 (t, 2H, J = 7.6 Hz, $PhCH_2$), 1.89-1.61 (m, 6H, 3 x CH_2), 1.48-1.28 (m, 6H, 3 x CH_2), 0.90 (t, 3H, J = 6.6 Hz, CH_3).
- 10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 193.7, 167.1, 157.2, 144.5, 133.9, 129.1, 126.1, 114.2, 67.8, 38.2, 34.6, 31.5, 31.1, 29.2, 25.6, 23.5, 22.5, 14.0.
- MS (ESI) m/z (%) : 346 $[M+H, 100]^+$

Compounds 20 to 24

- 15 (a) $Br(CH_2)_3COOC_2H_5$, K_2CO_3 , KI, acetone, reflux; (b) i. $LiAlH_4$, dry Et_2O , $-20^\circ C$, ii. $NaOCl$, $NaHCO_3$, $NaBr$, 4-AcNH-TEMPO, toluene, $AcOEt$, H_2O , $-5^\circ C$; (c) thiazole, $n-BuLi$, dry Et_2O , $-78^\circ C$; (d) $NaOCl$, $NaHCO_3$, $NaBr$, 4-AcNH-TEMPO, toluene, $AcOEt$, H_2O , $-5^\circ C$.

- 20 **Ethyl 4-(4-octylphenoxy)butanoate (21)**

- 48 -

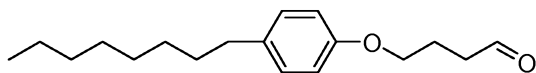
Procedure O $C_{20}H_{32}O_3$

MW: 320.47.

5 Colorless oil. Yield 100%.

1H NMR (200 MHz, $CDCl_3$) δ = 7.08 (d, 2H, J = 7.8 Hz, CH, Ph), 6.81 (d, 2H, J = 7.6 Hz, CH, Ph), 4.15 (q, 2H, J = 7.0 Hz, $COOCH_2$), 3.99 (t, 2H, J = 5.8 Hz, $PhOCH_2$), 2.58-2.42 (m, 4H, 2 x CH_2), 2.17-2.06 (m, 2H, CH_2CH_2COO), 1.57-1.45 (m, 2H, CH_2CH_2Ph), 1.27 (br, 13H, 5 x CH_2 , CH_3), 0.89 (t, 3H, J = 5.2 Hz, CH_3).

10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 173.2, 156.8, 135.0, 129.1, 114.2, 66.6, 60.3, 35.0, 31.7, 30.8, 29.4, 29.2, 24.6, 22.6, 14.1, 14.0.

MS (ESI) m/z (%) : 321 $[M+H, 100]^+$.**4-(4-Octylphenoxy)butanal (22)**15 **Procedure N then G** $C_{18}H_{28}O_2$

MW : 276.41.

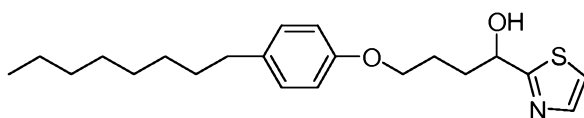
Colorless oil. Yield 97%.

20 1H NMR (200 MHz, $CDCl_3$) δ = 9.84 (t, 1H, J = 1.4 Hz, CHO), 7.09 (d, 2H, J = 8.6 Hz, CH, Ph), 6.81 (d, 2H, J = 8.8 Hz, CH, Ph), 3.99 (t, 2H, J = 6.0 Hz, $PhOCH_2$), 2.70-2.52 (m, 4H, 2 x CH_2), 1.63-1.52 (m, 2H, CH_2CH_2Ph), 1.31-1.24 (br, 10H, 5 x CH_2), 0.90 (t, 3H, J = 6.4 Hz, CH_3).

25 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 201.7, 156.6, 135.2, 129.2, 114.1, 66.6, 40.6, 35.0, 31.8, 31.7, 29.4, 29.2, 22.6, 22.0, 14.0.

4-(4-Octylphenoxy)-1-(thiazol-2-yl)butan-1-ol (23)**Procedure A**

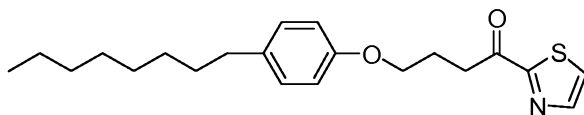
- 49 -

 $C_{21}H_{31}NO_2S$

MW: 361.54.

Orange oil. Yield 73%.

- 5 1H NMR (200 MHz, $CDCl_3$) δ = 7.72 (d, 1H, J = 3.2 Hz, ArH), 7.29 (d, 1H, J = 3.2 Hz, ArH), 7.08 (d, 2H, J = 8.8 Hz, CH, Ph), 6.81 (d, 2H, J = 8.6 Hz, CH, Ph), 5.11 (dd, 1H, J_1 = 4.4 Hz, J_2 = 7.6 Hz, $CHOH$), 4.00 (t, 2H, J = 6.0 Hz, $PhOCH_2$), 3.92 (s, 1H, OH), 2.54 (t, 2H, J = 7.2 Hz, CH_2Ph), 2.32-1.90 (m, 4H, 2 x CH_2), 1.67-1.48 (m, 2H, CH_2CH_2Ph), 1.30-1.23 (br, 10H, 5 x CH_2), 0.88 (t, 3H, J = 6.2 Hz, CH_3).
- 10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 175.4, 156.6, 142.0, 135.3, 129.2, 118.9, 114.3, 71.5, 67.7, 35.1, 35.0, 31.9, 31.7, 29.5, 29.2, 25.2, 22.6, 14.1.
- MS (ESI) m/z (%) : 362 $[M+H, 100]^+$.

4-(4-Octylphenoxy)-1-(thiazol-2-yl)butan-1-one (24)15 **Procedure G** $C_{21}H_{29}NO_2S$

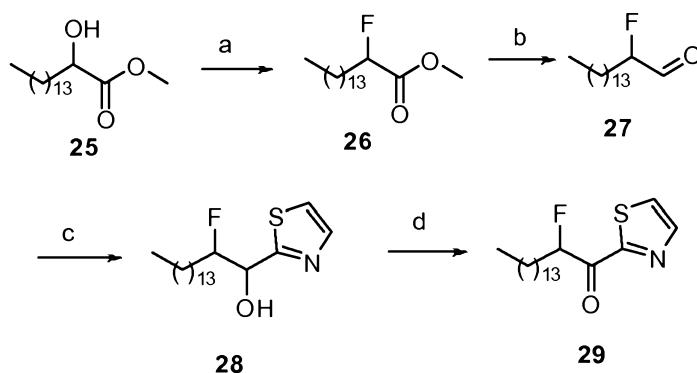
MW: 359.53.

Yellowish oil. Yield 85%.

- 20 1H NMR (200 MHz, $CDCl_3$) δ = 7.99 (d, 1H, J = 3.0 Hz, ArH), 7.65 (d, 1H, J = 3.0 Hz, ArH), 7.07 (d, 2H, J = 8.6 Hz, CH, Ph), 6.80 (d, 2H, J = 8.8 Hz, CH, Ph), 4.06 (t, 2H, J = 6.2 Hz, $PhOCH_2$), 3.39 (t, 2H, J = 7.2 Hz, $CH_2C=O$), 2.54 (t, 2H, J = 7.4 Hz, CH_2Ph), 2.26 (quintet, 2H, J = 6.2 Hz, $CH_2CH_2C=O$), 1.68-1.45 (m, 2H, CH_2CH_2Ph), 1.30-1.23 (br, 10H, 5 x CH_2), 0.89 (t, 3H, J = 6.2 Hz, CH_3).
- 25 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 193.2, 166.9, 156.7, 144.6, 135.0, 129.1, 126.0, 114.2, 66.7, 35.1, 35.0, 31.8, 31.7, 29.4, 29.2, 23.6, 22.6, 14.0.
- MS (ESI) m/z (%) : 360 $[M+H, 100]^+$.

Compounds 25 to 29

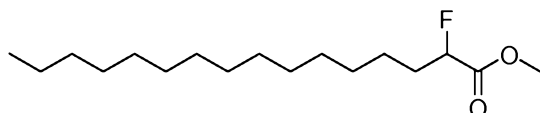
- 50 -



- (a) DAST, dry CH_2Cl_2 , -78°C ; (b) i. LiAlH_4 , dry Et_2O , -20°C , ii. $(\text{COCl})_2$, dry Et_3N , dry DMSO , dry CH_2Cl_2 , -60°C ; (c) thiazole, $n\text{-BuLi}$, dry THF , -78°C ; (d) Dess-Martin periodinane, dry CH_2Cl_2 .

Methyl 2-fluorohexadecanoate (26)

Procedure P



10

 $\text{C}_{17}\text{H}_{33}\text{FO}_2$

MW: 288.44.

White solid. Yield 78%.

m.p.: $36\text{--}38^\circ\text{C}$.

- ^1H NMR (200 MHz, CDCl_3) δ = 4.91 (dt, 1H, $J_{\text{H-H}} = 6.0$ Hz, $J_{\text{H-F}} = 48.8$ Hz, CHF), 3.80 (s, 3H, COOCH_3), 2.00-1.77 (m, 2H, CH_2CHF), 1.49-1.18 (m, 24H, 12 x CH_2), 0.88 (t, 3H, $J = 6.8$ Hz, CH_3).

- ^{13}C NMR (50 MHz, CDCl_3) δ = 170.5 (d, $J_{\text{C-C-F}} = 24$ Hz, COO), 89.0 (d, $J_{\text{C-F}} = 183$ Hz, CF), 52.2, 32.3 (d, $J_{\text{C-C-F}} = 21$ Hz, CH_2CHF), 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 24.4, 24.3, 22.7, 14.1.

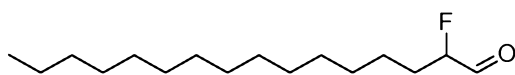
20

 ^{19}F NMR (186 MHz, CDCl_3) δ = -192.5 (quintet, CHF).

2-Fluorohexadecanal (27)

Procedure N then Q

- 51 -

 $C_{16}H_{31}FO$

MW: 258.42.

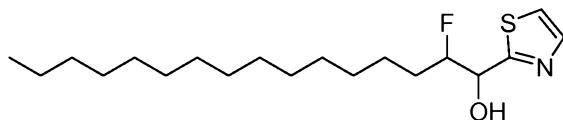
White solid. Yield 86%.

5 m.p. : 68-71 °C.

1H NMR (200 MHz, $CDCl_3$) δ = 9.76 (d, 1H, J = 5.8 Hz, CHO), 4.74 (dt, 1H, J_{H-H} = 4.8 Hz, J_{H-F} = 49.0 Hz, CHF), 1.86-1.68 (m, 2H, CH_2CHF), 1.47-1.10 (m, 24H, 12 x CH_2), 0.88 (t, 3H, J = 5.8 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.4 (d, J_{C-C-F} = 36 Hz, CO), 95.0 (d, J_{C-F} = 178 Hz, CF), 31.9, 30.3 (d, J_{C-C-F} = 20 Hz, CH_2), 29.6, 29.5, 29.3, 29.2, 24.2, 24.1, 22.7, 14.1.

^{19}F NMR (186 MHz, $CDCl_3$) δ = -200.0 (m, CHF).

2-Fluoro-1-(thiazole-2-yl)hexadeca-1-ol (28)15 **Procedure A** $C_{19}H_{34}FNOS$

MW: 343.54.

Yellowish solid. Yield 40%.

20 m.p. : 46-49 °C.

1H NMR (200 MHz, $CDCl_3$) δ = 7.89 (d, 1/7H, J = 3.2 Hz, ArH), 7.75 (d, 6/7H, J = 3.4 Hz, ArH), 7.45 (d, 1/7H, J = 3.2 Hz, ArH), 7.35 (d, 6/7H, J = 3.2 Hz, ArH), 5.22-5.05 (dm, 1H, J = 13.4 Hz, $CHOH$), 5.01-4.66 (dm, 1H, J = 51.6 Hz, CHF), 4.15 (d, 2/3H, J = 4.6 Hz, $CHOH$), 3.91 (d, 1/3H, J = 5.6 Hz, $CHOH$), 1.94-1.08 (m, 26H, 13 x CH_2), 0.88 (t, 3H, J = 6.2 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.0, 142.1, 119.7, 95.4 (d, J_{C-F} = 173 Hz, CF), 73.2 (d, J_{C-C-F} = 22 Hz, 1/3COH), 73.0 (d, J_{C-C-F} = 24 Hz, 2/3COH), 31.9, 30.6 (d, J_{C-C-F} = 21 Hz, CH_2), 29.6, 29.5, 29.4, 29.3, 25.0, 24.9, 22.7, 14.1.

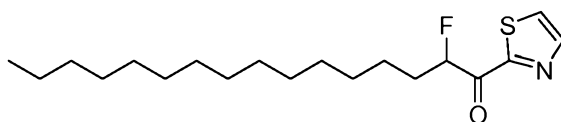
^{19}F NMR (186 MHz, $CDCl_3$) δ = -190.2 (m, CHF), -194.3 (m, CHF).

- 52 -

MS (ESI) m/z (%) : 344 [M+H, 100]⁺.

2-Fluoro-1-(thiazole-2-yl)hexadeca-1-one (29)**Procedure B**

5



$C_{19}H_{32}FNOS$

MW: 341.53.

White solid. Yield 60%.

m.p. : 55-56 °C.

10 1H NMR (200 MHz, $CDCl_3$) δ = 8.05 (d, 1H, J = 3.0 Hz, ArH), 7.76 (d, 1H, J = 3.0 Hz, ArH), 6.07 (ddd, 1H, J_{H-F} = 49.8 Hz, J_{H-H} = 3.8 Hz, J_{H-H} = 8.2 Hz, CHF), 2.19-1.91 (m, 2H, CH_2CHF), 1.66-1.08 (m, 24H, 12 x CH_2), 0.87 (t, 3H, J = 6.6 Hz, CH_3).

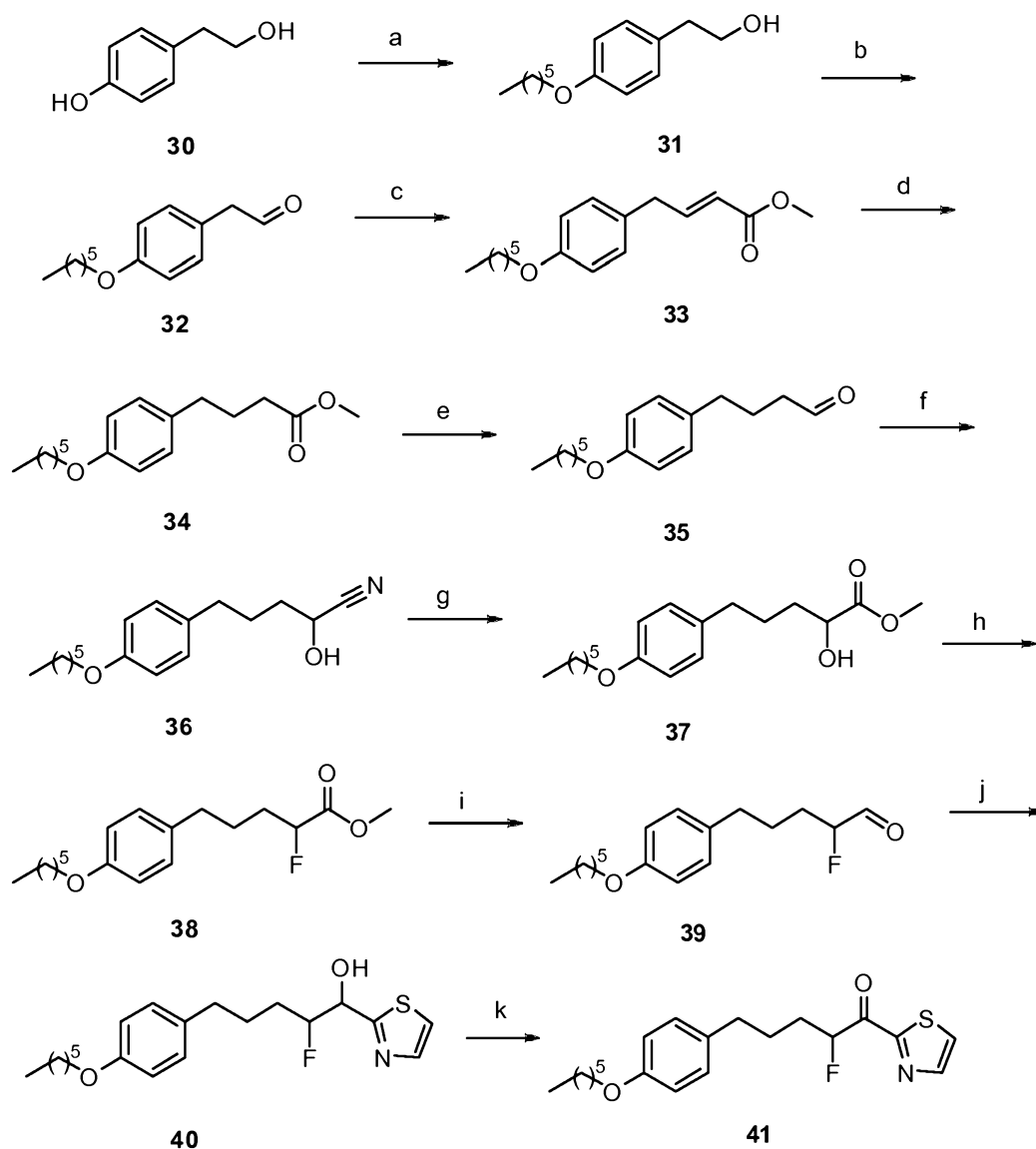
15 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 189.4 (d, J_{C-C-F} = 19 Hz, CO), 164.1, 145.3, 127.1, 92.9 (d, J_{C-F} = 182 Hz, CF), 32.8 (d, J_{C-C-F} = 21 Hz, CH_2), 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 24.9, 22.9, 14.3.

^{19}F NMR (186 MHz, $CDCl_3$) δ = -196.6 (m, CHF).

MS (ESI) m/z (%) : 342 [M+H, 100]⁺.

Compounds 30 to 41

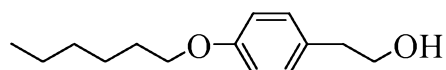
- 53 -



- (a) $\text{CH}_3(\text{CH}_2)_5\text{Br}$, K_2CO_3 , KI, acetone, reflux ; (b) NaOCl, NaHCO_3 , NaBr, 4-AcNH-TEMPO, toluene, AcOEt, H_2O , -5°C ; (c) $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$, dry THF, reflux; (d) H_2 , 10% Pd/C, 1,4-dioxane; (e) i. LiAlH_4 , dry Et_2O , -20°C , ii. NaOCl, NaHCO_3 , NaBr, 4-AcNH-TEMPO, toluene, AcOEt, H_2O , -5°C ; (f) NaHSO_3 , KCN, CH_2Cl_2 , H_2O ; (g) 6N HCl/MeOH; (h) DAST, dry CH_2Cl_2 , -30°C ; (i) i. LiAlH_4 , dry Et_2O , -20°C , ii. $(\text{COCl})_2$, dry Et_3N , dry DMSO, dry CH_2Cl_2 , -65°C ; (j) thiazole, *n*-BuLi, dry Et_2O , -78°C ; (k) Dess-Martin periodinane, dry CH_2Cl_2 .

The following target compounds of the invention are synthesised according to the protocols above:

5

2-(4-(Hexyloxy)phenyl)ethanol (31)**Procedure O** $C_{14}H_{22}O_2$

10

MW: 222.32.

Colorless oil. Yield 97%.

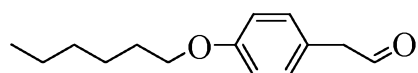
1H NMR (200 MHz, $CDCl_3$) δ = 7.14 (d, 2H, J = 8.6 Hz, CH, Ph), 6.85 (d, 2H, J = 8.8 Hz, CH, Ph), 3.94 (t, 2H, J = 6.4 Hz, CH_2OPh), 3.82 (t, 2H, J = 5.2 Hz, CH_2OH), 2.81 (t, 2H, J = 6.4 Hz, $PhCH_2$), 1.81-1.71 (m, 2H, CH_2CH_2OPh), 1.50-1.26 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.8 Hz, CH_3).

15

^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.8, 130.2, 129.8, 114.6, 68.0, 63.7, 38.2, 31.5, 29.2, 25.6, 22.5, 14.0.

2-(4-(Hexyloxy)phenyl)acetaldehyde (32)

20

Procedure G $C_{14}H_{20}O_2$

MW: 220.31.

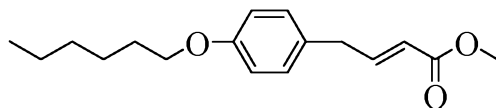
Yellow oil. Yield 97%.

25

1H NMR (200 MHz, $CDCl_3$) δ = 9.72 (t, 1H, J = 2.4 Hz, CHO), 7.13 (d, 2H, J = 8.4 Hz, CH, Ph), 6.90 (d, 2H, J = 8.6 Hz, CH, Ph), 3.96 (t, 2H, J = 6.4 Hz, CH_2OPh), 3.63 (d, 2H, J = 2.4 Hz, $PhCH_2$), 1.92-1.74 (m, 2H, CH_2CH_2OPh), 1.54-1.27 (m, 6H, 3 x CH_2), 0.92 (t, 3H, J = 6.8 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.4, 158.2, 130.3, 123.1, 114.7, 67.7, 49.4, 31.2, 28.9, 25.4, 22.3, 13.7.

30

(E)-Methyl 4-(4-(hexyloxy)phenyl)but-2-enoate (33)**Procedure R**5 $C_{17}H_{24}O_3$

MW: 276.37.

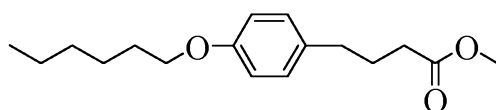
Yellowish oil. Yield 86%.

1H NMR (200 MHz, $CDCl_3$) δ = 7.16-7.05 (m, 3H, CH_2CHCH , CH, Ph), 6.84 (d, 2H, J = 8.0 Hz, CH, Ph), 5.79 (d, 1H, J = 15.6 Hz, $CHCOOMe$), 3.94 (t, 2H, J = 6.4 Hz, CH_2OPh), 3.72 (s, 3H, $COOCH_3$), 3.46 (d, 2H, J = 6.4 Hz, $PhCH_2$), 1.83-1.64 (m, 2H, CH_2CH_2OPh), 1.45-1.23 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.8 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.9, 157.9, 148.1, 129.6, 129.3, 121.5, 114.6, 68.0, 51.4, 37.6, 31.5, 29.2, 25.7, 22.5, 14.0.

MS (ESI) m/z (%) : 277 [$M+H$, 100] $^+$.

15

Methyl 4-(4-(hexyloxy)phenyl)butanoate (34)**Procedure S**20 $C_{17}H_{26}O_3$

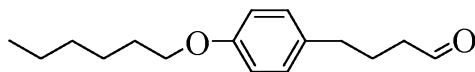
MW: 278.39.

Colorless oil. Yield 91%.

1H NMR (200 MHz, $CDCl_3$) δ = 7.08 (d, 2H, J = 8.6 Hz, CH, Ph), 6.83 (d, 2H, J = 8.6 Hz, CH, Ph), 3.93 (t, 2H, J = 6.6 Hz, CH_2OPh), 3.67 (s, 3H, $COOCH_3$), 2.60 (t, 2H, J = 7.2 Hz, $PhCH_2$), 2.33 (t, 2H, J = 7.2 Hz, CH_2COOMe), 2.05-1.89 (m, 2H, CH_2CH_2COOMe), 1.86-1.71 (m, 2H, CH_2CH_2OPh), 1.54-1.23 (m, 6H, 3 x CH_2), 0.92 (t, 3H, J = 6.6 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 173.9, 157.4, 133.0, 129.2, 114.3, 67.9, 51.3, 34.1, 33.2, 31.5, 29.2, 26.6, 25.7, 22.5, 13.9.

- 56 -

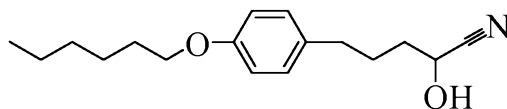
4-(4-(Hexyloxy)phenyl)butanal (35)**Procedure N then G** $C_{16}H_{24}O_2$

5 MW: 248.36.

Yellow oil. Yield 99%.

1H NMR (200 MHz, $CDCl_3$) δ = 9.76 (t, 1H, J = 1.6 Hz, CHO), 7.08 (d, 2H, J = 8.6 Hz, CH, Ph), 6.83 (d, 2H, J = 8.6 Hz, CH, Ph), 3.94 (t, 2H, J = 6.6 Hz, CH_2OPh), 2.61 (t, 2H, J = 7.4 Hz, $PhCH_2$), 2.49-2.37 (m, 2H, CH_2CHO), 2.06-1.90 (m, 2H, CH_2CH_2CHO), 1.86-1.71 (m, 2H, CH_2CH_2OPh) 1.49-1.27 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.8 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 202.4, 157.4, 133.0, 129.2, 114.4, 68.0, 43.1, 34.1, 31.6, 29.3, 25.7, 23.8, 22.6, 14.0.

15 **5-(4-(Hexyloxy)phenyl)-2-hydroxypentanenitrile (36)****Procedure T** $C_{17}H_{25}NO_2$

MW: 275.39.

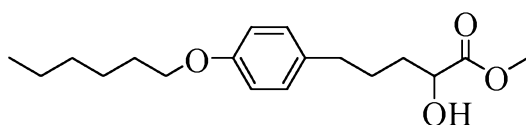
20 Colorless oil. Yield 74%.

1H NMR (200 MHz, $CDCl_3$) δ = 7.08 (d, 2H, J = 8.8 Hz, CH, Ph), 6.83 (d, 2H, J = 8.8 Hz, CH, Ph), 4.43 (t, 1H, J = 6.2 Hz, $CHOH$), 3.94 (t, 2H, J = 6.6 Hz, CH_2OPh), 2.63 (t, 2H, J = 6.4 Hz, $PhCH_2$), 2.28 (br s, 1H, OH), 1.93-1.61 (m, 6H, 3 x CH_2), 1.53-1.23 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.8 Hz, CH_3).

25 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.4, 132.9, 129.2, 119.9, 114.5, 68.0, 61.0, 34.5, 34.0, 31.5, 29.2, 26.3, 25.7, 22.5, 14.0.

MS (ESI) m/z (%) : 293 $[M+H_2O, 100]^+$.**Methyl 5-(4-(hexyloxy)phenyl)-2-hydroxypentanoate (37)**30 **Procedure U**

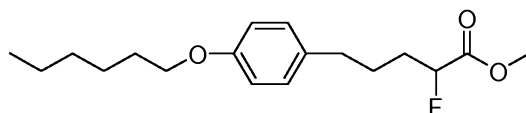
- 57 -

 $C_{18}H_{28}O_4$

MW: 308.41.

Colorless oil. Yield 86%.

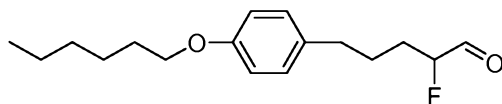
- 5 1H NMR (200 MHz, $CDCl_3$) δ = 7.08 (d, 2H, J = 8.6 Hz, CH, Ph), 6.81 (d, 2H, J = 8.6 Hz, CH, Ph), 4.20 (t, 1H, J = 6.8 Hz, $CHOH$), 3.93 (t, 2H, J = 6.6 Hz, CH_2OPh), 3.78 (s, 3H, $COOCH_3$), 3.00 (br s, 1H, $CHOH$), 2.58 (t, 2H, J = 6.6 Hz, $PhCH_2$), 1.86-1.55 (m, 6H, 3 x CH_2), 1.52-1.17 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.6 Hz, CH_3).
- 10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 175.5, 157.2, 133.7, 129.1, 114.3, 70.3, 67.9, 52.4, 34.5, 33.8, 31.5, 29.2, 26.7, 25.7, 22.5, 14.0.
- MS (ESI) m/z (%) : 309 $[M+H, 100]^+$.

Methyl 2-fluoro-5-(4-(hexyloxy)phenyl)pentanoate (38)15 **Procedure P** $C_{18}H_{27}FO_3$

MW : 310.40.

Colorless oil. Yield 37% (182 mg).

- 20 1H NMR (200 MHz, $CDCl_3$) δ = 7.08 (d, 2H, J = 8.6 Hz, CH, Ph), 6.83 (d, 2H, J = 8.8 Hz, CH, Ph), 4.93 (dt, 1H, J_{H-H} = 5.8 Hz, J_{H-F} = 50.2 Hz, CHF), 3.94 (t, 2H, J = 6.6 Hz, CH_2OPh), 3.79 (s, 3H, $COOCH_3$), 2.61 (t, 2H, J = 7.4 Hz, $PhCH_2$), 2.05-1.62 (m, 6H, 3 x CH_2), 1.56-1.23 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.6 Hz, CH_3).
- 25 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.3 (d, J_{C-C-F} = 23 Hz, COO), 157.4, 133.2, 129.2, 114.4, 88.8 (d, J_{C-F} = 183 Hz, CF), 68.0, 52.3, 34.3, 32.0, 31.6, 29.3, 26.3, 25.7, 22.6, 14.0.
- ^{19}F NMR (186 MHz, $CDCl_3$) δ = -192.4 (m, CHF).
- MS (ESI) m/z (%) : 328 $[M+H_2O, 100]^+$, 311 $[M+H, 15]^+$.

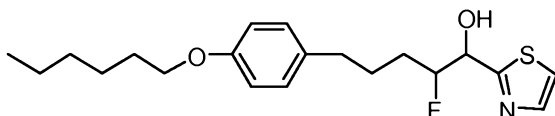
2-Fluoro-5-(4-(hexyloxy)phenyl)pentanal (39)**Procedure N then Q**5 $C_{17}H_{25}FO_2$

MW: 280.38.

Yellow oil. Yield 50%.

1H NMR (200 MHz, $CDCl_3$) δ = 9.74 (d, 1H, J = 6.2 Hz, CHO), 7.08 (d, 2H, J = 8.4 Hz, CH, Ph), 6.84 (d, 2H, J = 8.4 Hz, CH, Ph), 4.76 (dm, 1H, J_{H-F} = 51.4 Hz, CHF), 3.94 (t, 2H, J = 6.6 Hz, CH_2O Ph), 2.62 (t, 2H, J = 7.2 Hz, $PhCH_2$), 1.93-1.72 (m, 6H, 3 x CH_2), 1.54-1.24 (m, 6H, 3 x CH_2), 0.93 (t, 3H, J = 6.6 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.0 (d, J_{C-C-F} = 34 Hz, CHO), 157.4, 133.0, 129.2, 114.4, 94.8 (d, J_{C-F} = 178 Hz, CF), 67.9, 34.3, 31.5, 29.6 (d, J_{C-C-F} = 20 Hz, CH_2CHF), 29.2, 26.1, 25.7, 22.6, 14.0.

15 ^{19}F NMR (186 MHz, $CDCl_3$) δ = -199.8 (m, CHF).**2-Fluoro-5-(4-(hexyloxy)phenyl)-1-(thiazol-2-yl)pentan-1-ol (40)****Procedure A**20 $C_{20}H_{28}FNO_2S$

MW: 365.51.

Yellow oil. Yield 38%.

1H NMR (200 MHz, $CDCl_3$) δ = 7.90 (d, 1/7H, J = 3.2 Hz, ArH), 7.83 (d, 6/7H, J = 3.2 Hz, ArH), 7.45 (d, 1/7H, J = 3.2 Hz, ArH), 7.35 (d, 6/7H, J = 3.2 Hz, ArH), 7.05 (d, 2H, J = 8.6 Hz, CH, Ph), 6.80 (d, 2H, J = 8.6 Hz, CH, Ph), 5.15 (dd, 1H, J_{H-H} = 4.6 Hz, J_{H-F} = 12.8 Hz, $CHOH$), 4.99-4.65 (dm, 1H, J_{H-F} = 48.2 Hz, CHF), 3.93 (t, 2H, J = 6.4 Hz, CH_2O Ph), 2.56 (t, 2H, J = 7.2 Hz, $PhCH_2$), 1.88-1.27 (m, 12H, 6 x CH_2), 0.91 (t, 3H, J = 6.8 Hz, CH_3).

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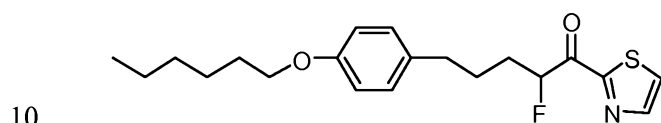
^{13}C NMR (50 MHz, CDCl_3) δ = 170.2, 157.2, 142.1, 133.7, 129.1, 119.7, 114.3, 95.1 (d, $J_{\text{C-F}}$ = 174 Hz, CF), 73.0 (d, $1/3\text{C}$, $J_{\text{C-C-F}}$ = 21 Hz, COH), 72.9 (d, $2/3\text{C}$, $J_{\text{C-C-F}}$ = 24 Hz, COH), 67.9, 34.5, 31.5, 30.4 (d, $J_{\text{C-C-F}}$ = 20 Hz, CH_2), 29.2, 26.9, 25.7, 22.5, 14.0.

5 ^{19}F NMR (186 MHz, CDCl_3) δ = -190.0 (m, CHF), -194.4 (m, CHF).

MS (ESI) m/z (%) : 366 $[\text{M}+\text{H}, 100]^+$.

2-Fluoro-5-(4-(hexyloxy)phenyl)-1-(thiazol-2-yl)pentan-1-one (41)

Procedure B



$\text{C}_{20}\text{H}_{26}\text{FNO}_2\text{S}$

MW: 363.49.

Colorless oil. Yield 60%.

15 ^1H NMR (200 MHz, CDCl_3) δ = 8.04 (d, 1H, J = 2.8 Hz, ArH), 7.75 (d, 1H, J = 3.0 Hz, ArH), 7.07 (d, 2H, J = 8.4 Hz, CH, Ph), 6.80 (d, 2H, J = 8.6 Hz, CH, Ph), 5.98 (ddd, 1H, $J_{\text{H-F}}$ = 49.6 Hz, $J_{\text{H-H}}$ = 7.6 Hz, $J_{\text{H-H}}$ = 3.6 Hz, CHF), 3.92 (t, 2H, J = 6.6 Hz, CH_2OPh), 2.75-2.52 (m, 2H, PhCH_2), 2.30-1.70 (m, 6H, 3 x CH_2), 1.59-1.26 (m, 6H, 3 x CH_2), 0.91 (t, 3H, J = 6.6 Hz, CH_3).

20 ^{13}C NMR (50 MHz, CDCl_3) δ = 188.9 (d, $J_{\text{C-C-F}}$ = 19 Hz, CO), 163.8, 157.4, 145.1, 133.3, 129.2, 126.9, 114.4, 92.3 (d, $J_{\text{C-F}}$ = 182 Hz, CF), 68.0, 34.3, 32.0 (d, $J_{\text{C-C-F}}$ = 21 Hz, CH_2CHF), 31.6, 29.3, 26.6, 25.7, 22.6, 14.0.

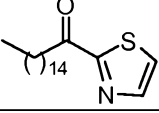
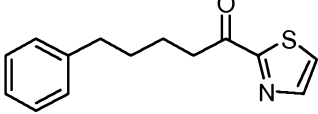
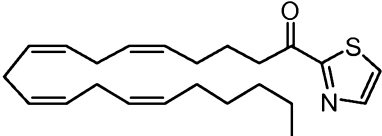
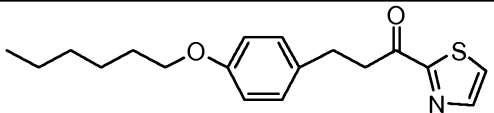
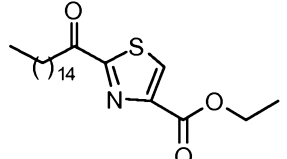
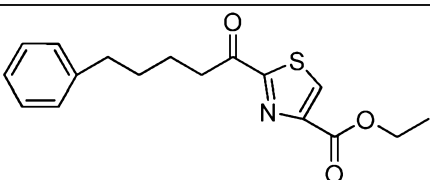
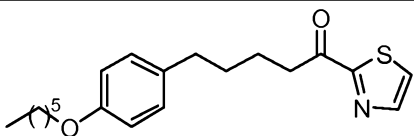
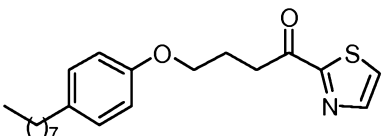
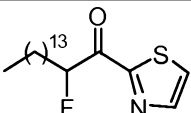
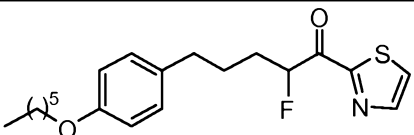
^{19}F NMR (186 MHz, CDCl_3) δ = -196.2 (m, CHF).

MS (ESI) m/z (%) : 364 $[\text{M}+\text{H}, 100]^+$.

25 The following new target compounds are therefore synthesised

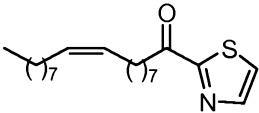
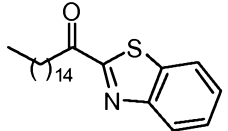
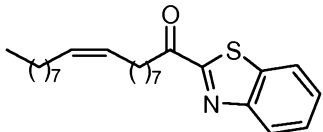
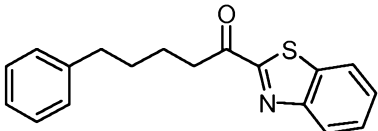
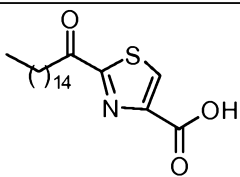
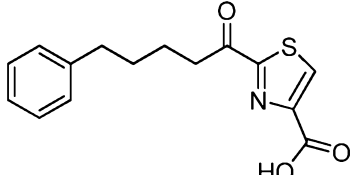
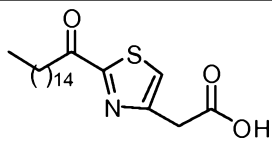
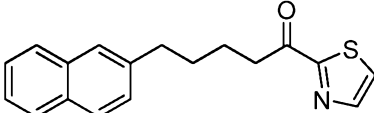
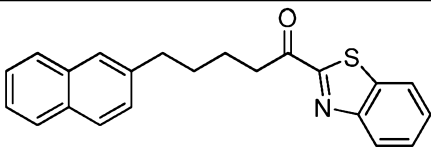
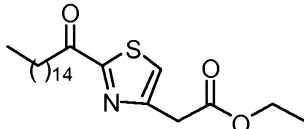
Table 1. 2-Oxo-thiazoles.

Number	Corres No.	Structure	MW	ClogP
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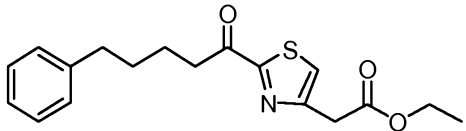
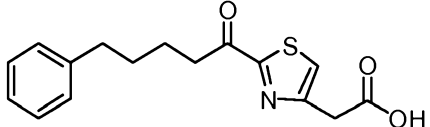
GK146	3a		323.54	8.1
GK147	3b		245.34	3.7
GK149	3d		371.58	8.3
GK150	9		317.45	5.4
GK151	15a		395.60	8.3
GK152	15b		317.40	3.8
GK153	19		345.50	6.3
GK154	24		359.53	7.1
GK155	29		341.53	7.8
GK156	41		363.49	6.0

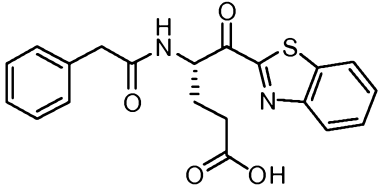
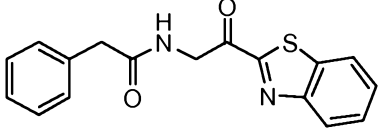
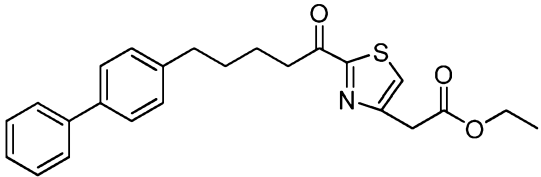
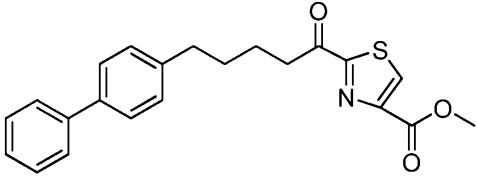
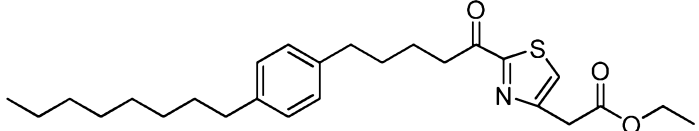
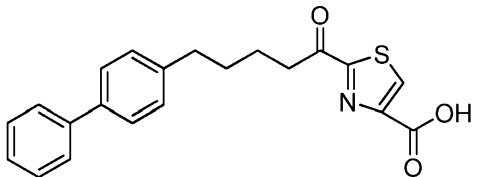
A series of further compounds have been synthesised based on the principles outlined above. These are listed in table 2

Table 2

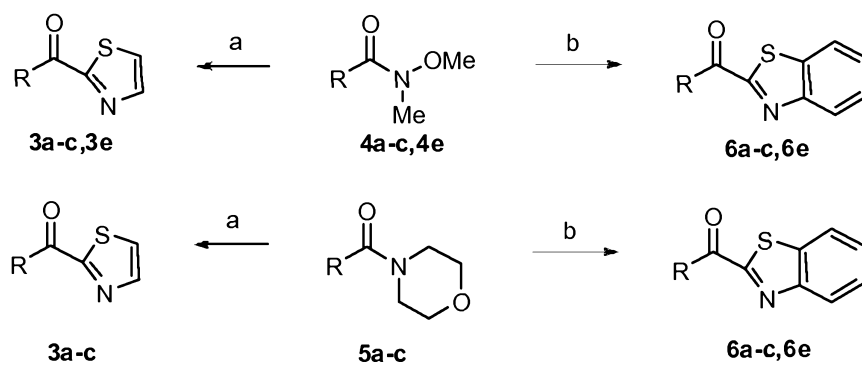
GK148	
GK157	
GK158	
GK159	
GK160	
GK162	
GK179	
GK180	
GK181	
GK182	

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GK183	
GK184	

GK198	
GK199	
GK201	
GK202	
GK203	
GK204	

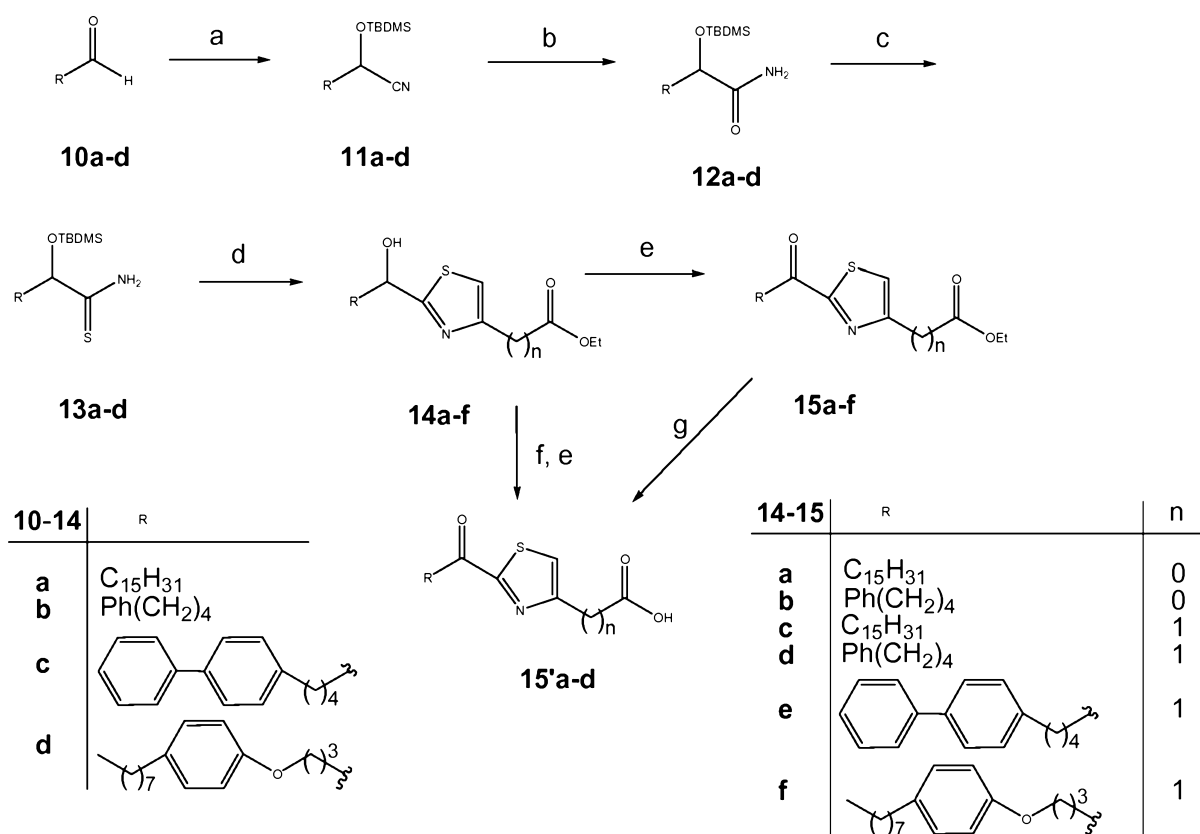
Synthetic schemes



3-6	R
a	C ₁₅ H ₃₁
b	Ph(CH ₂) ₄
c	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇
e	

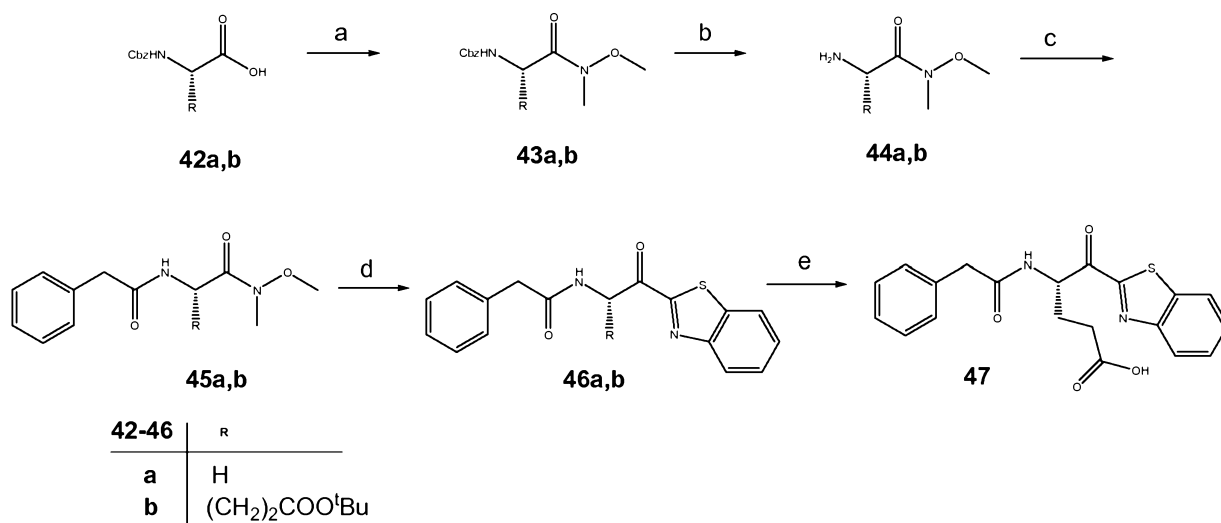
5 (a) thiazole, *n*-BuLi, dry Et₂O, -78 °C; (b) benzothiazole, *n*-BuLi, dry Et₂O, -78 °C.

- 64 -



- (a) TBDMSCN, KCN, 18-crown-6, CH₂Cl₂; (b) 30% H₂O₂, Bu₄NHSO₄, NaOH, CH₂Cl₂; (c) Lawesson's reagent, THF; (d) Br(CH₂)_nCOCOOEt, conc. H₂SO₄, EtOH, 40 °C; (e) Dess Martin periodinane, dry CH₂Cl₂; (f) 1N NaOH, EtOH; (g) Cs₂CO₃, EtOH.

- 65 -



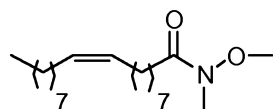
(a) *N,O*-dimethyl hydroxylamine hydrochloride, DMAP, *N*-methyl morpholine, WSCI.HCl, CH₂Cl₂; (b) ammonium formate; 10% Pd/C, MeOH; (c) PhCH₂COOH, Et₃N, WSCI, HOBt, CH₂Cl₂; (d) benzothiazole, *n*-BuLi, dry Et₂O, -78 °C; (e) 50% TFA/CH₂Cl₂.

Characterization data

The following target compounds of the invention are synthesised according to the protocols above:

N-methoxy-*N*-methyloleamide (4c)

Prepared by Procedure C



C₂₀H₃₉NO₂

MW: 325.53

Colorless oil. Yield 86% (985 mg).

¹H NMR (200 MHz, CDCl₃) δ = 5.34-5.29 (m, 2H, CH=CH), 3.65 (s, 3H, OMe),

3.15 (s, 3H, NMe), 2.38 (t, 2H, *J* = 7.4 Hz, CH₂CO), 1.99 (m, 4H, CH₂CH=CHCH₂),

- 66 -

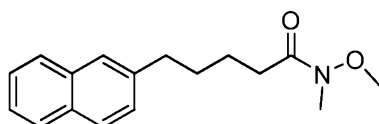
1.60 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 1.29-1.24 (m, 20H, 10 x CH_2), 0.85 (t, 3H, $J = 5.2$ Hz, CH_3).

^{13}C NMR (50 MHz, CDCl_3) $\delta = 174.5, 129.8, 129.6, 61.0, 31.8, 29.6, 29.6, 29.4, 29.3, 29.2, 27.0, 25.5, 24.5, 22.5, 14.0$.

5

***N*-methoxy-*N*-methyl-5-(naphthalen-2-yl)pentanamide (4e)**

Prepared by Procedure C



$\text{C}_{17}\text{H}_{21}\text{NO}_2$

10 MW: 271.35

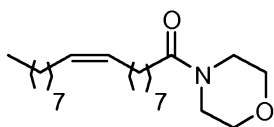
Colorless oil. Yield 75% (310 mg).

^1H NMR (CDCl_3): $\delta = 7.90\text{-}7.30$ (m, 7H, ArH), 3.65 (s, 3H, OMe), 3.18 (s, 3H, NMe), 2.82 (t, 2H, $J = 7.2$ Hz, CH_2), 2.47 (t, 2H, $J = 7.0$ Hz, CH_2), 1.98-1.60 (m, 4H, 2 x CH_2).

15 MS (ESI) m/z (%) : 272 [$\text{M}+\text{H}$, 100] $^+$.

(*Z*)-1-morpholinooctadec-9-en-1-one (5c)

Prepared by Procedure D



20 $\text{C}_{22}\text{H}_{41}\text{NO}_2$

MW: 351.57

Colorless oil. Yield 98% (1.59 g).

^1H NMR (200 MHz, CDCl_3) $\delta = 5.31\text{-}5.25$ (m, 2H, $\text{CH}=\text{CH}$), 3.62-3.57 (m, 6H, CH_2OCH_2 , CHHNCHH), 3.40 (t, 2H, $J = 5.0$ Hz, CHHNCHH), 2.25 (t, 2H, $J = 7.4$ Hz, CH_2CO), 1.97-1.93 (m, 4H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.60-1.53 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 1.26-1.21 (m, 20H, 10 x CH_2), 0.82 (t, 3H, $J = 6.2$ Hz, CH_3).

25

^{13}C NMR (50 MHz, CDCl_3) $\delta = 171.6, 129.8, 129.5, 66.8, 66.5, 45.8, 41.7, 32.9, 31.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 27.0, 25.0, 22.5, 13.9$.

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(Z)-1-(Thiazol-2-yl)octadec-9-en-1-one (3c)

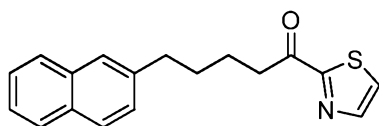
Prepared by Procedure E

Yield when the Weinreb amide was used: 70%

5 Yield when the morpholine amide was used: 70%

5-(Naphthalen-2-yl)-1-(thiazol-2-yl)pentan-1-one (3e)

Prepared by Procedure E

10 $C_{18}H_{17}NOS$

MW: 295.40

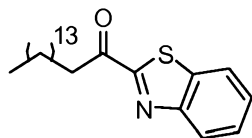
Yellow solid. Yield 70%

1H NMR (200 MHz, $CDCl_3$) δ = 7.97 (d, 1H, J = 3.0 Hz, ArH), 7.80-7.75 (m, 3H, ArH), 7.75-7.63 (m, 2H, ArH), 7.50-7.30 (m, 3H, ArH), 3.21 (t, 2H, J = 7.0 Hz, CH_2), 2.83 (t, 2H, J = 6.8 Hz, CH_2), 1.98-1.80 (m, 4H, 2 x CH_2).

15 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 193.8, 167.1, 144.6, 139.6, 133.5, 131.9, 127.8, 127.5, 127.4, 127.3, 126.3, 126.1, 125.8, 125.0, 38.2, 35.7, 30.8, 23.6.

MS (ESI) m/z (%) : 296 $[M+H, 100]^+$.**20 1-(Benzo[d]thiazol-2-yl)hexadecan-1-one (6a)**

Prepared by Procedure E

 $C_{23}H_{35}NOS$

MW: 373.60

25 Yellowish solid.

Yield via Weinreb amide 60% (140 mg).

Yield via morpholine amide 85% (180 mg).

m.p. : 74-76 °C.

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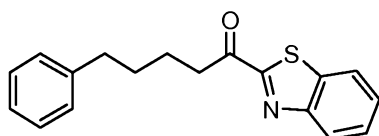
^1H NMR (200 MHz, CDCl_3) δ = 8.19 (d, 1H, J = 7.4 Hz, benzothiazole), 7.98 (d, 1H, J = 7.4 Hz, benzothiazole), 7.62-7.49 (m, 2H, benzothiazole), 3.27 (t, 2H, J = 7.2 Hz, CH_2CO), 1.86-1.74 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 1.44-1.21 (m, 24H, 12 x CH_2), 0.88 (t, 3H, J = 6.0 Hz, CH_3).

5 ^{13}C NMR (50 MHz, CDCl_3) δ = 195.6, 166.6, 153.5, 137.2, 127.5, 126.8, 125.3, 122.4, 38.5, 31.9, 29.6, 29.6, 29.4, 29.3, 29.3, 29.1, 23.9, 22.6, 14.1.

MS (ESI) m/z (%) : 374 $[\text{M}+\text{H}, 100]^+$.

1-(Benzo[d]thiazol-2-yl)-5-phenylpentan-1-one (6b)

10 Prepared by Procedure E



$\text{C}_{18}\text{H}_{17}\text{NOS}$

MW: 295.40

Yellow solid.

15 Yield via Weinreb amide 77% (204 mg).

Yield via morpholine amide 72% (126 mg).

m.p. : 66-68 °C.

^1H NMR (200 MHz, CDCl_3) δ = 8.19 (d, 1H, J = 7.4 Hz, benzothiazole), 7.96 (d, 1H, J = 7.6 Hz, benzothiazole), 7.61-7.47 (m, 2H, benzothiazole), 7.34-7.15 (m, 5H, Ph), 3.31 (t, 2H, J = 6.8 Hz, CH_2CO), 2.70 (t, 2H, J = 7.4 Hz, PhCH_2), 1.96-1.69 (m, 4H, 2 x CH_2).

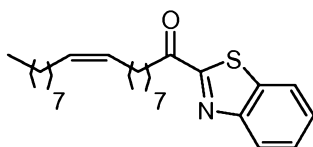
20 ^{13}C NMR (50 MHz, CDCl_3) δ = 195.2, 166.3, 153.4, 142.0, 137.1, 128.3, 128.2, 127.5, 126.8, 125.6, 125.2, 122.3, 38.2, 35.5, 30.8, 23.4.

MS (ESI) m/z (%) : 296 $[\text{M}+\text{H}, 100]^+$.

25

(Z)-1-(Benzo[d]thiazol-2-yl)octadec-9-en-1-one (6c)

Prepared by Procedure E



- 69 -

 $C_{25}H_{37}NOS$

MW: 399.63

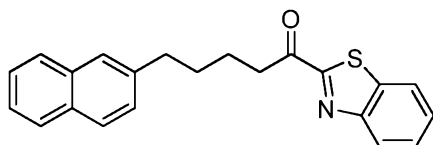
Yellow oil.

Yield via Weinreb amide 70% (170 mg).

- 5 1H NMR (200 MHz, $CDCl_3$) δ = 8.17 (d, 1H, J = 7.0 Hz, benzothiazole), 7.95 (d, 1H, J = 6.2 Hz, benzothiazole), 7.60-7.45 (m, 2H, benzothiazole), 5.42-5.27 (m, 2H, CH=CH), 3.26 (t, 2H, J = 7.4 Hz, CH_2CO), 2.02-2.00 (m, 4H, $CH_2CH=CHCH_2$), 1.88-1.73 (m, 2H, CH_2CH_2CO), 1.43-1.25 (m, 20H, 10 x CH_2), 0.87 (t, 3H, J = 6.4 Hz, CH_3).
- 10 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 195.4, 166.5, 153.4, 137.1, 129.9, 129.6, 127.4, 126.8, 125.2, 122.3, 38.5, 31.8, 29.7, 29.6, 29.4, 29.2, 29.2, 29.1, 29.0, 27.1, 27.1, 23.8, 22.6, 14.0.
- MS (ESI) m/z (%) : 400 $[M+H, 100]^+$.

15 **1-(Benzo[d]thiazol-2-yl)-5-(naphthalen-2-yl)pentan-1-one (6e)**

Prepared by Procedure E

 $C_{22}H_{19}NOS$

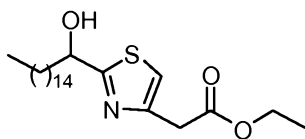
MW: 345.46

- 20 Yellow solid. Yield 72%.
- 1H NMR (200 MHz, $CDCl_3$) δ = 8.20 (d, 1H, J = 6.0 Hz, ArH), 7.97 (d, 1H, J = 8.0 Hz, ArH), 7.90-7.70 (m, 3H, ArH), 7.70-7.30 (m, 6H, ArH), 3.35 (t, 2H, J = 7.0 Hz, CH_2), 2.90 (t, 2H, J = 6.8 Hz, CH_2), 2.05-1.82 (m, 4H, 2 x CH_2).
- 25 ^{13}C NMR (50 MHz, $CDCl_3$) δ = 195.3, 166.4, 153.5, 139.6, 137.2, 133.5, 131.9, 127.8, 127.6, 127.5, 127.4, 127.3, 126.9, 126.4, 125.8, 125.3, 125.0, 122.4, 38.3, 35.8, 30.7, 23.6.
- MS (ESI) m/z (%) : 246 $[M+H, 100]^+$.

Ethyl 2-(2-(1-hydroxyhexadecyl)thiazol-4-yl)acetate (14c)

- 30 Prepared by Procedure K

- 70 -

C₂₃H₄₁NO₃S

MW: 411.64

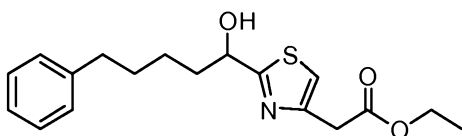
White solid.

5 ¹H NMR (300 MHz, CDCl₃): δ = 7.15 (s, 1H, SCH), 4.97 (dd, *J*₁ = 7.8 Hz, *J*₂ = 4.5 Hz, 1H, CHOH), 4.20 (q, *J* = 7.2 Hz, 2H, COOCH₂), 3.82 (s, 2H, CH₂COO), 2.07–1.78 (m, 2H CH₂), 1.59–1.20 (m, 29H, 13×CH₂, CH₃), 0.89 (t, *J* = 6.3 Hz, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃): δ = 174.98, 170.36, 148.18, 115.97, 71.95, 61.08,
10 38.32, 36.93, 31.91, 29.68, 29.66, 29.56, 29.49, 29.36, 25.20, 22.69, 14.14.

MS (ESI) *m/z* (%): 412 [M+H, 100]⁺.**Ethyl 2-(2-(1-hydroxy-5-phenylpentyl)thiazol-4-yl)acetate (14d)**

Prepared by Procedure K



15

C₁₈H₂₃NO₃S

MW: 333.45

Pale yellow solid; Yield 44%.

m.p. 53-55 °C

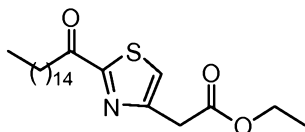
20 ¹H NMR (200 MHz, CDCl₃): δ 7.35-7.07 (m, 6H, SCH, Ph), 4.93 (dd, *J*₁ = 7.8 Hz, *J*₂ = 4.8 Hz, 1H, CHOH), 4.18 (q, *J* = 7.0 Hz, COOCH₂), 3.79 (s, 2H, CH₂COO), 2.61 (t, *J* = 7.2 Hz, CH₂Ph), 2.06-1.37 (m, 6H, 3×CH₂), 1.26 (t, *J* = 7.2 Hz, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ 174.95, 170.37, 148.20, 142.38, 128.34, 128.24,
25 125.65, 116.00, 71.80, 61.08, 38.12, 36.90, 35.74, 31.19, 24.89, 14.15.

MS (ESI) *m/z* (%): 334 [M+H, 100]⁺.**Ethyl 2-(2-palmitoylthiazol-4-yl)acetate (15c)**

- 71 -

Prepared by Procedure B

 $C_{23}H_{39}NO_3S$

MW: 409.63

5 White solid. Yield 90%.

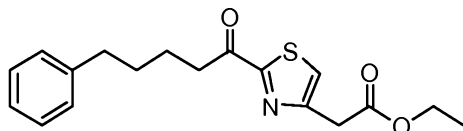
m.p. 46-48 °C

1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1H, SCH), 4.21 (q, J = 7.2 Hz, 2H, $COOCH_2$), 3.90 (s, 2H, CH_2COO), 3.12 (t, J = 7.5 Hz, 2H, CH_2CO), 1.82–1.62 (m, 2H CH_2), 1.55–1.19 (m, 27H, 12 \times CH_2 , CH_3), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

10 ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.09, 170.00, 166.52, 150.95, 123.56, 61.24, 38.43, 37.00, 31.91, 29.65, 29.47, 29.39, 29.35, 29.18, 23.91, 22.68, 14.13.

MS (ESI) m/z (%): 410 $[M+H, 100]^+$.**Ethyl 2-(2-(5-phenylpentanoyl)thiazol-4-yl)acetate (15d)**

15 Prepared by Procedure B

 $C_{18}H_{21}NO_3S$

MW: 331.43

White oil. Yield 81%.

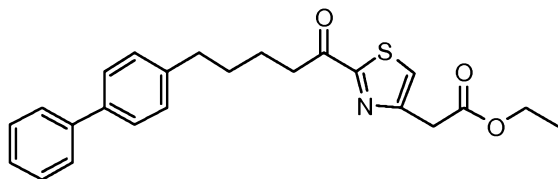
20 1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H, SCH), 7.34–7.16 (m, 5H, Ph), 4.22 (q, J = 7.2 Hz, 2H, $COOCH_2$), 3.91 (s, 2H, CH_2COO), 3.17 (t, J = 7.5 Hz, 2H, CH_2CO), 2.68 (t, J = 7.2 Hz, 2H, CH_2Ph), 1.85–1.63 (m, 4H 2 \times CH_2), 1.30 (t, J = 7.2 Hz, 3H, CH_3).

25 ^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.82, 169.99, 166.42, 150.99, 142.17, 128.39, 128.27, 125.71, 123.69, 61.26, 38.17, 36.99, 35.65, 30.92, 23.56, 14.16.

MS (ESI) m/z (%): 332 $[M+H, 99]^+$.**Ethyl 2-(2-(5-(biphenyl-4-yl)pentanoyl)thiazol-4-yl)acetate (15e)**

- 72 -

Prepared by Procedure B

 $C_{24}H_{25}NO_3S$

MW: 407.53

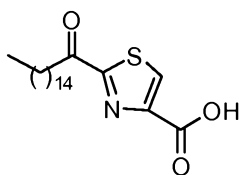
5 White solid.

1H NMR (200 MHz, $CDCl_3$): δ = 7.65-7.18 (m, 10H, Ar, SCH), 4.21 (q, J = 7.4 Hz, 2H, $COOCH_2$), 3.90 (s, 2H, CH_2COO), 3.18 (t, J = 6.6 Hz, CH_2CO), 2.70 (t, J = 7.2 Hz, CH_2Ph), 1.94-1.65 (m, 4H, $2 \times CH_2$), 1.28 (t, J = 7.2 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.79, 169.95, 166.40, 151.01, 141.29, 141.06, 138.66, 128.80, 128.66, 127.01, 126.95, 123.67, 61.22, 38.15, 36.97, 35.25, 30.85, 23.57, 14.14.

MS (ESI) m/z (%): 408 $[M+H, 100]^+$.**2-palmitoylthiazole-4-carboxylic acid (15'a)**

15 Prepared by Procedures L, then B

 $C_{20}H_{33}NO_3S$

MW: 367.55

White solid. Yield 50%.

20 m.p. 98-100 °C.

1H NMR (200 MHz, $CDCl_3$): δ = 8.39 (s, 1H, CH), 3.25-3.00 (m, 2H, CH_2), 1.80-1.55 (m, 2H, CH_2), 1.40-1.00 (m, 24H, 12 x CH_2), 0.88 (t, 3H, J = 6.8 Hz, CH_3).

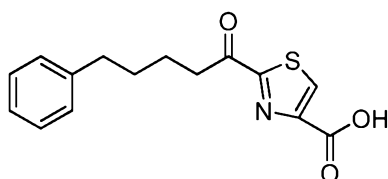
^{13}C NMR (50 MHz, $CDCl_3+CD_3OD$): δ = 193.9, 166.4, 164.6, 151.5, 131.8, 37.9, 31.5, 29.2, 29.0, 28.9, 28.7, 23.2, 22.2, 13.4.

25 MS (ESI) m/z (%): 366 $[M-H, 100]^-$.

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2-(5-Phenylpentanoyl)thiazole-4-carboxylic acid (15'b)

Prepared by Procedure M

 $C_{15}H_{15}NO_3S$

5 MW: 289.35

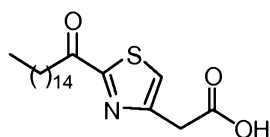
White solid. Yield 86% (25 mg).

1H NMR ($CDCl_3$): δ = 8.55 (s, 2H, ArH, COOH), 7.30-7.10 (m, 5H, Ph), 3.26 (t, 2H, J = 6.8 Hz, CH_2), 2.66 (t, 2H, J = 7.0 Hz, CH_2), 1.90-1.63 (m, 4H, $2 \times CH_2$).

^{13}C NMR ($CDCl_3$): δ = 193.5, 167.8, 164.6, 147.4, 142.0, 134.9, 128.4, 128.3, 125.8, 38.2, 35.6, 30.7, 23.2.

10 MS (ESI) m/z (%): 290 $[M+H, 47]^+$.**2-(2-Palmitoylthiazol-4-yl)acetic acid (15'c)**

Prepared by Procedures L, then B



15

 $C_{21}H_{35}NO_3S$

MW: 381.57

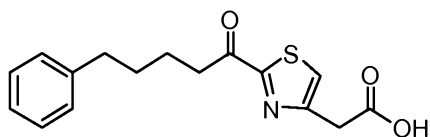
White solid.

1H NMR (300 MHz, $CDCl_3$): δ 7.55 (s, 1H, SCH), 3.98 (s, 2H, CH_2COO), 3.13 (t, J = 7.6 Hz, 2H, CH_2CO), 1.82-1.69 (m, 2H, CH_2), 1.43-1.18 (m, 24H, $12 \times CH_2$), 0.89 (t, J = 6.9 Hz, 3H, CH_3).

20 MS (ESI) m/z (%): 336 $[M-COOH-H, 100]^-$, 380 $[M-H, 46]^-$.**2-(2-(5-Phenylpentanoyl)thiazol-4-yl)acetic acid (15'd)**

25 Prepared by Procedure M

- 74 -

C₁₆H₁₇NO₃S

MW: 303.38

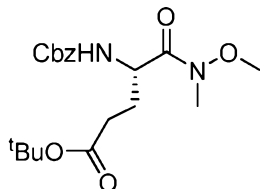
White oil. Yield 89%.

- 5 ¹H NMR (300 MHz, CDCl₃): δ 7.49 (s, 1H, SCH), 7.35–7.08 (m, 5H, Ph), 3.88 (s, 2H, CH₂COO), 3.11 (t, *J* = 7.5 Hz, 2H, CH₂CO), 2.63 (t, *J* = 7.0 Hz, 2H, CH₂Ph), 1.85–1.63 (m, 4H 2×CH₂).

MS (ESI) *m/z* (%): 304 [M+H, 77]⁺.

- 10 **(*S*)-*tert*-Butyl 4-(benzyloxycarbonylamino)-5-(methoxy(methyl)amino)-5-oxopentanoate (43b)**

Prepared by Procedure C

C₁₉H₂₈N₂O₆

- 15 MW: 380.44

Colorless oil. Yield 100%.

¹H NMR (200 MHz, CDCl₃) δ = 7.35–7.20 (m, 5H, ArH), 5.67 (d, 1H, *J* = 8.0 Hz, NH), 5.06 (s, 2H, CH₂), 4.80–4.60 (m, 1H, CH), 3.73 (s, 3H, OMe), 3.15 (s, 3H, NMe), 2.40–1.70 (m, 4H, CH₂), 1.38 (s, 9H, ^tBu).

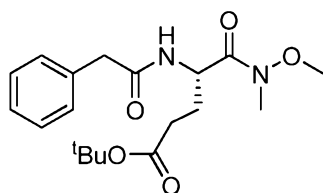
- 20 ¹³C NMR (50 MHz, CDCl₃) δ = 171.9, 155.9, 136.1, 128.3, 127.9, 127.8, 80.3, 66.6, 61.4, 50.3, 31.9, 31.0, 27.9, 27.4.

MS (ESI) *m/z* (%) : 381 [M+H, 100]⁺.

- 25 **(*S*)-*tert*-Butyl 5-(methoxy(methyl)amino)-5-oxo-4-(2-phenylacetamido)pentanoate (45b)**

Prepared by Procedures V, then W

- 75 -

C₁₉H₂₈N₂O₅

MW: 364.44

Colorless oil.

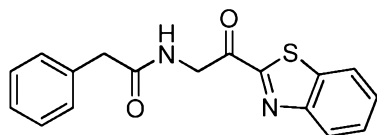
- 5 ¹H NMR (200 MHz, CDCl₃) δ = 7.40-7.20 (m, 5H, ArH), 6.38 (d, 1H, J = 8.0 Hz, NH), 5.02-4.90 (m, 1H, CH), 3.65 (s, 3H, OMe), 3.55 (s, 2H, CH₂), 3.18 (s, 3H, NMe), 2.25-1.70 (m, 4H, CH₂), 1.40 (s, 9H, ^tBu).

¹³C NMR (50 MHz, CDCl₃) δ = 172.1, 170.9, 166.3, 134.6, 129.3, 128.9, 127.2, 80.5, 61.6, 48.7, 43.6, 31.1, 28.0, 27.2.

- 10 MS (ESI) m/z (%) : 365 [M+H, 100]⁺.

***N*-(2-(Benzo[d]thiazol-2-yl)-2-oxoethyl)-2-phenylacetamide (46a)**

Prepared by Procedure E



- 15 C₁₇H₁₄N₂O₂S

MW: 310.37

Orange solid.

- ¹H NMR (200 MHz, CDCl₃) δ = 8.11 (d, 1H, J = 8.0 Hz, ArH), 7.94 (d, 1H, J = 8.0 Hz, ArH), 7.65-7.40 (m, 2H, ArH), 7.39-7.20 (m, 5H, ArH), 6.34 (b, 1H, NH), 4.95 (d, 2H, J = 5.2 Hz, CH₂), 3.67 (s, 2H, CH₂).

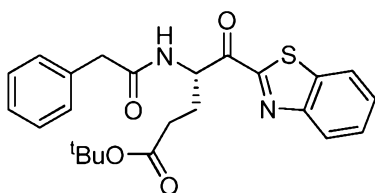
- 20 ¹³C NMR (50 MHz, CDCl₃) δ = 189.7, 171.4, 163.1, 153.3, 136.9, 134.4, 129.5, 129.0, 128.1, 127.4, 127.1, 125.6, 122.3, 46.8, 43.5.

MS (ESI) m/z (%) : 311 [M+H, 100]⁺.

- 25 ***(S)*-tert-Butyl 5-(benzo[d]thiazol-2-yl)-5-oxo-4-(2-phenylacetamido)pentanoate (46b)**

Prepared by Procedure E

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 $C_{24}H_{26}N_2O_4S$

MW: 438.54

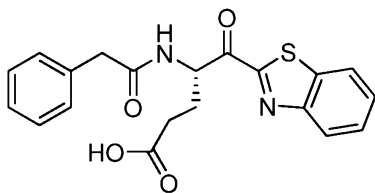
Colorless Oil. Yield 50%.

5 1H NMR (200 MHz, $CDCl_3$) δ = 8.10 (d, 1H, J = 8.0 Hz, ArH), 7.91 (d, 1H, J = 8.0 Hz, ArH), 7.62-7.20 (m, 7H, ArH), 6.77 (d, 1H, J = 8.0 Hz, NH), 5.68-5.70 (m, 1H, CH), 3.61 (s, 2H, CH_2), 2.50-1.98 (m, 4H, CH_2), 1.38 (s, 9H, tBu).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 192.5, 172.1, 170.9, 163.5, 153.2, 137.0, 134.4, 129.3, 128.8, 127.9, 127.2, 127.0, 125.8, 122.2, 80.7, 55.1, 43.4, 30.3, 30.6, 27.9, 27.3.

MS (ESI) m/z (%) : 439 $[M+H, 55]^+$.**(S)-5-(Benzo[d]thiazol-2-yl)-5-oxo-4-(2-phenylacetamido)pentanoic acid (47)**

Prepared by Procedure X



15

 $C_{20}H_{18}N_2O_4S$

MW: 382.43

Yellow solid. Yield 50%.

20 1H NMR (200 MHz, $CDCl_3$) δ = 8.11 (d, 1H, J = 8.0 Hz, ArH), 7.94 (d, 1H, J = 8.0 Hz, ArH), 7.65-7.40 (m, 2H, ArH), 7.38-7.10 (m, 5H, ArH), 6.71 (d, 1H, J = 8.0 Hz, NH), 5.90-5.60 (m, 1H, CH), 3.63 (s, 2H, CH_2), 2.55-2.25 (m, 3H, CH_2), 2.20-1.90 (m, 1H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 192.3, 177.0, 171.6, 163.3, 153.3, 137.1, 134.2, 129.4, 129.0, 128.2, 127.5, 127.2, 126.1, 125.8, 122.3, 55.2, 43.5, 30.1, 27.5.

25 MS (ESI) m/z (%) : 381 $[M-H, 100]^-$.

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Some of the compounds above were tested using an in vitro cPLA₂ enzyme activity assay.

***In vitro* cPLA₂ assay**

5 Assay for cPLA₂ activity was performed by the use of sonicated vesicles of 1-palmitoyl-2-arachidonoyl-*sn*-glycerol-3-phosphorylcholine (100 µM) containing 100,000 cpm of 1-palmitoyl-2-[1-¹⁴C]arachidonoyl-*sn*-glycerol-3-phosphorylcholine in 100 mM Hepes, pH 7.5, 80 µM Ca²⁺, 2 mM dithiothreitol, and 0.1 mg/ml BSA as
10 described. Following a 35-min incubation at 37 °C, the reaction was terminated (derived from Wijkander et al). The lower phase was separated by thin layer chromatography, and the spot corresponding to free [1-¹⁴C]arachidonic acid was visualized by digital imaging and quantified with a PhosphorImager (Fuji Instruments). The source of cPLA₂ enzyme was recombinant overexpression of the
15 human gene for group IVa PLA₂ in baculovirus insect cell expression system, as described in Abdullah et al.

Wijkander, J., and Sundler, R. (1991) *Eur. J. Biochem.* **202**, 873–880

20 Abdullah, K., et al. (1995) Human cytosolic phospholipase A₂ expressed in insect cells is extensively phosphorylated on Ser-505. *Biochim Biophys Acta*. 1995 May 11;1244(1):157-64.

The results are presented below:

Compound No.	Enzyme Assay IC ₅₀
3b	3050 nM
24	3650 nM
41	3700 nM

25

Further testing was carried out as follows:

Reagents

- 78 -

The Cell Culture SW982 model cell line at a confluent or spheroid state (Wada Y, 2005) was used since gene expression and generation of proinflammatory cytokines resemble RA-derived synovial fibroblast-like cells.

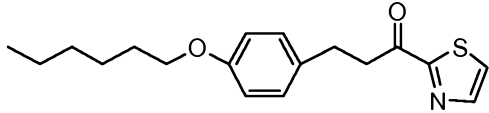
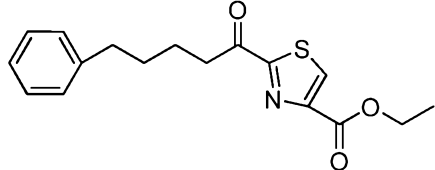
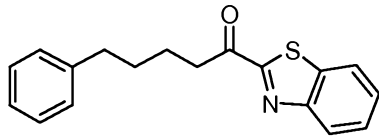
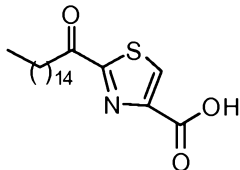
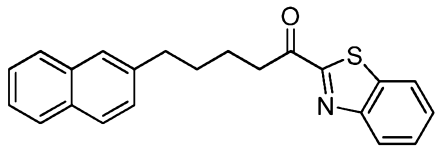
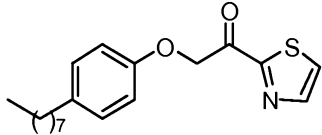
- 5 AA release assay: 1h preincubation at 50 and 25 μ M – 4h IL-1B stimulation, repeated 2-3 times. Only inhibitors that showed a ~50% inhibition in either of the initial two concentrations were further tested in a dose-response. IC50 is evaluated from dose-response inhibitions curves.

10 **PGE₂ analysis**

PGE₂ detection

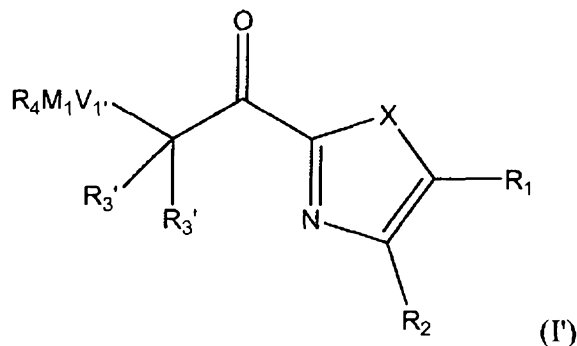
- Samples and controls were slowly thawed and diluted (between 1:1 and 1:2500) in the standard diluent. The maximal dilution was 1:10 for one step. That is why several intermediate dilutions were prepared. In the beginning all values were
- 15 determined from duplicates. After having minimized technical errors, samples were only analyzed as individuals. All further steps, except for some minor corrections, were performed according to the manufacturer's recommendations as can be found in the manual of the EIA kit. In order to optimize the results, the incubation time of the alkaline phosphatase substrate was prolonged by 15 minutes. During the
- 20 incubation, the plates were kept in the dark. An example of the arrangements of the samples and controls is illustrated in the appendix. The read-out was carried out with a Multiscan plate reader (Ascent Labsystems) at wavelengths of 414 and 595 nm after 10 seconds shaking at 120 rpm. The corresponding software to obtain the data was the Ascent software for Multiscan, Version 2.4.1.
- 25 Data were processed using Microsoft Office Excel 2003 and SigmaPlot 10.0.

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Code	Structure	AA release SW982 cells	cPLA2 in vitro assay	PGE2- assay
		IC50 (μ M)	IC50 (μ M)	% inhibition
GK150		5,8		Not yet known
GK152		7,4 (2h) >25 (4h)	>5	0.1 μ M: 41% 3 μ M::38% 10 μ M::30% 30 μ M:31%
GK159		<2 (2h) ~25 (4h)	>5	0.3 μ M::76% 3 μ M: 18% 10 μ M:23% 30 μ M:10%
GK160		4,9	7,2	10 μ M: 12% 30 μ M: 30%
GK181		1,4		10 μ M: 16.3% 30 μ M: 22.5%
GK185		2,8	2	Not yet known

Claims

1. A compound of formula (I')



wherein X is S;

R_2 is selected from the group consisting of H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$, $CONHC_{1-6}alkyl$, $CON(C_{1-6}alkyl)_2$, $OCOC_{1-6}alkyl$, $C_{1-6}alkylCOOH$, $C_{1-6}alkylCOOC_{1-6}alkyl$ and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R_1 is H;

or R_1 or R_1 and R_2 taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R_5 ;

each $R_{3'}$ is the same or different and is selected from the group consisting of H, $C_{1-6}alkylCOOR_a$ halo, and $CHal_3$;

R_a is selected from the group consisting of H and $C_{1-6}alkyl$;

each R_5 is defined as for R_2 ;

$V_{1'}$ is a covalent bond, -O-, or a $C_{1-20}alkyl$ group, or C_{2-20} -mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6}alkyl)$, S, SO, or SO_2 ;

M_1 is absent or is a C_{5-10} cyclic group or a C_{5-15} aromatic group (e.g. C_{6-14} aromatic group); and

R_4 is selected from the group consisting of H, $C_{1-10}alkyl$ group, and $C_{1-10}alkoxy$;

with the proviso that the group $V_1M_1R_4$ as a whole provides at least 4 backbone atoms from the $C(R_3')$ group;

with the proviso that $R_4M_1V_1C(R_3')_2$ is not oleyl or $-(CH_2)_6Ph$;

or a salt, ester, solvate or N-oxide thereof

5 when used for the treatment of:

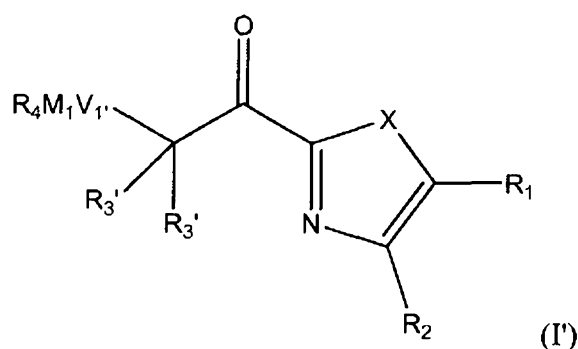
(i) a chronic inflammatory condition;

(ii) atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, pityriasis rosea, lichen planus or drug eruptions; or

10 (iii) arthritis, dermatoses, inflammatory CNS diseases, multiple sclerosis, chronic obstructive pulmonary disease, chronic lung inflammatory conditions, inflammatory bowel disease such as ulcerative colitis and crohns disease or cardiovascular disease.

15 2. The compound of claim 1 wherein R_3' is H, halo, or $CHal_3$.

3. A compound of formula (I')



20 wherein X is S;

R_2 is selected from the group consisting of H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$, $CONHC_{1-6}alkyl$, $CON(C_{1-6}alkyl)_2$, $OCOC_{1-6}alkyl$, $C_{1-6}alkylCOOH$, $C_{1-6}alkylCOOC_{1-6}alkyl$ and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

25

R_1 is H or R_1 and R_2 taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R_5H ;

each $R_{3'}$ is the same or different and is selected from the group consisting of H, $C_{1-6}alkylCOOR_a$, halo, and $CHal_3$;

5 R_a is H or $C_{1-6} alkyl$;

each R_5 is defined as for R_2 ;

V_1 is a $C_{1-20}alkyl$ group, or C_{2-20} - multiply unsaturated alkenyl group; said alkyl group being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6} alkyl)$, S, SO, or SO_2 ;

10 M_1 is absent or is a C_{5-10} cyclic group or a C_{5-15} aromatic group (e.g. C_{6-14} aromatic group); and

R_4 is selected from the group consisting of H, a $C_{1-10}alkyl$ group, and C_{1-10} alkoxy group;

15 with the proviso that the group $V_1M_1R_4$ as a whole provides at least 4 backbone atoms from the $C(R_3)$ group, preferably at least 10 backbone atoms from the $C(R_3)$ group;

or a salt, ester, solvate or N-oxide thereof

with the proviso that $R_4M_1V_1C(R_3)_2$ is not oleyl or $-(CH_2)_6Ph$.

20 4. The compound of claim 3 in which R_2 is selected from the group consisting of COOH, $COOC_{1-6}alkyl$ and $C_{1-6}alkylCOOH$.

5. The compound of any one of claims 1 to 3 in which R_1 and R_2 can be taken together to form a ring system such as a phenyl ring or pyridine ring optionally substituted by 1 or 2 groups R_5 .

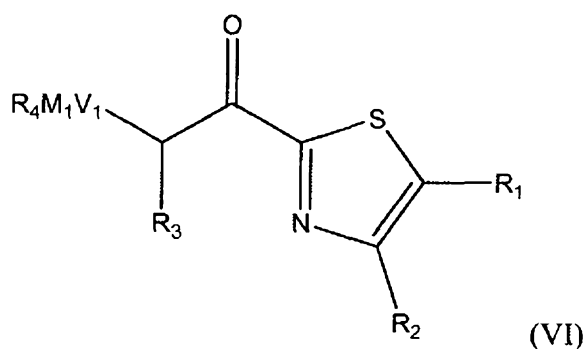
6. The compound as claimed in any preceding claim in which each $R_{3'}$ is hydrogen or halo.

30 7. The compound as claimed in any preceding claim in which $V_1M_1R_4$ provides at least 10 backbone atoms from the $C(R_3)$ group.

8. The compound as claimed in any preceding claim in which V_1 is a C_{1-15} -alkyl group, or is a $-C_{1-6}$ alkylO- group (i.e. where the O atom bonds to M_1).

9. The compound as claimed in any preceding claim in which M_1 is either
5 absent or is an C_{6-10} aryl group.

10. The compound of claim 1 of formula (VI)



10

wherein R_1 is H;

R_2 is selected from the group consisting of H, COOH, COOC $_{1-6}$ alkyl, C $_{1-6}$ alkylCOOH, and C $_{1-6}$ alkylCOOC $_{1-6}$ alkyl;

R_3 is H or F;

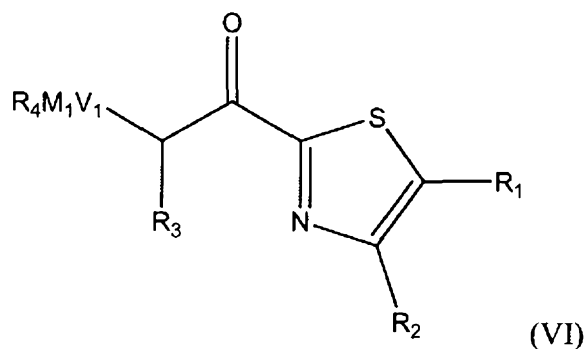
15 V_1 is selected from the group consisting of C_{1-15} -alkyl group, C_{2-20} -alkenyl group and $-C_{1-6}$ -alkylO- group;

M_1 is absent or is a phenyl group;

R_4 is selected from the group consisting of H, C $_{1-10}$ alkyl group and C $_{1-10}$ alkoxy group.

20

11. The compound of claim 3 of formula (VI)



wherein R_1 is H;

R_2 is selected from the group consisting of H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, and C₁₋₆alkylCOOC₁₋₆alkyl;

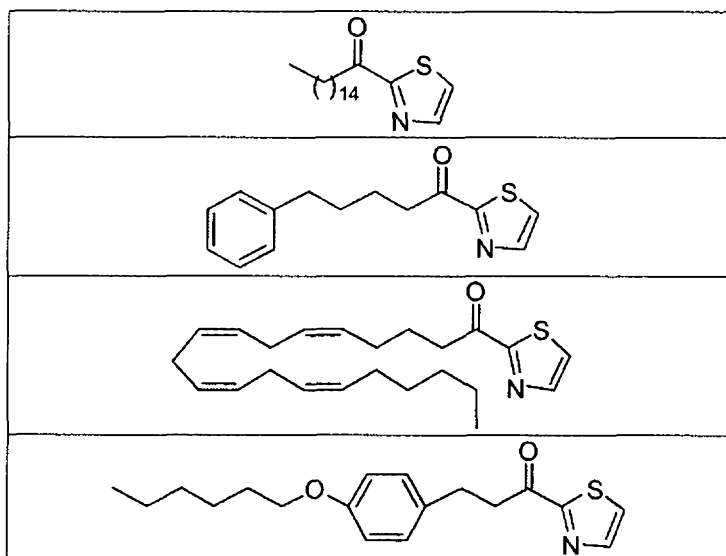
R_3 is H or F;

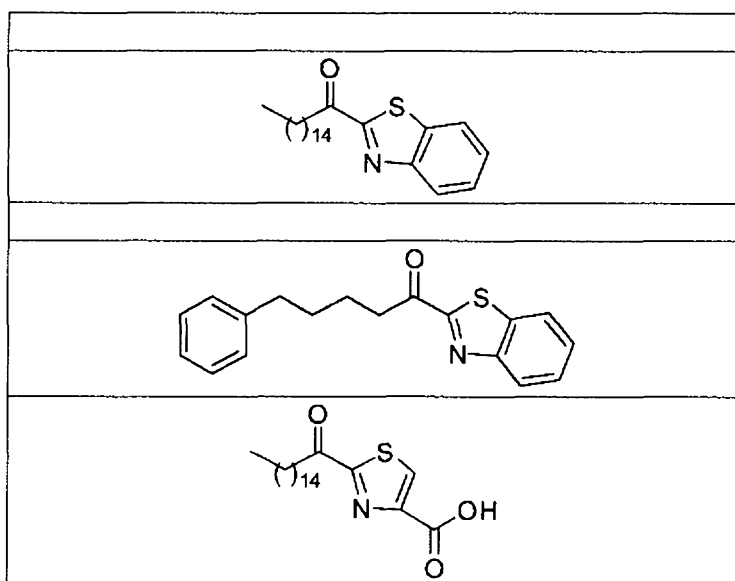
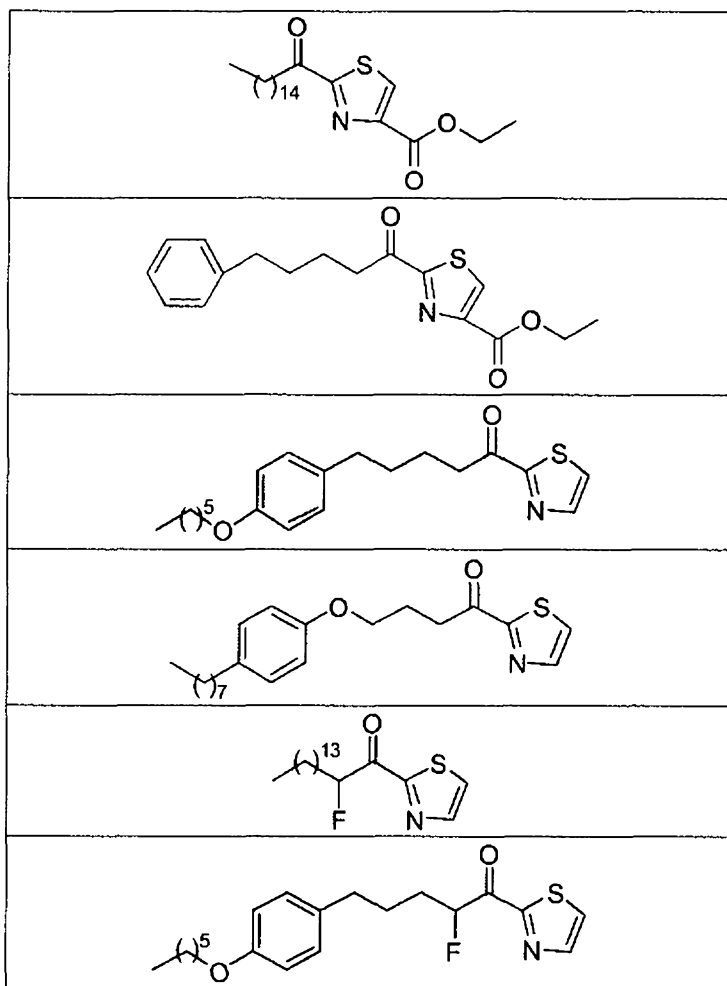
V_1 is C₁₋₁₅-alkyl group or is a -C₁₋₆-alkylO- group;

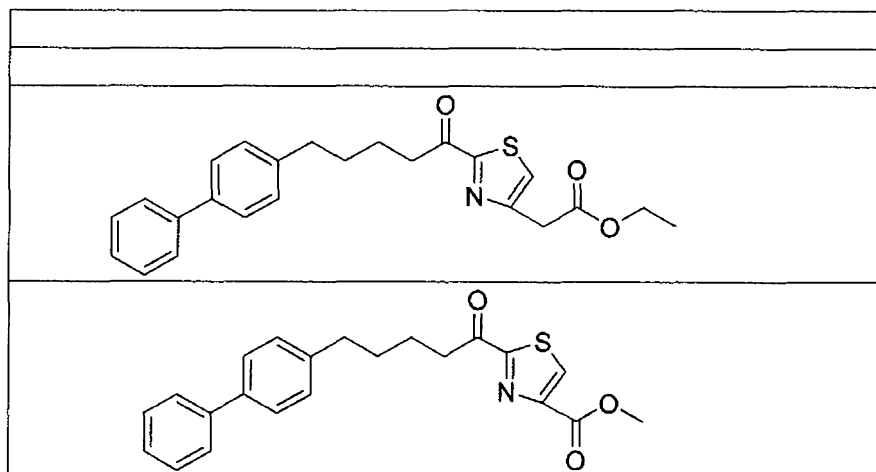
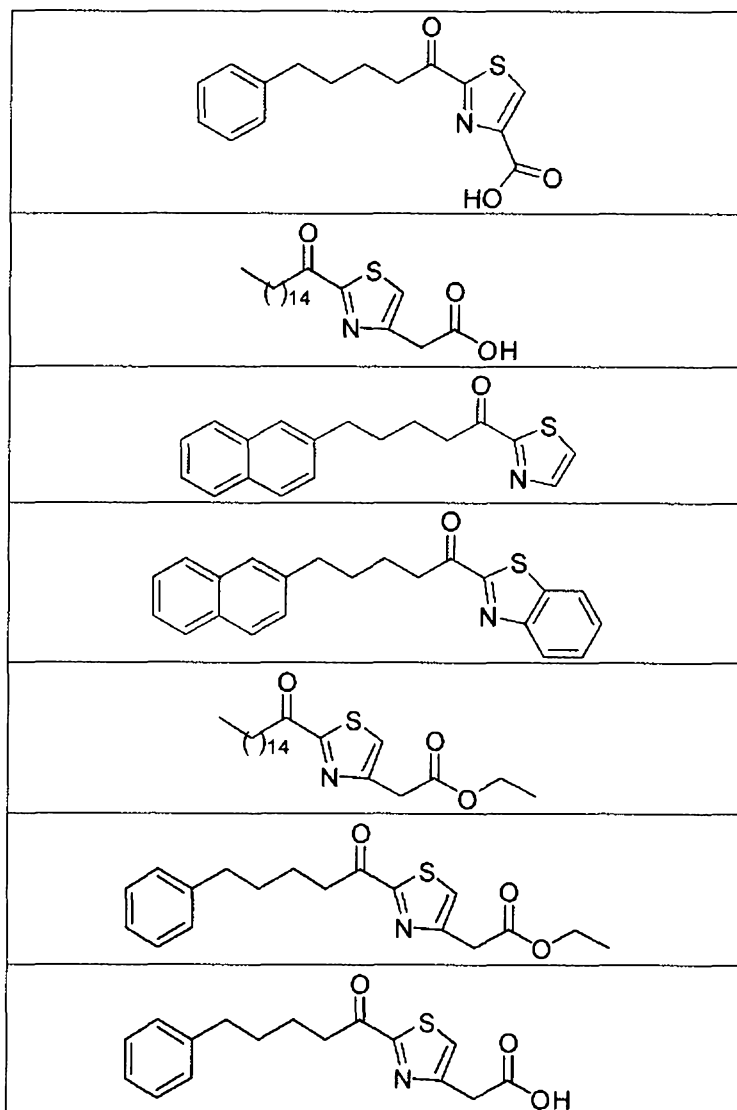
M_1 is absent or is a phenyl group;

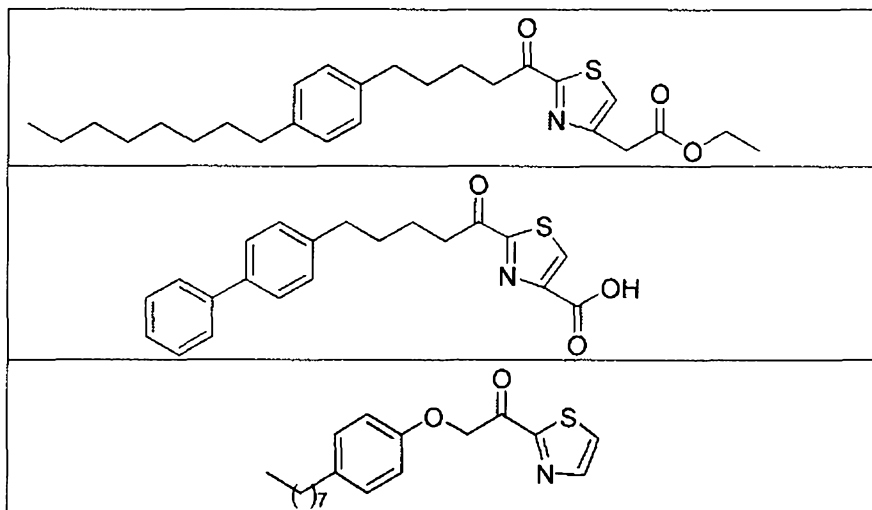
R_4 is selected from the group consisting of H, C₁₋₁₀alkyl group and C₁₋₁₀alkoxy group.

12. A compound as claimed in claim 3 being







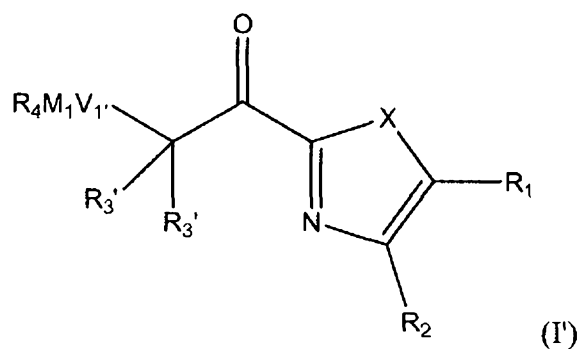


or a salt, ester, solvate or N-oxide thereof

13. The compound of claim 1 wherein said chronic inflammatory condition is
5 glomerulonephritis, rheumatoid arthritis or psoriasis.

14. A pharmaceutical composition comprising a compound of formula (I') as
claimed in claim 3.

10 15. Use of:
(i) a compound of formula (I')



wherein X is S;

15 R_2 is selected from the group consisting of H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$,

CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, OCOC₁₋₆alkyl, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R₁ is H;

5 or R₁ or R₁ and R₂ taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R₅;

each R₃ is the same or different and is selected from the group consisting of H, C₁₋₆alkylCOOR_a halo, and CHal₃;

R_a is selected from the group consisting of H and C₁₋₆ alkyl;

10 each R₅ is defined as for R₂;

V₁ is a covalent bond, -O-, or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆ alkyl), S, SO, or SO₂;

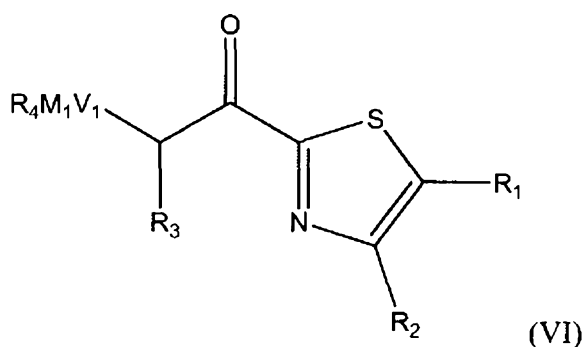
15 M₁ is absent or is a C₅₋₁₀ cyclic group or a C₅₋₁₅ aromatic group (e.g. C₆₋₁₄ aromatic group); and

R₄ is selected from the group consisting of H, C₁₋₁₀alkyl group, and C₁₋₁₀ alkoxy;

with the proviso that the group V₁M₁R₄ as a whole provides at least 4 backbone atoms from the C(R₃) group;

20 with the proviso that R₄M₁V₁C(R₃)₂ is not oleyl or -(CH₂)₆Ph; or a salt, ester, solvate or N-oxide thereof;

(ii) a compound of formula (VI)



25

wherein R₁ is H;

R_2 is selected from the group consisting of H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, and C₁₋₆alkylCOOC₁₋₆alkyl;

R_3 is H or F;

V_1 is selected from the group consisting of C₁₋₁₅-alkyl group, C₂₋₂₀-alkenyl group and -C₁₋₆-alkylO- group;

M_1 is absent or is a phenyl group;

R_4 is selected from the group consisting of H, C₁₋₁₀alkyl group and C₁₋₁₀alkoxy group; or

(iii) the compound of any one of claims 3 to 9, 11 or 12;
in the manufacture of a medicament for the treatment of:

(a) a chronic inflammatory condition;

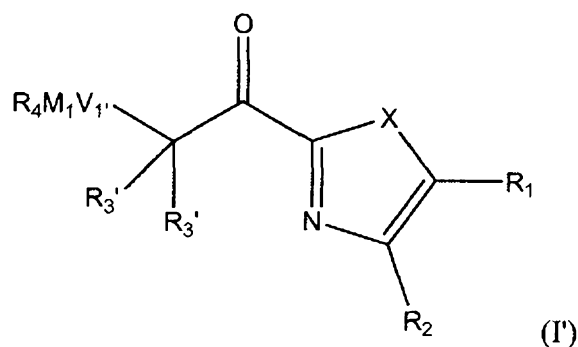
(b) atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, pityriasis rosea, lichen planus or drug eruptions; or

(c) arthritis, dermatoses, inflammatory CNS diseases, multiple sclerosis, chronic obstructive pulmonary disease, chronic lung inflammatory conditions, inflammatory bowel disease such as ulcerative colitis and crohns disease or cardiovascular disease.

16. The use of claim 15, wherein for the compound of (i) R_3 is H, halo, or CHal₃.

17. A method of treating a chronic inflammatory disorder comprising administering to a patient in need thereof an effective amount of:

(i) a compound of formula (I')



wherein X is S;

R₂ is selected from the group consisting of H, OH, SH, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, halo, haloC₁₋₆alkyl, CN, C₁₋₆-alkyl, OC₁₋₆alkyl, C₂₋₆-alkenyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, C₁₋₆alkylC₆₋₁₀aryl, heterocyclyl, heteroaryl, CONH₂, CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, OCOC₁₋₆alkyl, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R₁ is H;

or R₁ or R₁ and R₂ taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R₅;

each R_{3'} is the same or different and is selected from the group consisting of H, C₁₋₆alkylCOOR_a halo, and CHal₃;

R_a is selected from the group consisting of H and C₁₋₆ alkyl;

each R₅ is defined as for R₂;

V_{1'} is a covalent bond, -O-, or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆ alkyl), S, SO, or SO₂;

M₁ is absent or is a C₅₋₁₀ cyclic group or a C₅₋₁₅ aromatic group (e.g. C₆₋₁₄ aromatic group); and

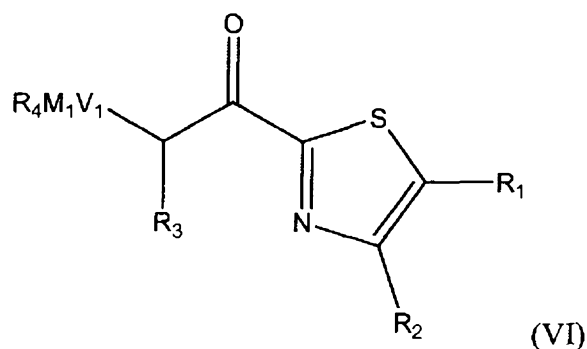
R₄ is selected from the group consisting of H, C₁₋₁₀alkyl group, and C₁₋₁₀ alkoxy;

with the proviso that the group V_{1'}M₁R₄ as a whole provides at least 4 backbone atoms from the C(R_{3'}) group;

with the proviso that R₄M₁V_{1'}C(R_{3'})₂ is not oleyl or -(CH₂)₆Ph;

or a salt, ester, solvate or N-oxide thereof;

(ii) a compound of formula (VI)



wherein R_1 is H;

R_2 is selected from the group consisting of H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, and C₁₋₆alkylCOOC₁₋₆alkyl;

R_3 is H or F;

V_1 is selected from the group consisting of C₁₋₁₅-alkyl group, C₂₋₂₀-alkenyl group and -C₁₋₆-alkylO- group;

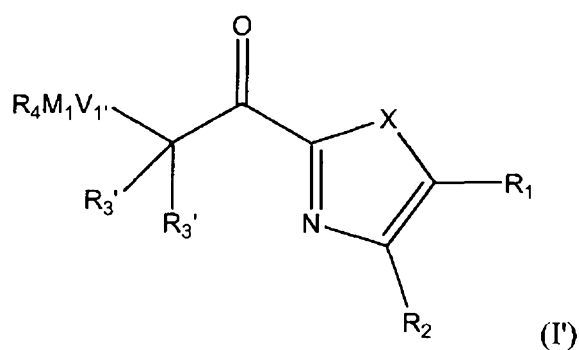
M_1 is absent or is a phenyl group;

R_4 is selected from the group consisting of H, C₁₋₁₀alkyl group and C₁₋₁₀alkoxy group; or

(iii) the compound of any one of claims 3 to 9, 11 or 12.

18. A method of treating atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, pityriasis rosea, lichen planus or drug eruptions comprising administering to a patient in need thereof an effective amount of:

(i) a compound of formula (I')



wherein X is S;

R₂ is selected from the group consisting of H, OH, SH, nitro, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, halo, haloC₁₋₆alkyl, CN, C₁₋₆-alkyl, OC₁₋₆alkyl, C₂₋₆-alkenyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, C₁₋₆alkylC₆₋₁₀aryl, heterocyclyl, heteroaryl, CONH₂, CONHC₁₋₆alkyl, CON(C₁₋₆alkyl)₂, OCOC₁₋₆alkyl, C₁₋₆alkylCOOH, C₁₋₆alkylCOOC₁₋₆alkyl and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R₁ is H;

or R₁ or R₁ and R₂ taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R₅;

each R_{3'} is the same or different and is selected from the group consisting of H, C₁₋₆alkylCOOR_a halo, and CHal₃;

R_a is selected from the group consisting of H and C₁₋₆ alkyl;

each R₅ is defined as for R₂;

V₁ is a covalent bond, -O-, or a C₁₋₂₀alkyl group, or C₂₋₂₀-mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, N(C₁₋₆ alkyl), S, SO, or SO₂;

M₁ is absent or is a C₅₋₁₀ cyclic group or a C₅₋₁₅ aromatic group (e.g. C₆₋₁₄ aromatic group); and

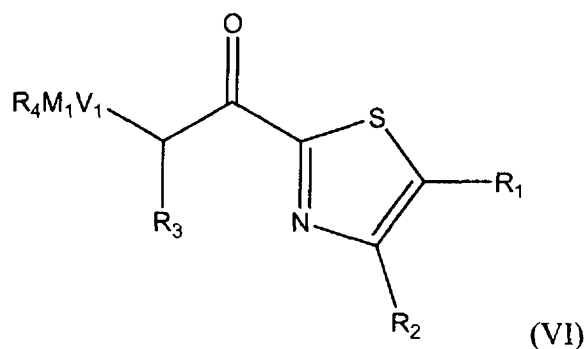
R₄ is selected from the group consisting of H, C₁₋₁₀alkyl group, and C₁₋₁₀alkoxy;

with the proviso that the group V₁M₁R₄ as a whole provides at least 4 backbone atoms from the C(R_{3'}) group;

with the proviso that R₄M₁V₁C(R_{3'})₂ is not oleyl or -(CH₂)₆Ph;

or a salt, ester, solvate or N-oxide thereof;

(ii) a compound of formula (VI)



wherein R_1 is H;

R_2 is selected from the group consisting of H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, and C₁₋₆alkylCOOC₁₋₆alkyl;

R_3 is H or F;

V_1 is selected from the group consisting of C₁₋₁₅-alkyl group, C₂₋₂₀-alkenyl group and -C₁₋₆-alkylO- group;

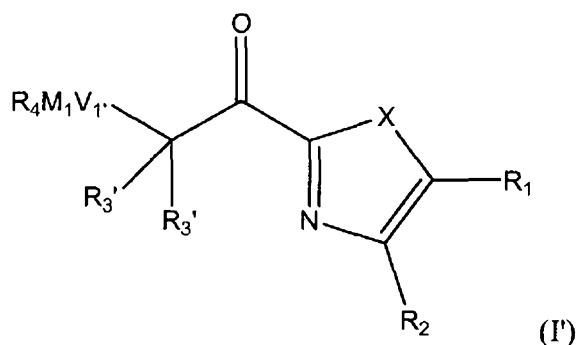
M_1 is absent or is a phenyl group;

R_4 is selected from the group consisting of H, C₁₋₁₀alkyl group and C₁₋₁₀alkoxy group; or

(iii) the compound of any one of claims 3 to 9, 11 or 12.

19. A method of treating arthritis, dermatoses, inflammatory CNS diseases, multiple sclerosis, chronic obstructive pulmonary disease, chronic lung inflammatory conditions, inflammatory bowel disease such as ulcerative colitis and crohns disease or cardiovascular disease comprising administering to a patient in need thereof an effective amount of:

(i) a compound of formula (I')



wherein X is S;

R_2 is selected from the group consisting of H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$,
 5 $CONHC_{1-6}alkyl$, $CON(C_{1-6}alkyl)_2$, $OCOC_{1-6}alkyl$, $C_{1-6}alkylCOOH$, $C_{1-6}alkylCOOC_{1-6}alkyl$ and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R_1 is H;

or R_1 or R_1 and R_2 taken together can form a 6-membered aromatic ring
 10 optionally substituted by up to 4 groups R_5 ;

each R_3 is the same or different and is selected from the group consisting of H, $C_{1-6}alkylCOOR_a$ halo, and $CHal_3$;

R_a is selected from the group consisting of H and $C_{1-6}alkyl$;

each R_5 is defined as for R_2 ;

15 V_1 is a covalent bond, -O-, or a $C_{1-20}alkyl$ group, or C_{2-20} -mono or multiply unsaturated alkenyl group; said alkyl or alkenyl groups being optionally interrupted by one or more heteroatoms selected from O, NH, $N(C_{1-6}alkyl)$, S, SO, or SO_2 ;

M_1 is absent or is a C_{5-10} cyclic group or a C_{5-15} aromatic group (e.g. C_{6-14} aromatic group); and

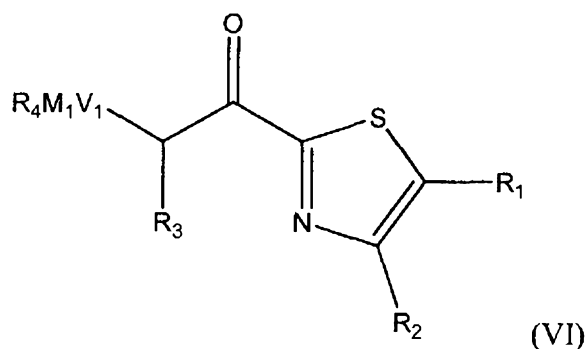
20 R_4 is selected from the group consisting of H, $C_{1-10}alkyl$ group, and $C_{1-10}alkoxy$;

with the proviso that the group $V_1M_1R_4$ as a whole provides at least 4 backbone atoms from the $C(R_3)$ group;

with the proviso that $R_4M_1V_1C(R_3)_2$ is not oleyl or $-(CH_2)_6Ph$;

25 or a salt, ester, solvate or N-oxide thereof;

(ii) a compound of formula (VI)



wherein R_1 is H;

R_2 is selected from the group consisting of H, COOH, COOC₁₋₆alkyl, C₁₋₆alkylCOOH, and C₁₋₆alkylCOOC₁₋₆alkyl;

R_3 is H or F;

V_1 is selected from the group consisting of C₁₋₁₅-alkyl group, C₂₋₂₀-alkenyl group and -C₁₋₆-alkylO- group;

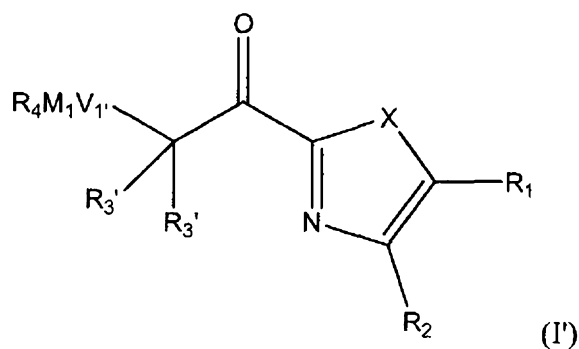
M_1 is absent or is a phenyl group;

R_4 is selected from the group consisting of H, C₁₋₁₀alkyl group and C₁₋₁₀alkoxy group; or

(iii) the compound of any one of claims 3 to 9, 11 or 12.

20. The method of any one of claims 17 to 19, wherein for the compound of (i) R_3 is H, halo, or CHal₃.

21. A compound of formula (I')



wherein X is S;

5 R_2 is selected from the group consisting of H, OH, SH, nitro, NH_2 , $NHC_{1-6}alkyl$, $N(C_{1-6}alkyl)_2$, halo, $haloC_{1-6}alkyl$, CN, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-10}cycloalkyl$, $C_{6-10}aryl$, $C_{1-6}alkylC_{6-10}aryl$, heterocyclyl, heteroaryl, $CONH_2$, $CONHC_{1-6}alkyl$, $CON(C_{1-6}alkyl)_2$, $OCOC_{1-6}alkyl$, $C_{1-6}alkylCOOH$, $C_{1-6}alkylCOOC_{1-6}alkyl$, and a group comprising a carboxyl, phosphate, phosphinate, sulfate, sulfonate, or tetrazolyl group;

R_1 is H or R_1 and R_2 taken together can form a 6-membered aromatic ring optionally substituted by up to 4 groups R_5H ;

10 each R_3 is the same or different and is selected from the group consisting of H, $C_{1-6}alkylCOOR_a$, halo, and $CHal_3$;

R_a is H or $C_{1-6}alkyl$;

each R_5 is defined as for R_1 ;

V_1 is -O-

15 M_1 is absent or is a C_{5-10} cyclic group or a C_{5-15} aromatic group (e.g. C_{6-14} aromatic group); and

R_4 is selected from the group consisting of H, a $C_{1-10}alkyl$ group, and $C_{1-10}alkoxy$ group;

with the proviso that the group $V_1M_1R_4$ as a whole provides at least 10 backbone atoms from the $C(R_3)$ group,

20 or a salt, ester, solvate, or N-oxide, thereof;

with the proviso that $R_4M_1V_1C(R_3)_2$ is not oleyl or $-(CH_2)_6Ph$.

22. A compound as claimed in claim 21 in which R_2 is selected from the group consisting of $COOH$, $COOC_{1-6}alkyl$ and $C_{1-6}alkylCOOH$.

25