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EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

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DE FECHA **30 DE SEPTIEMBRE DE 2004** EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL **29 DE DICIEMBRE DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ___ **X** _____

Bogotá D.C, SEPTIEMBRE DE 2007

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/06, 239/56, 239/52, 401/14, 403/06, 405/06, 417/06, A61K 31/505		A1	(11) International Publication Number: WO 99/24420 (43) International Publication Date: 20 May 1999 (20.05.99)
(21) International Application Number: PCT/EP98/06988 (22) International Filing Date: 23 October 1998 (23.10.98) (30) Priority Data: 9723352.2 6 November 1997 (06.11.97) GB 9723358.9 6 November 1997 (06.11.97) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HICKEY, Deirdre, Mary, Bernadette [IE/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Har- low, Essex CM19 5AW (GB). IFE, Robert, John [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Sci- ence Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEACH, Colin, Andrew [GB/GB]; SmithK- line Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). PINTO, Ivan, Leo [GB/GB]; SmithKline Beecham Phar- maceuticals, New Frontiers Science Park South, Third Av- enue, Harlow, Essex CM19 5AW (GB). PORTER, Roder- ick, Alan [GB/GB]; SmithKline Beecham Pharmaceuticals,			New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). SMITH, Stephen, Allan [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Sci- ence Park South, Third Avenue Harlow, Essex CM19 5AW (GB). (74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: <u>PYRIMIDINONE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM</u>			
(57) Abstract A group of novel pyrimidone compounds are inhibitors of the enzyme LDL PLA2 and therefore of use in treating atherosclerosis.			

PYRIMIDINONE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A2 enzyme Lipoprotein Associated Phospholipase A2 (Lp-PLA₂), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996;16:591-9) wherein it is referred to as LDL-PLA₂. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA₂ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA₂ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA₂ action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA₂ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

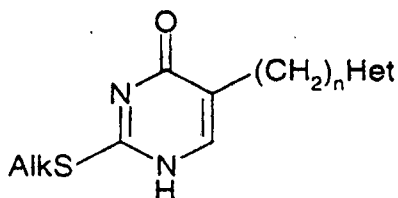
The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA₂ could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA₂ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In addition, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA₂ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Patent applications WO 96/12963, WO 96/13484, WO96/19451, WO 97/02242, WO97/217675, WO97/217676, WO 96/41098, and WO97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-PLA₂. These are irreversible, acylating inhibitors (Tew *et al*, Biochemistry, 37, 10087, 1998).

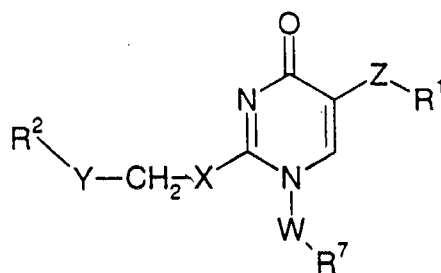
GB 1 582 527 describes, as compounds of formula (7), a group of pyrimidone compounds of the formula (A):



in which Alk is lower alkyl, Het is selected from 2- or 4-imidazolyl, 2-pyridyl, 2-thiazolyl, 3-isothiazolyl, 1,2,5-thiadiazolyl and n is from 1 to 4. These compounds are said to be useful as intermediates in the preparation of further compounds which are H₂ antagonists.

A new class of pyrimidone compounds has now been identified which are inhibitors of the enzyme Lp-PLA₂.

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



(I)

in which:

Z is a bond and R¹ is halogen; or

5 Z is CR³R⁴, where R³ and R⁴ are each hydrogen or C₍₁₋₄₎alkyl, or R³ and R⁴ together with the intervening carbon atom form a C₍₃₋₆₎cycloalkyl ring; and

R¹ is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, oxo, hydroxy, halogen, CN, COR⁵, COOR⁵, CONR⁵R⁶, NR⁵COR⁶, SO₂NR⁵R⁶,
10 NR⁵SO₂R⁶, NR⁵R⁶, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

X is O or S;

Y is a group of formula A¹-A²=A³ in which A¹ and A³ each represent a bond or a straight chain or branched C₍₁₋₁₀₎alkylene group and A² represents a bond or O, S, SO,
15 SO₂, CO, C=CH₂, CH=CH, C≡C, CONH, NHCO, or CR⁵R⁶, providing that when A² is O, S, SO, SO₂ or CONH, A³ contains at least two carbon atoms linking the A² group and the CH₂ group in formula (I);

R² is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents selected from the substituents hereinbefore defined for R¹, as well as aryl and
20 arylC₍₁₋₄₎alkyl;

W is a bond and R⁷ is hydrogen; or

W is SO₂ or a bond; and

R⁷ is R¹ or a hydrocarbyl group, which hydrocarbyl group may be optionally interrupted within the carbon chain by a group selected from O, COO, OCO, CO, CONR⁸,
25 NR⁸CO, NR⁸CONR⁹, NR⁸COO, OCONR⁸, and NR⁸, and which hydrocarbyl group may also be optionally substituted by 1 or 2 substituents selected from mono to perfluoro-C₍₁₋₄₎alkyl, OR⁸, COOR⁸, CONR⁸R⁹, NR⁸COR⁹, NR⁸CONR⁹R¹⁰, NR⁸COOR⁹, OCONR⁸R⁹, NR¹¹R¹² and R¹;

R⁵ and R⁶ are independently hydrogen, or C₍₁₋₂₀₎alkyl, for instance C₍₁₋₄₎alkyl
30 (e.g. methyl or ethyl);

R⁸, R⁹ and R¹⁰ are independently selected from hydrogen, C₍₁₋₂₀₎alkyl (for instance C₍₁₋₁₅₎alkyl), (which may optionally be fluorinated, including up to

United States Patent [19]

Yamaguchi et al.

[11] **Patent Number:** 6,048,823[45] **Date of Patent:** Apr. 11, 2000[54] **-PYRIDONE DERIVATIVES AND
HERBICIDES -**

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§ 371 Date: Aug. 3, 1998

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[30] **Foreign Application Priority Data**

Feb. 2, 1996 [JP] Japan 8-40744

[51] **Int. Cl.⁷** A01N 43/40; C07D 213/64

[52] **U.S. Cl.** 504/130; 546/290; 546/300;
546/301; 546/302; 546/303

[58] **Field of Search** 546/290, 300,
546/301, 302, 303; 504/116, 130

[56] **References Cited****U.S. PATENT DOCUMENTS**

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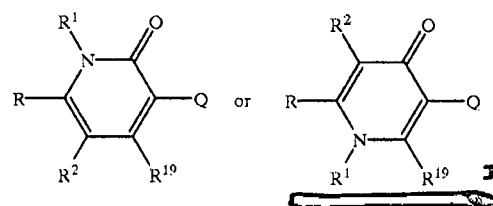
Primary Examiner—Alan L. Rotman

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[57] **ABSTRACT**

A pyridone derivative represented by the general formula:



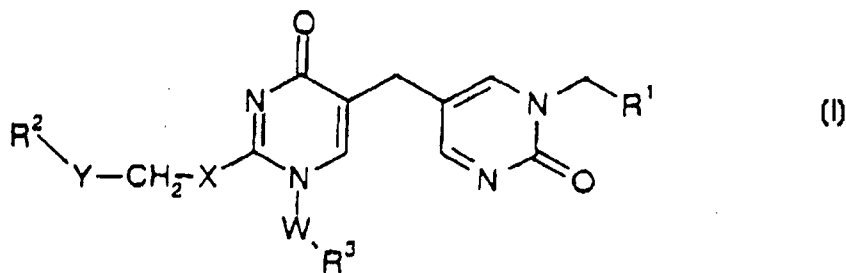
{wherein R is an alkyl group or a haloalkyl group, R¹ is a hydrogen atom, an alkyl group, a haloalkyl group, an acetyl group, an amino group, an alkoxy carbonylamino group, an alkyl carbonylamino group or the like, R² is a hydrogen atom, an alkyl group, a carboxyl group or an alkoxy carbonyl group, R¹⁹ is a hydrogen atom, a halogen atom, a cyano group or the like, Q is a phenyl group which may be substituted or a condensed hetero ring which may be substituted}, a herbicide containing it and an intermediate for its production, are provided.

4 Claims, No Drawings



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(21) International Application Number: PCT/EP99/06093		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
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(30) Priority Data: 9818375.9 21 August 1998 (21.08.98) GB 9902009.1 29 January 1999 (29.01.99) GB		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): LEACH, Colin, Andrew [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). SMITH, Stephen, Allan [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).			
(74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			

(54) Title: PYRIMIDINONE DERIVATIVES FOR THE TREATMENT OF ATHEROSCLEROSIS

(57) Abstract

Pyrimidones of formula (I) are inhibitors of the enzyme LpPLA2 and thereof use in treating inter alia atherosclerosis. In formula (I), R¹ is COOH or a salt thereof, COOR¹⁰, CONR¹¹R¹², CN or CH₂OH; R² is a mono- or bicyclic aromatic ring system, or a mono- or bicyclic heteroaromatic ring system; R³ is C₁₋₂₀alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₅alkyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, or an aromatic or heteroaromatic ring system; W is SO₂ or a bond; X is O or S; and Y is a group of the formula A¹-A²-A³ in which A¹ and A³ each represent a bond or a straight chain or branched alkylene group, said alkylene group(s) containing a total of 1 to 10 carbon atoms and A² represents a bond or O, S, SO, SO₂, CO, C=CH₂, CONH, NHCO, CR¹⁵R¹⁶, CH=CH or C≡C, providing that when A² is O, S, SO, SO₂ or CONH, A³ contains at least two carbon atoms linking the A² group and the CH₂ group in formula (I).

PYRIMIDINONE DERIVATIVES FOR THE TREATMENT OF ATHEROSCLEROSIS

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

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A₂ enzyme Lipoprotein Associated Phospholipase A₂ (Lp-PLA₂), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996;16:591-9) wherein it is referred to as LDL-PLA₂. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA₂ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA₂ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA₂ action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA₂ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA₂ could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA₂ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In addition, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

5

Furthermore, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA₂ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

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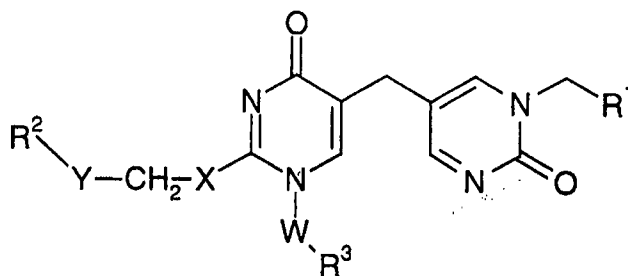
Patent applications WO 96/12963, WO 96/13484, WO96/19451, WO 97/02242, WO97/217675, WO97/217676, WO 96/41098, and WO97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-PLA₂. These are irreversible, acylating inhibitors (Tew *et al*, Biochemistry, 37, 10087, 1998).

15

WO 99/24420 (SmithKline Beecham) describes a new class of compounds which are inhibitors of Lp-PLA₂, namely a group of pyrimidine compounds. We have now identified a particular subset of pyrimidine compounds which have a 5-(2-oxopyrimidin-5-ylmethyl) substituent and which are potent inhibitors of Lp-PLA₂.

20

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



(I)

in which:

30

R¹ is COOH or a salt thereof, COOR¹⁰, CONR¹¹R¹², CN or CH₂OH;

R² is a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, or a mono- or bicyclic heteroaromatic ring system including up to 4 heteroatoms selected from N, O and S; optionally substituted by 1, 2, 3 or 4 substituents

selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, aryl, aralkyl, hydroxy, oxo, halogen, CN, COOH or a salt thereof, $COO-C_{1-6}$ alkyl, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $SO_2NR^{15}R^{16}$, $NR^{15}SO_2R^{16}$, $NR^{15}R^{16}$, ~~mono to perfluoro C_{1-4} alkyl and mono to perfluoro C_{1-4} alkoxy;~~

R^3 is C_{1-20} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-5} alkyl, or C_{1-10}

5 alkoxy C_{1-10} alkyl, ~~each optionally substituted by 1 or 2 substituents selected from hydroxy, C_{1-10} alkoxy, COOH or a salt thereof, $COOC_{1-15}$ alkyl, $CONR^{17}R^{18}$, $NR^{17}R^{18}$, $NR^{17}COR^{18}$, NR^{19} or an aromatic or heteroaromatic ring system as defined for R^2 , or R^3 is an aromatic or heteroaromatic ring system as hereinbefore defined for R^2 ;~~

R^{10} is C_{1-4} alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester
10 group;

R^{11} and R^{12} which may be the same or different is each selected from hydrogen, C_{1-12} alkyl, CH_2R^{13} , $CHR^{14}CO_2H$ or a salt thereof, or R^{11} and R^{12} together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and
15 optionally substituted by one or two substituents selected from hydroxy, oxo, C_{1-4} alkyl, C_{1-4} alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R^{13} is COOH or a salt thereof, $COOR^{10}$, $CONR^{11}R^{12}$, CN or CH_2OH ;

R^{14} is an amino acid side chain such as CH_2OH from serine;

20 R^{15} and R^{16} are independently hydrogen or C_{1-4} alkyl e.g. methyl or ethyl;

~~R^{17} and R^{18} are independently hydrogen, C_{1-15} alkyl, eg methyl or ethyl, C_{1-10} alkoxy C_{1-10} alkyl or aryl C_{1-10} alkyl, e.g. benzyl;~~

R^{19} together with the nitrogen atom to which it is attached forms a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from
25 oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, C_{1-4} alkyl, aryl, e.g. phenyl, or aralkyl, e.g. benzyl;

~~W is SO_2 or a bond;~~

~~X is O or S; and~~

~~Y is a group of the formula $A^1-A^2-A^3$ in which A^1 and A^3 each represent a
30 bond or a straight chain or branched alkylene group, said alkylene group(s) containing a total of 1 to 10 carbon atoms and A^2 represents a bond or O, S, SO, SO_2 , CO, $C=CH_2$, CONH, NHCO, $CR^{15}R^{16}$, $CH=CH$ or $C\equiv C$, providing that when A^2 is O, S, SO, SO_2 or CONH, A^3 contains at least two carbon atoms linking the A^2 group and the CH_2 group in formula (I).~~

35

Representative examples of R^1 include carboxy (COOH) and corresponding salts, esters ($COOR^{10}$) and amides ($CONR^{11}R^{12}$) thereof, for instance a sodium salt, an ethyl ester or an amide comprising an N-alkyl substituent, for instance, methyl, 2-methoxyethyl,

octyl, dodecyl, N-benzyl, N-naphthylmethyl or a disubstituted amide comprising a combination thereof, or an amide in which the N forms part of a heterocyclic ring, for instance a piperidine ring.

- 5 Representative examples of the aromatic ring system represented by R^2 include phenyl and naphthyl. Representative examples of the heteroaromatic ring system which may be represented by R^2 include pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl. Representative examples of R^2 include the phenyl group optionally substituted by 1, 2 or 3 substituents selected from
- 10 halogen (e.g. chlorine or fluorine), C_{1-4} alkyl (e.g. methyl or ethyl) or C_{1-4} alkoxy (e.g. methoxy), for instance 4-fluorophenyl. Examples of the aryl and aralkyl substituents in the R^2 group include respectively phenyl and benzyl.

- Representative examples of R^3 include C_{1-20} alkyl, for instance methyl and undecyl, and
- 15 $R^{17}R^{18}NHCOCH_2$ in which R^{17} and R^{18} is each independently C_{1-15} alkyl, for instance R^{17} is methyl and R^{18} is methyl, octyl, or dodecyl.

Preferably, W is a bond.

- 20 Preferably, R^3W is N-(1-Dodecyl)-N-methylaminocarbonylmethyl.

The group X is preferably S.

- Preferred compounds of formula (I) include those in which Y is a bond, i.e. A^1 , A^2 and
- 25 A^3 each representing a bond. Other preferred examples of the groups A^1 and A^3 are straight chain alkylene groups. When A^2 is other than a bond, A^1 is preferably a bond. Preferred examples of A^2 above include CO, $C=CH_2$ and O, the CO group being especially preferred. Other preferred examples of Y are $(CH_2)_7$ or $CO(CH_2)_6$.

- 30 Pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^{10} include those which break down readily in the human body to leave the parent acid or its salt.

Representative examples of values of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^{10} include:

- 35 $-CH(R^a)O.CO.R^b$;
 $-CH(R^a)O.CO.OR^c$;
 $-CH(R^a)CO.NR^eR^f$
 $-R^dNR^eR^f$;