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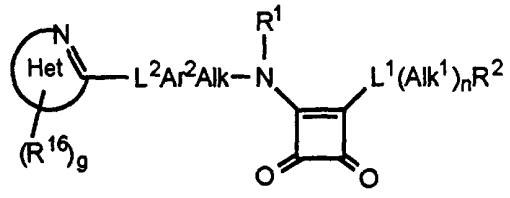
(54) Title: SQUARIC ACID DERIVATIVES CONTAINING A BICYCLIC HETEROAROMATIC RING AS INTEGRIN ANTAGONISTS



(1)

(57) Abstract: Squaric acid derivatives of formula (1) are described, wherein Het is an optionally substituted bicyclic fused ring heteroaromatic group; L^2 is a covalent bond or an atom or group -O-, -S-, -C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^8)$-or-$C(R^8)(R^{8a})$-; Ar^2 is an optionally substituted aromatic or heteroaromatic group; Alk is a chain, in which R is a carboxylic acid (-CO_2H) or a derivative or biostere thereof; R^1 is a hydrogen atom or a C_{1-6}alkyl group; L^1 is a covalent bond or a linker atom or group; Alk^1 is an optionally substituted aliphatic chain; n is zero or the integer 1; R^2 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloalphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group other than a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl group: and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration of cells.

WO 02/04426 A1

SQUARIC ACID DERIVATIVES CONTAINING A BICYCLIC HETEROAROMATIC RING AS INTEGRIN ANTAGONISTS

This invention relates to a series of bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A., Nature, 346, 425, (1990); Springer, T. A., Cell, 76, 301, (1994)]. Specific cell surface molecules collectively referred to as cell adhesion molecules mediate many of these interactions.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 16 different integrin alpha chains and 8 different integrin beta chains have been identified [Newman, P. *et al*, Molecular Medicine Today, 304, (1996)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in the field. Thus the integrin $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised to date [Sonnenberg, A., Current Topics in Microbiology and Immunology, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is defective. Thus in the disease termed Leukocyte Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed on leukocytes [Marlin, S. D. *et al*, J. Exp. Med. 164, 855, (1986)]. Patients

suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)].

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al,* J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al* , Cardiovascular Res. 36, 408 (1997)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin αIIbβ3 is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A., *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L., Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al,* Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays

an important role in leukocyte migration and activation [Yednock, T. A. *et al,* Nature, 356, 63, (1992); Podolsky, D. K. *et al*, J. Clin. Invest. 92, 372, (1993); Abraham, W. M. *et al,* J. Clin. Invest. 93, 776, (1994)].

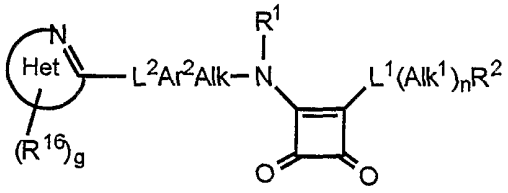
The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., EMBO J. 8, 1735, (1989)]. The α4β7 pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al,* J. Immunol. 153, 517 (1994)]. Like α4β1, α4β7 binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between α4β7 and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, PNAS, 91, 12604, (1994)].

Regions of the peptide sequence recognizeded by α4β1 and α4β7 when they bind to their ligands have been identified. α4β1 seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al, ibid*] whilst α4β7 recognises a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al,* J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, J. Biol. Chem., 269, 18668, (1994); Shorff, H. N. *et al,* Biorganic Med. Chem. Lett., 6, 2495, (1996); Vanderslice, P. *et al*, J. Immunol., 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the α4β1 binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, PNAS, 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of bicyclicheteroaromatic compounds which are potent and selective inhibitors of α4-integrins. Members of the group are able to inhibit α4 integrins such as α4β1 and α4β7 at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds also possess good pharmacokinetic properties, especially low plasma clearance. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1):



(1)

wherein

Het is a bicyclic fused ring heteroaromatic group;

g is zero or the integer 1, 2, 3 or 4;

Each R^{16}, which may be the same or different is an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3 and L^4, which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl, $-OR^5$ [where R^5 is a hydrogen atom, an optionally substitued C_{1-6}alkyl or C_{3-8} cycloalkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, $-CN$, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

L^2 is a covalent bond or an atom or group -O-, -S-, -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$, $-N(R^8)$- [where R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group] or $-C(R^8)(R^{8a})$- [where R^{8a} is an atom or group as defined for R^8 and may be the same or different];

Ar^2 is an optionally substituted aromatic or heteroaromatic group;

Alk is a chain

$-CH_2CH(R)-$, $-CH=C(R)-$, $-CH(CH_2R)-$ or $-C(=CHR)-$

in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

L^1 is a covalent bond or a linker atom or group;

Alk^1 is an optionally substituted aliphatic chain;

n is zero or the integer 1;

R^2 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloalphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group;

provided that Het is not a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl group;

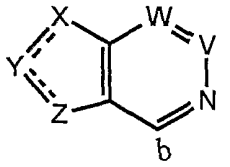
and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto($-CH_2C=O$)-enol-(CHCHOH) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

Bicyclic fused ring heteroaromatic groups represented by Het in the compounds of formula (1) include those bicyclic fused ring heteroaromatic groups containing a N heteroatom adjacent to the carbon atom that joins the Het group to the remainder of the compound of formula (1). Bicyclic

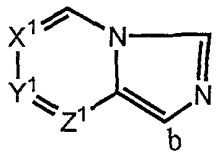
heteroaromatic groups of this type include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two, three or more further heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particular examples of heteroaromatic groups of this type include indol-2-yl, indazol-3-yl, benzoimidazol-2-yl, benzoxazol-2-yl, benzisoxazol-3-yl, benzthiazol-2-yl, purin-8-yl, purin-6-yl, purin-2-yl, quinolin-2-yl, cinnolin-3-yl, phthalazin-1-yl, quinoxalin-2-yl, pyrano[3,4-b]pyrrol-2-yl, pyrido[3,4-b]pyridin-2-yl, pyrido[3,4-b]pyridin-8-yl, pyrido[3,2-b]pyridin-2-yl, pyrido[4,3-b]pyridin-2-yl, pyrido[4,3-b]pyridin-5-yl, 1H-imidazo[4,5-b]pyrazin-2-yl, imidazo[1,5-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and pteridin-4-yl groups.

Further bicyclic fused ring heteroaromatic groups represented by Het in the compounds of formula (1) include groups of formula:



(1a)

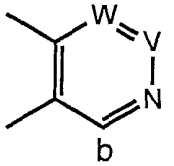
or



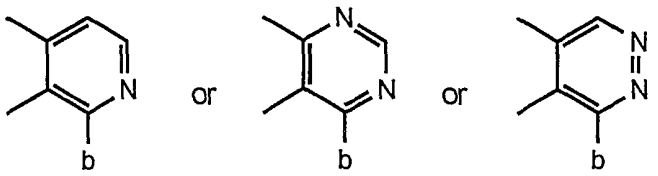
(1b)

in which V and W is each independently selected from a nitrogen atom or a CH group, provided that both V and W are not nitrogen atoms, X, Y and Z is each independently selected from a nitrogen, oxygen or sulphur atom or CH group, X^1, Y^1 and Z^1 is each independently selected from a nitrogen atom or a CH group provided that when two of X^1, Y^1 and Z^1 are nitrogen atoms the other is a CH group, the broken line (- - -) represents saturation or unsaturation and the carbon atom identified by the letter b represents the point of attachment to the group L^2Ar^2 in compounds of formula (1).

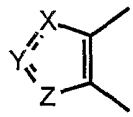
In bicyclic fused ring heteroaromatic groups represented by formula (1a) the partial ring structure:



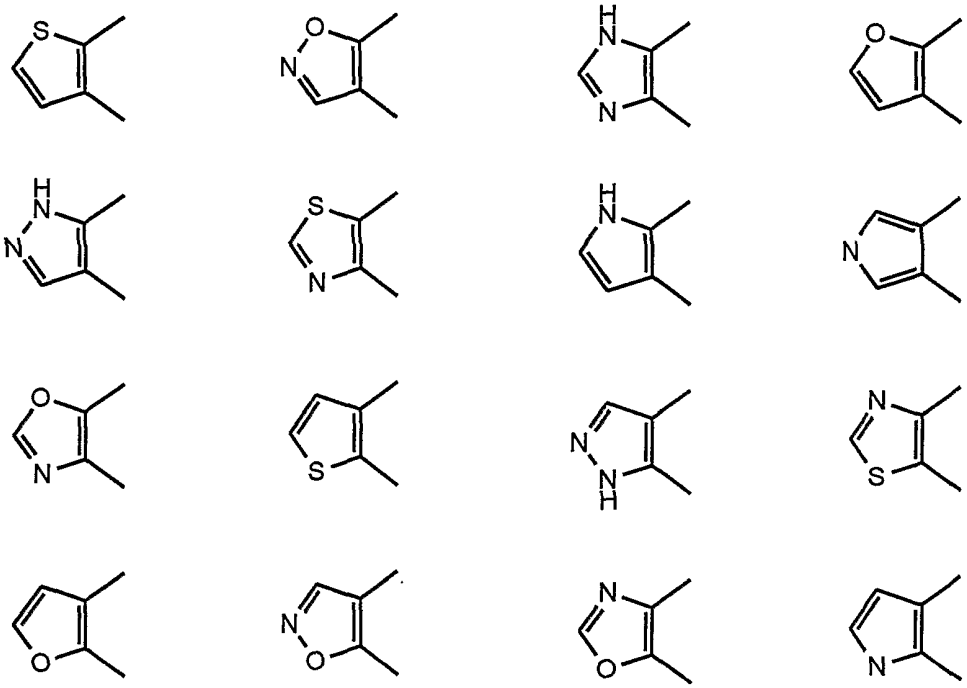
includes for example optionally substituted rings selected from

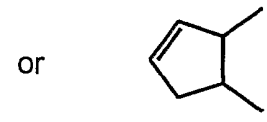


In fused ring bicyclic heteroaromatic groups represented by formula (1a) the partial ring structure:

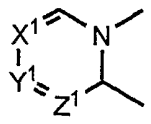


includes for example optionally substituted rings selected from:

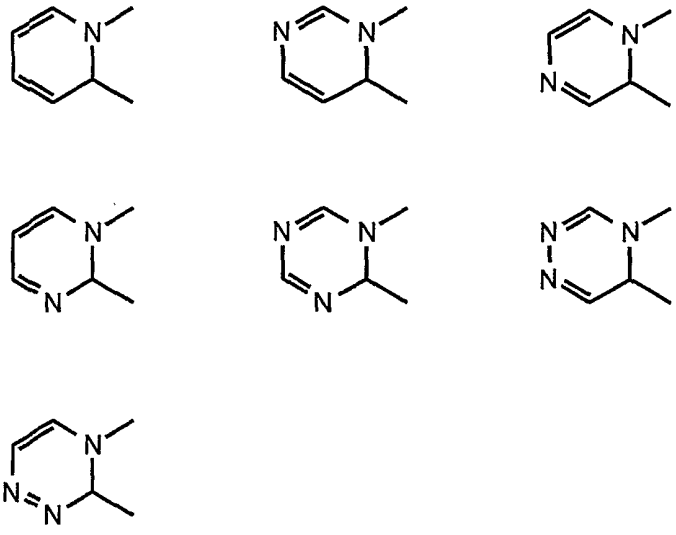




In fused ring bicyclic heteroaromatic groups represented by formula (1b) the partial ring structure:



includes for example optionally substituted rings selected from:



Optional substituents which may be present on any available carbon atom of the bicyclic fused ring heteroaromatic groups represented by Het include those R^{16} atoms and groups as previously defined and as described hereinafter.

When L^3 and/or L^4 is present in the optional R^{16} substituents in compounds of formula (1) as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is as previously defined], $-N(R^8)O-$, $-N(R^8)N-$, $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$ groups. Where the linker group contains two R^8 substituents, these may be the same or different.

When R^4, R^5, R^6, R^7 and/or R^8 is present as a C_{1-6}alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a

methyl, ethyl, propyl or i-propyl group. C_{3-8}cycloalkyl groups represented by R^4, R^5, R^6, R^7 and/or R^8 include C_{3-6}cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy e.g. methoxy or ethoxy groups.

When the groups R^5 and R^6 or R^6 and R^7 are both C_{1-6}alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or -N(R^5)-. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When Alk^2 is present as an aliphatic or heteroaliphatic chain in the optional R^{16} substituents represented by $-L^3(Alk^2)_tL^4(R^4)_u$ it may be for example any divalent chain corresponding to the below-mentioned aliphatic chains described for Alk^1 or heteroaliphatic groups described for R^2 in which one of the terminal hydrogen atoms is replaced by a bond.

Halogen atoms represented by R^4 in the optional R^{16} substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by $-L^3(Alk^2)_tL^4(R^4)_u$ when present as R^{16} atoms or groups in compounds of the invention include atoms or groups $-L^3Alk^2L^4R^4$, $-L^3Alk^2R^4$, $-L^3R^4$, $-R^4$ and $-Alk^2R^4$ wherein L^3, Alk^2, L^4 and R^4 are as defined above. Particular examples of such substituents include $-L^3CH_2L^4R^4$, $-L^3CH(CH_3)L^4R^4$, $-L^3CH(CH_2)_2L^4R^4$, $-L^3CH_2R^4$, $-L^3CH(CH_3)R^4$, $-L^3(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and $-R^4$ groups.

Thus the Het group in compounds of the invention may be optionally substituted for example by one, two, three or four R^{16} atoms or groups whee R^{16} may be a halogen atom, e.g. fluorine, chlorine, bromine or

iodine atom, and/or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8}cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or -C(OH)$(CF_3)_2$, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. $-CF_3$ or $-CHF_2$, or $-CH_2F$, haloC_{1-6}alkoxy, e.g. $-OCF_3$, $-OCHF_2$ or $-OCH_2F$, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylamino-ethyl, C_{1-6} dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^3$ [where Alk^3 is as defined below for Alk^7], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3Alk^3$, C_{1-6}alkylsulphinyl, e.g. methylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methyl-sulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethyl-aminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethyl-aminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonyl-amino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethyl-aminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methyl-aminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothio-carbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothio-carbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylamino-thiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothio-carbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino,

C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino group.

Optionally substituted aromatic or heteroaromatic groups represented by Ar^2 include those aromatic or heteroaromatic groups described hereinafter in relation to R^2 aromatic or heteroaromatic groups respectively. The optional substituents which may be present on these groups include those optional substituents described in relation to R^2 aromatic or heteroaromatic groups.

When the group R is present in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include -CO_2Alk^7 and -$CONR^5R^6$ groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

Esters (-CO_2Alk^7) and amide (-$CONR^5R^6$) derivatives of the carboxylic acid group (-CO_2H) in compounds of formula (1) may advantageously be used as prodrugs of the active compound. Such prodrugs are compounds which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to prodrugs of the acids of formula (1). Such prodrugs are well known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177),

Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H., (Design of Prodrugs, 1985, Elsevier, Amsterdam.

Esterified carboxyl groups represented by the group $-CO_2Alk^7$ include those wherein Alk^7 is a straight or branched optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C_{2-8}alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8}alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8}cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8}cycloalkylC_{1-8}alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8}heterocycloalkylC_{1-6}alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted C_{1-6}alkylthioC_{1-6}alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6}alkylsulfinylC_{1-6}alkyl group such as an methylsulfinylethyl group; an optionally substituted C_{1-6}alkylsulfonylC_{1-6}alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8}cycloalkyloxyC_{1-6}alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C_{3-8}cycloalkylthioC1-6alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8}cycloalkylsulfinylC_{1-6}alkyl group such as a cyclopentyl-sulfinylmethyl group; an optionally substituted C_{3-8}cycloalkylsulfonylC_{1-6}alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkyl group such as isobutoxy-carbonylpropyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C_{1-6}alkyloxy-carbonyloxyC_{1-6}alkyl group such as an isopropoxycarbonyloxyethyl e.g a 1-(isopropoxycarbonyloxy)ethyl, 2-(isopropoxy-carbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C_{3-}

$_8$cycloalkyloxycarbonyloxyC_{1-6}alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C_{1-8}alkylaminoC_{1-8}alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C_{6-12}aryl-N-C_{1-6}alkylaminoC_{1-6}alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C_{1-8}alkylcarbamoylC_{1-8}alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C_{6-10}arylC_{1-6}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-10}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-10}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C_{6-12}arylthioC_{1-8}alkyl group such as an optionally substituted phenylthioethyl group; a C_{6-12}arylsulfinylC_{1-8}alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C_{6-12}arylsulfonylC_{1-8}alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C_{4-8}imidoC_{1-8}alkyl group such as a succinimidomethyl or phthalamidoethyl group; a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C_{1-8}alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk^7 group include R^{13a} substituents described above.

It will be appreciated that in the forgoing list of Alk^7 groups the point of attachment to the remainder of the compound of formula (1) is via the last described part of the Alk^7 group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl groupwould be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk^7 groups, where not specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined for the group

Alk^1. Additionally these alkyl, alkenyl or alkynyl groups may optionally be interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L^3.

When the group R^1 is present in compounds of the invention as a C_{1-6}alkyl group it may be for example a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group.

The linker atom or group represented by L^1 in compounds of formula (1) may be any linker atom or group as described above for the linker atom or group L^3.

When the group Alk^1 is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ groups.

Heteroaliphatic groups represented by the group R^2 in the compounds of formula (1) include the aliphatic chains just described for Alk^1 but with each containing a further terminal hydrogen atom and additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^5 where L^5 is as defined above for L^3 when L^3 is a linker atom or group. Each L^5 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^5CH_3$, $-CH_2L^5CH_3$,

-$L^5CH_2CH_3$, -$CH_2L^5CH_2CH_3$, -$(CH_2)_2L^5CH_3$, -$(CH_2)_3L^5CH_3$, -$L^5C(CH_3)_3$, and -$(CH_2)_2L^5CH_2CH_3$ groups.

The optional substituents which may be present on aliphatic chains or heteroaliphatic groups represented by Alk^1 and R^2 respectively include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO_2H, -CO_2R^9, where R^9 is an optionally substituted straight or branched C_{1-6}alkyl group or C_{3-8}cycloalkyl group as defined above for R^4, -$CONHR^9$, -$CON(R^9)_2$, -COR^9 e.g. -$COCH_3$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, -$S(O)R^9$, -$S(O)_2R^9$, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR^9 and -$N(R^9)_2$ groups . Where two R^9 groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R^2 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group R^2 include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7} hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^5 as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R^2 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R^2 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^5 atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group R^2 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group R^2 include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk^4)_vR^{10}$ groups in which Alk^4 is a straight or branched C_{1-3}alkylene chain, v is zero or an integer 1 and R^{10} is a -OH, -SH, $-N(R^{11})_2$, (in which R^{11} is an atom or group as defined herein for R^8), -CN, $-CO_2R^{11}$, $-NO_2$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-COR^{11}$, $-CSN(R^{11})_2$, $-N(R^{11})COR^{11}$, $-N(R^{11})CSR^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})SO_2R^{11}$, $-N(R^{11})CON(R^{11})_2$, $-N(R^{11})CSN(R^{11})$, $-N(R^{11})SO_2N(R^{11})_2$ or optionally substituted phenyl group. Where two R^{11} atoms or groups are present in these substituents these may be the same or different. Additionally, when two R^{11} groups are present as optionally substituted C_{1-6}alkyl groups these groups may be joined together with the atoms to which they are attached to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or

$-N(R^{11})-$. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings. Optionally substituted phenyl groups represented by R^{10} include phenyl substituted by one, two or three of the R^{13} groups described below

Particular examples of Alk^4 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$ chains.

Additionally, when the group R^2 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^6)_p(Alk^5)_qR^{12}$ in which L^6 is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^{11})-$, $-CSN(R^{11})-$ or $SO_2N(R^{11})-$; p is zero or an integer 1; Alk^5 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{12} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^5 include those optionally substituted chains described above for Alk^1 and R^2 respectively where in the case of R^2 a terminal hydrogen atom is replaced by a bond.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or heteropolycycloaliphatic groups represented by R^{12} include those groups just described for the group R^2. Optional substituents which may be present on these groups include those described above in relation to Alk^1 aliphatic chains.

Aromatic and heteroaromatic groups represented by R^{12} include those groups described hereinafter for the group R^2. Optional substituents which may be present on these groups include those described in relation to R^2 aromatic groups.

Optionally substituted aromatic groups represented by R^2 when present in the group R^1 include for example optionally substituted monocyclic or

bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups represented by the group R^2 include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R^2 include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^6(R^{13a})_m$, where R^{13a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^6(R^{13a})_m$,

cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group], -CSR^{14}, -SO_3H, -SOR^{14}, -SO_2R^{14}, -SO_3R^{14}, -SO_2NH_2, -SO_2NHR^{14}, -$SO_2N(R^{14})_2$, -$CONH_2$, -$CSNH_2$, -$CONHR^{14}$, -$CSNHR^{14}$, -$CON(R^{14})_2$, -$CSN(R^{14})_2$, -$N(R^{11})SO_2R^{14}$, -$N(SO_2R^{14})_2$, -$N(R^{11})SO_2NH_2$, -$N(R^{11})SO_2NHR^{14}$, -$N(R^{11})SO_2N(R^{14})_2$, -$N(R^{11})COR^{14}$, -$N(R^{11})CONH_2$, -$N(R^{11})CONHR^{14}$, -$N(R^{11})CON(R^{14})_2$, -$N(R^{11})CSNH_2$, -$N(R^{11})CSNHR^{14}$, -$N(R^{11})CSN(R^{14})_2$, -$N(R^{11})CSR^{14}$, -$N(R^{11})C(O)OR^{14}$, -SO_2NHet^1 [where -$NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or -$N(R^{11})$-, -C(O)-, -C(S)-, S(O) or -$S(O)_2$ groups], -$CONHet^1$, -$CSNHet^1$, -$N(R^{11})SO_2NHet^1$, -$N(R^{11})CONHet^1$, -$N(R^{11})CSNHet^1$, -$SO_2N(R^{11})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or -$N(R^{11})$-, -C(O)- or -C(S)- groups], -Het^2, -$CON(R^{11})Het^2$, -$CSN(R^{11})Het^2$, -$N(R^{11})CON(R^{11})Het^2$, -$N(R^{11})CSN(R^{11})Het^2$, cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk^6 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or -$S(O)_n$ [where n is an integer 1 or 2] or -$N(R^{15})$- groups [where R^{15} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.

When in the group -$Alk^6(R^{13a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in -Alk^6. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^6. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^6 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group -NHR^{14} [where R^{14} is as defined above] or a group -$N(R^{14})_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^7$, wherein Alk^7 is a group as defined hereinbefore.

When Alk^6 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^9)-$ groups.

Cycloaliphatic or heterocycloaliphatic groups represented by the groups R^{13a} or R^{14} include those optionally substituted C_{3-10}cycloaliphatic or C_{3-10} heterocycloaliphatic groups described above for R^2.

Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^2. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{13} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ or $-Het^2$ include those R^7 substituents described above.

Particularly useful atoms or groups represented by R^{13} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl,

i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, oxazolidinyl, thiazolidinyl, imidazolidinyl or piperidinyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{4-7}cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino, ethylamino or propylamino, C_{6-12}arylC_{1-6}alkylamino, e.g.benzylamino, 4-fluorobenzylamino or 4-hydroxyphenylethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC1-6alkylamino, e.g. aminoethylamino or aminopropylamino, optionally substituted Het^1NC_{1-6}alkylamino, e.g. 3-morpholinopropylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino, e.g. 2-hydroxyethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^7$ [where Alk^7 is as defined above], C_{1-6} alkanoyl e.g. acetyl, propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), $-SO_3Alk^7$, C_{1-6}alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl, ethyl-aminosulphonyl or propylaminosulphonyl C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylamino-

carbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}alkylaminoC_{1-6}alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl, C_{1-6}dialkyl-aminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, haloC_{1-6}alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^2.

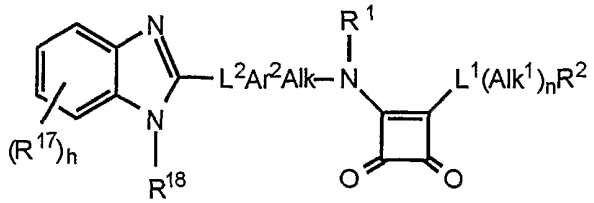
The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

A particularly useful group of compounds according to the invention has the formula (2a):



(2a)

wherein R^{17} is an atom or group R^{16} as previously generally and particularly defined , h is the integer g-1 where g is the integer 1, 2, 3 or 4 and R^{18} is a hydrogen atom or an atom or group R^{16};
L^1, L^2, Ar^2, Alk, R^1, Alk^1, n and R^2 are as defined for formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

Particularly useful R^{17} substituents when present in compounds of formula (2a) include halogen atoms, especially fluorine or chlorine atoms, or straight or branched C_{1-6}alkyl especially methyl, ethyl, propyl or isopropyl, haloC_{1-6}alkyl especially halomethyl, most especially $-CF_3$ or $-CHF_2$ C_{1-6}alkoxy especially methoxy or ethoxy, haloC_{1-6}alkoxy especially halomethoxy, most especially $-OCF_3$, or $-OCHF_2$, $-SR^5$ especially methylthio or ethylthio, -CN, $-CO_2Alk^3$, especially $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$), especially $-N(CH_3)_2$, $-N(R^5)COCH_3$, especially $-NHCOCH_3$ and $-COR^5$, especially $-COCH_3$ groups.

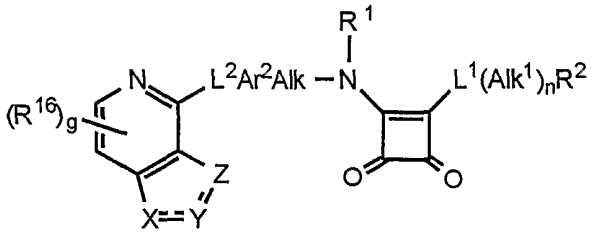
In one preferred class of compounds of formula (2a) h is zero.

In another preferred class of compounds of formula (2a) h is the integer 1 or 2 and each R^{17} is independently chosen from a hydrogen, fluorine or chlorine atom or a C_{1-6}alkyl especially methyl or ethyl, $-N(CH_3)_2$, -CN, $-CF_3$, methoxy or $-OCF_3$ group.

In another preferred class of compounds of formula (2a) R^{18} is a hydrogen atom.

In another preferred class of compounds of formula (2a) R^{18} is a straight or branched C_{1-6}alkyl group, especially a methyl, ethyl, propyl or isopropyl group.

Another particularly useful group of compounds according to the invention has the formula (2b):



(2b)

wherein R^{16} is a hydrogen atom or an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3, Alk^2, t, L^4, R^4, and u are as previously generally and particularly defined;

X, Y, Z, the broken line (---), g, L^1, L^2, Ar^2, Alk, R^1, Alk^1, n and R^2 are as defined previously;

and the salts, solvates, hydrates and N-oxides thereof.

In one preferred class of compounds of formulae (1) and (2b) X is an O or S atom and Y and Z are each a CH group, a single bond joins X and Y and a double bond joins Y and Z.

In another preferred class of compounds of formulae (1) and (2b) Z is an O or S atom and X and Y are each a CH group, a single bond joins Y and Z and a double bond joins X and Y.

Particularly useful R^{16} substituents when present in compounds of formula (2) include halogen atoms, especially fluorine or chlorine atoms, or straight or branched C_{1-6}alkyl especially methyl, ethyl, propyl or isopropyl, C_{3-8}cycloalkyl especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, haloC_{1-6}alkyl especially halomethyl, most especially $-CF_3$ or $-CHF_2$ C_{1-6}alkoxy especially methoxy or ethoxy, haloC_{1-6}alkoxy especially halomethoxy, most especially $-OCF_3$, or $-OCHF_2$, $-SR^5$ especially methylthio or ethylthio, -CN, $-CO_2Alk^3$, especially $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$), and $-N(R^5)COCH_3$, especially $-NHCOCH_3$ and $-COR^5$, especially $-COCH_3$ groups.

Alk in compounds of the invention is preferably:

$-\underset{\displaystyle CH_2R}{\underset{|}{CH}}-$ or, especially, $-CH_2CH(R)-$.

In one prefered class of compounds of formulae (1), (2a) and (2b) R is a $-CO_2H$ group.

In another prefered class of compounds of formulae (1), (2a) and (2b) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this class of compound Alk^7 is preferably a C_{1-8}alkyl group, especially a methyl, ethyl, propyl or i-propyl group, an optionally substituted C_{6-10}aryl group, especially a phenyl group, an optionally substituted $C_{6-10}arylC_{1-6}$alkyl group, especially a benzyl group, a $C_{3-8}heterocycloalkylC_{1-6}$alkyl group, especially a morpholinyl-N-ethyl group or a $C_{1-6}alkyloxyC_{1-6}$alkyl group, especially a methyloxyethyl group. Especially preferred esterified carboxyl groups include $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

In general in compounds of formulae (1), (2a) and (2b) R^1 is preferably a hydrogen atom.

In general in compounds of formulae (1), (2a) and (2b) L^2 is preferably a -O- atom or $-N(R^8)-$ group. Especially useful $-N(R^8)-$ groups include -NH- and $-N(CH_3)-$, most especially -NH-.

The group Ar^2 in compounds of formulae (1), (2a) and (2b) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

In general in compounds of formulae (1) and (2) when n is zero or the integer 1 the group R^2 may especially be an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{2-6}heteroalkyl, particularly $C_{1-3}alkoxyC_{1-3}$alkyl, especially methoxypropyl, optionally substituted C_{3-7}cycloalkyl, especially optionally substituted cyclopropyl, cyclobutyl cyclopentyl or cyclohexyl, optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl, morpholinyl, thiomorpholinyl, or thiazolidinyl, especially optionally substituted phenyl and optionally

substituted C_{5-7}heteroaromatic, especially optionally substituted pyridyl and pyrimidinyl groups. Optional substituents on these groups include in particular R^{13} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^6)_p(Alk^5)_qR^{12}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful $-(L^6)_p(Alk^5)_qR^{12}$ groups include those in which L^6 is a -CO- group. Alk^5 in these groups is preferably present (i.e. q is preferably an integer 1) and in particular is a $-CH_2$ chain. Compounds of this type in which R^{12} is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

In one preferred class of compounds of formulae (1) and (2) L^1 is present as a $-N(R^8)-$ group. Particularly useful $-N(R^8)-$ groups include -NH-, $-N(CH_3)-$, $-N(CH_2CH_3)-$ and $-N(CH_2CH_2CH_3)-$ groups. In this class of compounds n is preferably the integer 1 and Alk^1 is preferably an optionally substituted straight or branched C_{1-6}alkylene chain. Particularly useful Alk^1 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-C(CH_3)_2CH_2-$. R^2 in this class of compounds is preferably a hydrogen atom.

In another preferred class of compounds of formulae (1) and (2) L^1 is a covalent bond, n is the integer (1) and Alk^1 is an optionally substituted straight or branched C_{1-6}alkylene chain. Particularly useful Alk^1 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and especially $-C(CH_3)_2CH_2-$ chains. R^2 in this class of compounds is preferably a hydrogen atom. A most especially useful optionally substituted Alk^1R^2 group is $-C(CH_3)_3$.

In another preferred class of compounds of formulae (1) and (2), L^1 is a covalent bond, n is zero and R^2 is an optionally substituted C_{5-7}heterocycloaliphatic group. Especially useful C_{5-7}heterocycloaliphatic groups include optionally substituted piperidinyl, homopiperidinyl, heptamethyleneiminyl, pyrrolidinyl, piperazinyl, homopiperazinyl, morpholinyl and thiomorpholinyl groups. Most preferred C_{5-7}heterocyclo-

aliphatic groups are those linked via a ring nitrogen atom to the remainder of the compound of formulae (1) or (2). Most especially useful C_{5-7} heterocycloaliphatic groups include optionally substituted pyrolidin-1-yl, piperidin-1-yl and homopiperidin-1-yl groups. Especially useful optional substituents on these C_{5-7}heterocycloaliphatic groups include optionally substituted C_{1-6}alkyl groups, especially methyl, ethyl and i-propyl groups. Most preferred optionally substitued C_{5-7}heterocycloaliphatic groups include 2-methylpyrrolidin-1-yl, cis and trans 2,5-dimethylpyrrolidin-1-yl, 2-methylpiperidin-1-yl, *cis* and *trans* 2,6-dimethylpiperidin-1-yl, homopiperidin-1-yl, 2-methylhomopiperidin-1-yl and cis and trans 2,7-dimethylhomopiperidin-1-yl groups.

Particularly useful compounds of the invention include:
S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;
S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;
S-2-{[2-(2-Methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;
(*S*)-3-[4-(Thiephen[2,3-d]pyrimidin-4-ylamino)phenyl]2-(2-(diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid esters, particularly the methyl, ethyl, propyl and i-propyl esters thereof.

Compounds according to the inventions are potent and selective inhibitors of $\alpha 4$ integrins and have advantageous clearance properties, especially those copounds where R is a carboxylic acid ester or amide. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of formula (1) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formula (1) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

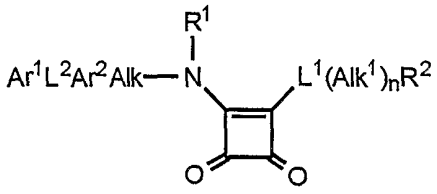
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the

active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar^2, Alk, R^1, R^2, L^1, L^2, Alk^1 and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (3):

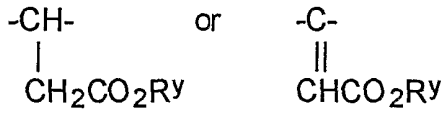


(3)

where Ar^1 represents a bicyclic fused-ring heteroaromatic group as previously generally and particularly described;

and Alk represents a group

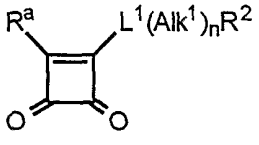
$-CH_2CH(CO_2R^y)-$, $-CH=CH(CO_2R^y)-$,



[where R^y is an alkyl group for example a C_{1-6}alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of R^y, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

According to a further aspect of the invention a compound of formula (1) may be prepared by displacement of a leaving group from a compound of formula (4):



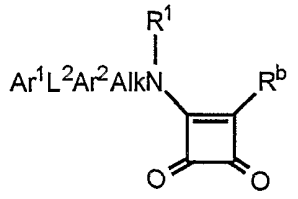
(4)

where R^a is a leaving group, with an amine $Ar^1L^2Ar^2AlkN(R^1)H$ or a salt thereof. Suitable leaving groups represented by R^a include halogen atoms, especially chlorine and bromine atoms, or alkoxy, e.g. methoxy, ethoxy or isopropoxy, aryloxy, e.g. dinitrophenyloxy, or aralkoxy, e.g. benzyloxy, groups.

The reaction may be performed in an inert solvent or mixture of solvents, for example a substituted amide such as dimethylformamide, an alcohol such as ethanol and/or a halogenated hydrocarbon such as dichloromethane, at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine $Ar^1L^2Ar^2AlkN(R^1)H$ is used, an organic base such as diisopropyl-ethylamine can be added.

Any carboxylic acid group present in the intermediate of formula (4) or the amine $Ar^1L^2Ar^2AlkN(R^1)H$ may need to be protected during the displacement reaction, for example as an ethyl ester. The desired acid may then be obtained through subsequent hydrolysis, for example as particularly described above and generally described below.

It will be appreciated that the displacement reaction may also be performed on a compound of formula (5):



(5)

where R^b is a leaving group as defined for R^a using an intermediate $R^2(Alk^1)_nL^1H$ where $-L^1H$ is a functional group such as an amine ($-NH_2$) using the reaction conditions just described.

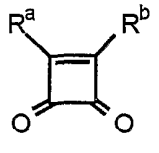
It will be further appreciated that when L^1 is a covalent bond the displacement reaction may be performed on a compound of formula (5) using an organometallic intermediate of formula $R^2(Alk^1)_nM$ [where M

represents a metal such as Li or MgHal, where Hal is a halogen atom such as a chlorine, bromine or iodine atom].

The reaction may be performed in an inert solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature from about -78°C to ambient temperature.

Where desired the displacement reaction may also be performed on an intermediate of formulae (4) or (5), $Ar^1L^2Ar^2AlkN(R^1)H$ or $R^2(Alk^1)_nL^1H$ which is linked, for example via its Ar^1 or R^2 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen.

Intermediates of formulae (4) and (5) are either readily available or may be prepared from an intermediate of formula (6):



(6)

where R^a and R^b are as previously defined and an amine $Ar^1L^2Ar^2AlkN(R^1)H$ or $R^2(Alk^1)_nL^1H$ or organometallic $R^2(Alk^1)_nM$ by displacement as just described for the preparation of compounds of formula (1).

Intermediates of formulae $Ar^1L^2Ar^2AlkN(R^1)H$, $R^2(Alk^1)_nL^1H$ and $R^2(Alk^1)_nM$ may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds. Thus such

intermediates may be prepared by methods known to those skilled in the art following procedures set forth in such references as Rodd's Chemisty of Carbon Compounds, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989); Fieser and Fieser's Reagents for Organic Synethesis, Voumes 1-19 (John Wiley & Sons, 1999); Comprehensive Heterocyclic Chemistry, Ed. Kartitzky *et al*,Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon); Comprehensive Organic Functional Group Transformations, Ed. Trost & Flemming, Volumes 1-8, (Pergamon, 1991); Encyclopedia of Reagents for Organic Synethesis Ed. Paquette, Volumes 1-9 (John Wiley & Sons, 1995); Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley & Sons, 1992).

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ or $-L^2H$ group (where L^1 and L^2 is each a linker atom or group) may be treated with a coupling agent $R^2(Alk^1)_nX^1$ or Ar^1X^1 respectively in which X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluene-sulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

Intermediates of formulae Ar^1X^1 and $R^2(Alk^1)_nX^1$ are generally known readily available compounds or may be prepared from known compounds by standard substitution and other synthetic procedures, for example as described herein. Thus for example compounds of formula Ar^1X^1 in which may be prepared from alcohols of formula Ar^1OH (or their ketotauomers)

by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride or thionyl chloride optionally or an inert solvent such as an amide e.g. a substituted amide such as dimethylformamide or a sulfonic acid e.g. methane sulfonic acid at an elevated temperature e.g. 110°C.

In a further example intermediates of formula $Ar^1L^2Ar^2AlkN(R^1)H$ may be obtained by reaction of a compound of formula Ar^1L^2H with a compound of formula $X^1Ar^2AlkN(R^1)H$ under the reaction conditions just described

Compounds of formula Ar^1L^2H in which, L^2 is a $-N(R^8)-$ group, may be prepared from compounds of formula Ar^1Hal [where Hal is a halogen atom such as a chlorine or bromine atom] by treatment with an amine, $(R^8)NH_2$, optionally in the presence of a base such as an inorganic base for example a carbonate e.g. potassium or caesium carbonate or an organic base such as an amine e.g. triethylamine or N-methylmorpholine in an inert solvent such as an amide e.g. a substituted amide such as dimethylformamide or an ether e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon such as dichloromethane at a temperature from around ambient to the reflux temperature.

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $C(S)X^2$, $-N(R^8)COX^2$or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methyl-morpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethyl-formamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a

catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^1 is replaced by a -S(O)Hal or $-SO_2Hal$ group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$ or $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^1 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, -diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^5$, $-CO_2Alk^3$ or $-CO_2Alk^7$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^5, Alk^3 or Alk^7. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^5$ or $-OR^{14}$ groups [where R^5 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{14}$ group (where R^{14} is an aryl group) using a metal

catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [CO_2Alk^5 or CO_2R^5] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^5$ or $-OR^{14}$ group by coupling with a reagent R^5OH or $R^{14}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NHR^2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with a sulphamide $R^2NHSO_2NH_2$ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSR^2$ or $-CSNHR^2$ group may be prepared by treating a corrsponding compound containing a $-NHCOR^2$ or $-CONHR^2$ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with

hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1 or L^2 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - N-methylmorpholine;
MeOH - methanol;
DCM - dichloromethane;
DIPEA - diisopropylethylamine;
Pyr - pyridine;
DMSO - dimethylsulphoxide;
Et_2O - diethylether;
THF - tetrahydrofuran,
FMOC - 9-fluorenylmethoxycarbonyl;
EtOAc - ethyl acetate;
BOC - butoxycarbonyl;
AcOH - acetic acid;
EtOH - ethanol;
Ar - aryl;
iPr - isopropyl;
Me - methyl;
DMF - N,N-dimethylformamide;
TFA - trifluoroactic acid;

All NMR's were obtained at 300mHz.

INTERMEDIATE 1

s-Chloro-*N*-methylbenzimidazole

2-Chlorobenzimidazole (5.0g, 32.7mmol) was added to an ice cold suspension of sodium hydride (1.44g, 36.0mmol, 60% suspension in oil) in DMF (50ml). After 30min methyl iodide (2.14ml, 34.3mmol) was added and the mxiture stirred at 0° for a further 1h. Water was then added and the product extracted into DCM, dried and evaporated to give the product as a brown solid (4.6g, 85%). δH ($CDCl_3$) 7.70 (1H, m), 7.28 (3H, m), and 3.79 (3H, s). m/z (ES^+, 70V) 167.5 (MH^+).

INTERMEDIATE 2

Ethyl *S*-2-amino-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl} propanoate trifluoroacetate salt

N-t-butoxycarbonyl-*p*-amino-*L*-phenylalanine ethylester (2.0g, 6.53mmol) and Intermediate 1 (1.2g, 7.19 mmol) were dissolved in ethoxyethanol (3ml) and heated to 100° for 3h. The reaction mixture was cooled and reduced to dryness *in vacuo*. The residue was dissolved in DCM (5ml) and TFA (2.5ml) added and the solution stirred for 2h at room temperature. The volatiles were removed *in vacuo* and the residue azeotroped with heptane. The sticky residue was triturated with diethyl ether to give a solid precipitate which was collected and dried to give the title compound (1.5g, 51%) δH (DMSO-d^6) 7.59 (1H, d, J 7.2Hz), 7.47 (2H, d, J 8.3Hz), 7.40-7.22 (5H, m), 4.30 (1H, m), 4.14 (2H, q, J 7.0Hz), 3.77 (3H, s), 3.17 (1H, dd, J 14.0, 6.0Hz), 3.06 (1H, dd, J 14.0 and 7.8Hz) and 1.14 (3H, t, J 7.0Hz). m/z (ES^+, 70V) 339 (MH^+).

INTERMEDIATE 3

Ethyl *S*-2-{[2-(isopropoxy)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate

Intermediate 2 (1.50g, 3.32mmol), diisopropylsquarate (0.72g, 3.65mmol) and DIPEA (0.87ml, 4.98mmol) were added to isopropanol (20ml) and heated to 60° for 6h. The mixture was then cooled and the volatiles removed *in vacuo*. Purification by flash chromatography (silica; 3:2 DCM/EtOAc) gave the title compound as an off white foam (1.3g), δH (MeOD) 7.45 (1H, m), 7.34 (1H, m), 7.22 (3H, m), 7.10 (2H, m), 5.30 (1H, m), 5.15-4.60 (1H, v br.m), 4.24 (2H, q, J 7.0Hz), 3.67 (3H, s), 3.30 (1H,

m), 2.96 (1H, dd, J 14.0, 10.4Hz), 1.40 (6H, m) and 1.29 (3H, t, J 7.0Hz). m/z (ES+, 70V) 477 (MH^+).

INTERMEDIATE 4

Methyl (*S*)-3-[4-{(thiophen[2,3-d]pyrimidin-4-yl)amino}phenyl]-2-(t-butoxycaronylamino)propanoate

A solution of methyl (*S*)-3-[4-(aminophenyl)-2-(t-butoxycarbonylamino) propanoate (1.01g, 3.6mmol), 4-chlorothiophen[2,3-d]pyrimidine (0.61g, 3.6mmol) and DIPEA (0.69ml, 4.0mmol) in ethoxyethanol (0.8ml) was heated to 120° under nitrogen for 5h, then cooled to room temperature. The reaction mixture was dissolved in EtOAc, washed with water, dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified by chromatography (silica; EtOAc/hexane, gradient elution 30 - 40%) to give the title compound (1.07g, 72%). δH ($CDCl_3$) 8.61 (1H,s), 7.59 (2H, d, J 8.4Hz), 7.35 (1H, d, J 6.0Hz), 7.14 (4H, m), 5.02 (1H, m), 4.58 (1H, m), 3.73 (3H, s), 3.10 (2H, m), 1.43 (9H, s). m/z (ES+, 70V) 429 (MH^+).

EXAMPLE 1

Methyl *S*-2-{[2-(dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate

Intermediate 3 (430mg, 0.91mmol) was dissolved in MeOH (20ml) and treated with dipropylamine (187μl, 1.37mmol) and heated to 60° overnight. The reaction was cooled and the volatiles removed *in vacuo*. The residue was purified by flash chromatography (silica; 3:2 DCM/EtOAc) to give the title compound as a white foam (250mg). δH (MeOD) 7.44 (2H, d, J 8.5Hz), 7.36 (1H, m), 7.24 (1H, m), 7.20 (2H, d, J 8.5Hz), 7.10 (2H, m), 5.33 (1H, dd, J 10.3, 4.7Hz), 3.79 (3H, s), 3.66 (3H, s), 3.49 (4H, br m), 3.35 (1H, dd, J 14.1, 4.7Hz), 3.03 (1H, dd, J 14.1, 10.3Hz), 1.59 (4H, m) and 0.88 (6H, t, J 7.3Hz); m/z (ES+, 70V) 504 (MH^+).

The compounds of Examples 2 and 3 were made in a similar manner to Example 1 using the amine indiciated

EXAMPLE 2

Methyl *S*-2-{[2-(2,5-dimethylpyrrolidin-1-yl)-3,4-dioxo-cyclobutenyl] amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate

Intermediate 3 treated with 2,5-dimethylpyrrolidine yielded the title compound (310mg). δH (MeOD) 7.50-7.20 (8H, m), 5.36 (1H, m), 4.22 (2H, m), 3.81 (3H, s), 3.76 (3H, s), 3.43 (1H, m), 3.09 (1H, dd, J 13.6, 10.7Hz), 2.20 (2H, m), 1.75 (2H, m), 1.34 (3H, d, J 6.5Hz) and 1.30 (3H, d, J 6.5Hz); m/z (ES+, 70V) 502 (MH^+).

EXAMPLE 3

Methyl *S*-2-{[2-(2-methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl] amino}-3-{4-[(1-methylbenzimidozol-2-yl)amino]phenyl}propanoate

Intermediate 3 treated with 2-methylpiperidine yielded the title compound (200mg) δH (MeOD) 7.45 (2H, d, J 8.2Hz), 7.36 (1H, m), 7.22 (3H, m), 7.09 (2H, m), 5.34 (1H, m), 4.46 (1H, m), 3.79 (3H, s), 3.66 (3H, s), 3.33 (1H, m), 3.00 (1H, m), 1.9-1.5 (8H, m) and 1.29 (3H, d, J 6.9Hz); m/z (ES+, 70V) 502 (MH^+).

EXAMPLE 4

***S*-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid**

The compound of Example 1 (250mg, 0.50mmol) was dissolved in THF (5ml) and water (5ml) and lithium hydroxide monohydrate (25mg, 0.55mmol) added. The mixture was stirred at room temperature overnight. The THF was removed *in vacuo* and the remaining aqueous solution acidified to ~pH 6 with 1M HCl. The product was extracted into DCM, the organic layer dried (Na_2SO_4) and evaporated. Purification by flash chromatography (silica; 10% MeOH in DCM) gave the title compound as a white solid (207mg). δH (DMSO-d^6, 350K) 7.74 (2H, d, J 8.5Hz), 7.39 (1H, m), 7.28 (1H, m,) 7.21 (2H, q, J 8.5Hz), 7.08 (2H, m), 5.09 (1H, m), 3.46 (4H, m), 3.26 (1H, dd, J 14.0, 4.8Hz), 3.09 (1H, dd, J 14.0, 9.3Hz), 1.58 (4H, m) and 0.89 (6H, t, J 7.4Hz); m/z (ES+, 70V) 490 (MH^+).

Examples 5 and 6 were made in a similar fashion to Example 4

EXAMPLE 5

***S*-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid**

Using the compound of Example 2 yielded the title compound (146mg) δH (DMSO-d^6, 350K) 7.60 (2H, d, J 8.6Hz), 7.42 (1H, m), 7.31 (1H, m), 7.25 (2H, d, J 8.6Hz), 7.11 (3H, m), 5.08 (1H, m), 4.40 (0.36H, (*trans* isomer), m), 4.28 (1.64H, (*cis* isomer), m), 3.74 (3H, s), 3.28 (1H, dd, J 14.1, 4.8Hz), 3.14 (1H, dd, J 14.1, 8.9Hz), 2.17 (2H, m), 1.76 (1.64H (*cis* isomer), m), 1.62 (0.36H, (*trans* isomer), m), 1.34 (2.45H, (cis isomer), d, J 6.4Hz), 1.30 (2.45H (*cis* isomer), d, J 6.4Hz), 1.17 (0.55H, (*trans* isomer), d, J 6.5Hz) and 1.10 (0.55H, (*trans* isomer), d, J 6.5Hz); m/z (ES$^+$, 70V) 488 (MH^+).

EXAMPLE 6

S-2-{[2-(2-Methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid

Using the compound of Example 3 yielded the title compound (183mg) δH (DMSO-d^6, 350K) 7.70 (2H, d, J 8.5Hz), 7.55 (1H, m), 7.45 (2H, m), 7.31 (2H, d, J 8.5Hz), 7.20 (2H, m), 5.22 (1H, m), 4.53 (1H, m), 4.11 (1H, m), 3.78 (3H, s), 3.30-3.15 (2H, m), 1.90-1.50 (8H, m) and 1.30 (3H, t, J 6.8Hz). m/z (ES$^+$, 70V) 488 (MH^+).

EXAMPLE 7

Methyl (S)-3-[4-{(thiophen[2,3-d]pyrimidin-4-yl)amino}phenyl]-2-[(isopropoxy-3,4-dioxocylobut-1-enyl)amino]propanoate

A solution of Intermediate 4 (1.07g, 2.5mmol) was stirred with a EtOAc solution of HCl (2.6M, 10ml) for 1.5h. The mixture was diluted with EtOAc (75ml) and $NaHCO_3$ solution added. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude proudct was dissoled in EtOH and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (0.49g, 2.5mmol) and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (0.49g, 2.5mmol) and DIPEA (0.46g,3.8mmol) added. The reaction was stirred for 16h then concentrated *in vacuo*, the residue dissolved in EtOAc, washed with 10% citric acid, $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (silica; DCM/MeOH 95:5) to give the title compound as a pale yellow solid (0.91g, 60%). δH ($CDCl_3$) 8.60 (1H, s), 7.62 (2H, d, J 8.5Hz), 7.38 (1H, d, J 6.0Hz), 7.24-7.13 (4H, m), 5.34 (1H, m), 3.82 (3H, s), 3.22 (2H, m), 1.41 (3H, d, J 6.1Hz), 1.39 (3H, d, J 6.1Hz); m/z (ES$^+$, 70V) 467 (MH^+).

EXAMPLE 8

Ethyl-(*S*)-3-[4-(thiophen[2,3-d]pyrimidin-4-ylamino)phenyl]-2-(2-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate

A solution of the compound of Example 7 (0.50g, 0.11mmol) in EtOH (8ml) was treated with diethylamine (0.22ml, 0.22mmol) and stirred at 45° for 16h. The reaction was concentrated *in vacuo*, the residue dissolved in EtOAc, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2; DCM/MeOH 9:1) to give the title compound as a yellow foam (0.46g, 89%). δ_H ($CDCl_3$) 8.58 (1H, s), 7.64 (2H, d, J 8.5Hz), 7.42 (1H, s), 7.36 (1H, d, J 5.95Hz), 7.28 (2H, nr m), 7.15 (2H, d, J 8.51Hz), 5.38 (1H, br s), 4.24 (2H, dd, J 14.3, 7.17Hz), 3.62-3.35 (2H, m), 3.3-3.1 (2H, m), 1.30 (3H, t, J 7.18Hz), 1.26-1.20 (6H, m). m/z (ES^+, 70V) 494 (MH^+).

EXAMPLE 9

(*S*)-3-[4-(Thiophen[2,3-d]pyrimidin-4-ylamino)phenyl]2-(2-(diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

A solution of the compound of Example 8 (0.45g, 0.09mmol) in dioxan (2ml), MeOH (1ml) and water (2ml) was treated with $LiOH.H_2O$ (58mg, 1.35mmol) and the reaction sitrred for 5h, acidified with AcOH and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2; DCM/MeOH/AcOH/H_2O 200/20/3/1) to give the title compound as a white solid (0.31g, 68%). δH (DMSO, 390K) 8.52 (1H, s), 7.82 (1H, d, J 6.0Hz), 7.77 (2H, d, J 8.5Hz), 7.65 (1H, d, J 6.0Hz), 7.33 (2H, d, J 8.7Hz), 5.22 (1H, br s), 3.67-3.57 (4H, m), 3.35 (1H, dd, J 14.2, 5.1Hz), 3.18 (1H, dd, J 14.2, 9.1Hz), 1.22 (6H, t, J 7.1Hz); m/z (ES^+, 70V) 466 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl MeOH for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5µg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100µl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200µl containing $2.5x\ 10^5$ K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200µl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100µl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50µg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

αIIb/β_3 -dependent human platelet aggregation

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5µM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the preferred compounds of the invention in which R^1 is an α_4 integrin binding group, such as the compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 µM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50µM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

The advantageous clearance properties of compounds according to the invention may be demonstrated as follows:

Hepatic clearance, whether metabolic or biliary, can make a substantial contribution to the total plasma clearance of a drug. The total plasma clearance is a principal parameter of the pharmacokinetic properties of a medicine. It has a direct impact on the dose required to achieve effective plama concentrations and has a major impact on the elimination half-life and therefore the dose-interval. Furthermore, high hepatic clearance is an indicator of high first-pass hepatic clearance after oral administration and therefore low oral bioavailability.

Many peptidic and non-peptidic carboxylic acids of therapeutic interest are subject to high hepatic clearance from plasma. Except for drugs which function in the liver, hepatic uptake from blood or plasma is undesirable because it leads to high hepatic clearance if the compound is excreted in bile or metabolised, or if the substance is not cleared from the liver, it may accumulate in the liver and interfere with the normal function of the liver.

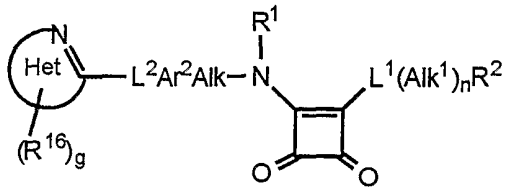
The total plasma clearance of a compound according to the invention can be determined as follows:
a small dose of the compound in solution is injected into a vein of a test animal. Blood samples are withdrawn from a blood vessel of the animal at several times after the injection, and the concentration of compound in the bleed or plasma is measured using a suitable assay. The area under the curve (AUCiv) is calculated by non-compartmental methods (for example, the trapezium method) or by pharmacokinetic modelling. The total plasma clearance (CL_p) is calculated by dividing the *intravenous* dose(D_{iv}) by the AUC_{iv} for the blood plasma concentration - time course of a drug administered by the *intravenous* route: $CL_p = D_{iv} \div AUC_{iv}$

When tested in this manner, compounds according to the invention are not rapidly or extensively extracted by the liver and have low total plasma clearance where low is defined as less than 10 ml/min/kg in the laboratory rat (Sprague Dawley CD). This compares favourably with functionally

equivalent integrin binding compounds in which the squaric acid framework of compounds of formula (1) is not present.

CLAIMS

1. A compound of formula (1):



(1)

wherein

Het is a bicyclic fused ring heteroaromatic group;

g is zero or the integer 1, 2, 3 or 4;

Each R^{16}, which may be the same or different is an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3 and L^4, which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl, $-OR^5$ [where R^5 is a hydrogen atom, an optionally substitued C_{1-6}alkyl or C_{3-8} cycloalkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

L^2 is a covalent bond or an atom or group -O-, -S-, -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$, $-N(R^8)$- [where R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group] or $-C(R^8)(R^{8a})$- [where R^{8a} is an atom or group as defined for R^8 and may be the same or different];

Ar^2 is an optionally substituted aromatic or heteroaromatic group;

Alk is a chain

$-CH_2CH(R)-$, $-CH=C(R)-$, $-CH(CH_2R)-$ or $-C(=CHR)-$

in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

L^1 is a covalent bond or a linker atom or group;

Alk^1 is an optionally substituted aliphatic chain;

n is zero or the integer 1;

R^2 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloalphatic, heteropolycyclo-aliphatic, aromatic or heteroaromatic group;

provided that Het is not a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which Alk is a chain

$-CH(CH_2R)-$ or $-CH_2CH(R)-$,

3. A compound according to Claim 1 or Claim 2 in which R is a carboxylic acid ($-CO_2H$) group.

4. A compound according to Claim 1 or Claim 2 in which R is an esterified carboxyl group of formula $-CO_2Alk^7$.

5. A compound according to any one of Claims 1 to 4 in which R^1 is a hydrogen atom.

6. A compound according to any one of Claims 1 to 5 in which Ar^2 is an optionally substituted phenylene group.

7. A compound according to any one of Claims 1 to 6 in which L^1 is a $-N(R^8)-$ group where R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group.

8. A compound according to Claim 7 in which R^8 is a methyl, ethyl or n-propyl group.

9. A compound according to any one of Claims 1 to 6 in which L^1 is a covalent bond.

10. A compound according to any one of Claims 1 to 9 in which n is the integer 1, Alk^1 is an optionally substituted straight or branched C_{1-6}alkylene chain and R^2 is a hydrogen atom.

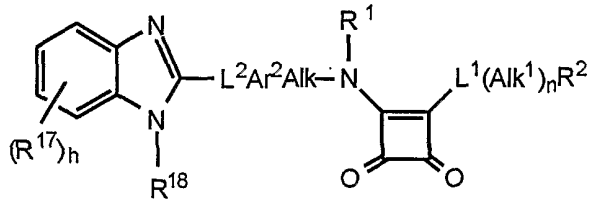
11. A compound according to Claim 10 in which Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-C(CH_3)_2CH_2-$ chain.

12. A compound according to any one of Claims 1 to 6 in which L^1 is a covalent bond, n is zero and R^2 is an optionally substituted C_{5-7}heterocycloaliphatic group.

13. A compound according to Claim 12 in which R^2 is an optionally substituted piperidinyl, homopiperidinyl, heptamethyleneiminyl, pyrrolidinyl, piperazinyl, homopiperazinyl, morpholinyl or thiomorpholinyl group.

14. A compound according to any one of Claims 1 to 13 in which L^2 is an -O- atom or $-N(R^8)-$ group in which R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group.

15. A compound according to Claim 1 of formula (2a):

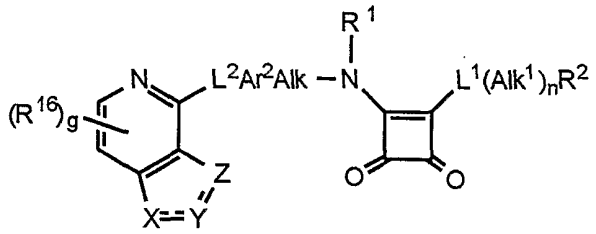


(2a)

wherein:

R^{17} is an atom or group R^{16} as previously defined;
g is the integer 1, 2, 3 or 4;
h is zero or the integer 1, 2 or 3;
R^{18} is a hydrogen atom or an atom or group R^{16} as previously defined;
and the salts, solvates, hydrates and N-oxides thereof.

16. A compound according to Claim 1 of formla (2b):



(2b)

wherein:
X, Y and Z is each independently selectd from a nitrogen, oxygen or sulphur atom or CH group;
the broken line (---) represents saturation or unsaturation;
and the salts, solvates, hydrates and N-oxides thereof.

17. A compound according to Claim 16 in which X is an O or S atom, Y and Z are each a group CH, a single bond joins X and Y and a double bond joins Y and Z.

18. A compound according to Claim 16 in which Z is an O or S atom, X and Y is each a CH group, a single bond joins Y and Z and a double bond joins X and Y.

19. A compound which is:
S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;
S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

S-2-{[2-(2-Methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;
(*S*)-3-[4-(Thiophen[2,3-d]pyrimidin-4-ylamino)phenyl]2-(2-(diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid esters, particularly the methyl, ethyl, propyl and i-propyl esters thereof.

20. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

21. A compound according to Claim 1 for use in the prophylaxis or treatment of a disease or disorder in a mammal in which the extravasation of leukocytes plays a role.

22. A compound according to Claim 1 for inhibiting, in a mammal, the binding of $\alpha 4$ integrins to the ligands thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03028

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/30 C07D495/04 A61K31/4184 A61K31/505 A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 47867 A (ALEXANDER RIKKI PETER ;ARCHIBALD SARAH CATHERINE (GB); CELLTECH CH) 5 July 2001 (2001-07-05) claim 1	1-22
P,X	WO 00 73260 A (ALEXANDER RIKKI PETER ;ARCHIBALD SARAH CATHERINE (GB); CELLTECH CH) 7 December 2000 (2000-12-07) claims; examples 44,47,250-252	1-22
X	WO 00 35855 A (AMERICAN HOME PROD) 22 June 2000 (2000-06-22) claims 1-4,36-39	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2001	10/10/2001

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

1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (part)

Present claim 1 relates to an extremely large number of possible compounds because of the unlimited terms "linker group", "optionally substituted", "derivative of a carboxylic acid". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein the linker group is defined as on p. 8, l. 12-20, optional substituents as on p.15-p.19, carboxylic acid derivatives as on p. 11, l. 20-23.

Present claim 1 relates to a compound defined by reference to a desirable characteristic or property, namely a biostere of a carboxylic acid. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds wherein R is a carboxylic acid or a biostere thereof as defined on p. 11, l. 23-26 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/03028

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0147867 A	05-07-2001	WO 0147867 A1	05-07-2001
		US 2001020017 A1	06-09-2001
WO 0073260 A	07-12-2000	AU 5088900 A	18-12-2000
		WO 0073260 A1	07-12-2000
WO 0035855 A	22-06-2000	AU 2357600 A	03-07-2000
		WO 0035855 A1	22-06-2000