(12) PATENT (11) Application No. AU 199941566 B2
(19) AUSTRALIAN PATENT OFFICE (10) Patent No. 765979

(54) Title
Aromatic amine derivatives as pharmaceutical agents

(51)[7] International Patent Classification(s)
C07D 401/12 **C07D 207/16**
A61K 031/44 **C07D 213/82**

(21) Application No: **199941566** (22) Application Date: **1999.06.03**

(87) WIPO No: **WO99/62901**

(30) Priority Data

(31) Number	(32) Date	(33) Country
9811969	**1998.06.03**	**GB**

(43) Publication Date : **1999.12.20**
(43) Publication Journal Date : **2000.03.02**
(44) Accepted Journal Date : **2003.10.09**

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(56) Related Art
AU 81633/98

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/12, 207/16, 213/82, A61K 31/44 — A1

(11) International Publication Number: WO 99/62901

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/GB99/01741

(22) International Filing Date: 3 June 1999 (03.06.99)

(30) Priority Data:
9811969.6 — 3 June 1998 (03.06.98) — GB

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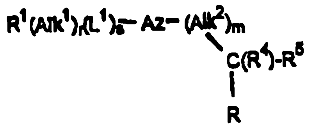
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AROMATIC AMINE DERIVATIVES AS PHARMACEUTICAL AGENTS



(1)

(57) Abstract

Aromatic amines of formula (1) are described: wherein Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group; L^1 is a linker atom or group; R is a carboxylic acid or a derivative thereof; and R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ or $-N(R^7)CS-$ group. The compounds are able to inhibit the binding of α_4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

AROMATIC AMINE DERIVATIVES AS PHARMACEUTICAL AGENTS

This invention relates to a series of aromatic amine 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)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

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 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha4\beta1$ 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 VLA4. 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 [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. et al Am. J. Physiol. 263, L723, (1992); Binns, R. M. et al J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

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 and eosinophils) 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, 373, (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. EMBO J. 8, 1735, (1989)] and like α4β1, 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 at sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised 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 [Briskin, 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); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. 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)].

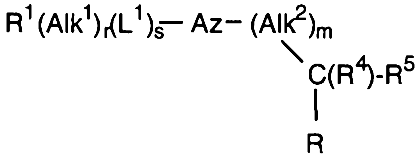
Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes inhibition of their ligand binding functions can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by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

We have now found a group of compounds which are potent and selective inhibitors of the binding of α4 integrins to their ligands. Members of the group are able to inhibit the binding of α4 integrins such as α4β1 and/or α4β7 to their ligands at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Description of the Invention

Accordingly, in a first aspect the present invention consists in a compound of formula (1):



(1)

wherein

Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group;

R^1 is an optionally substituted C_{6-12}aromatic or C_{1-9}heteroaromatic group;

$-(Alk^1)_r(L^1)_s-$ is a $-CH_2O-$, $-S(O)_2O-$ or $-CON(R^8)-$ group where R^8 is a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group;

Alk^2 is a straight or branched C_{1-3}alkylene chain;

m is zero or the integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched C_{1-6}alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted C_{1-10}aliphatic, C_{1-10}heteroaliphatic, C_{3-10}cycloaliphatic, C_{7-10}polycycloaliphatic, C_{3-10}heterocycloaliphatic, C_{7-10}polyheterocycloaliphatic, C_{6-12}aromatic or C_{1-9}heteroaromatic group;

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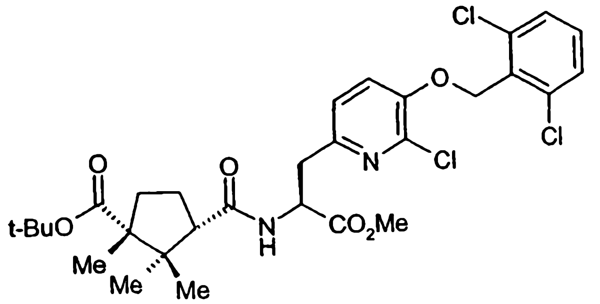
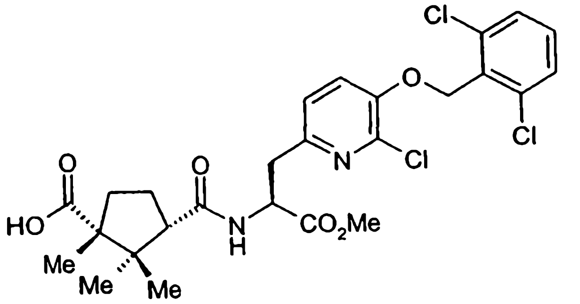
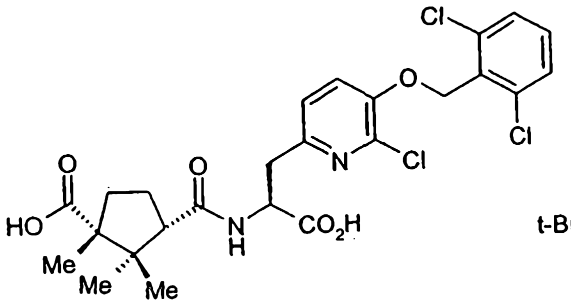
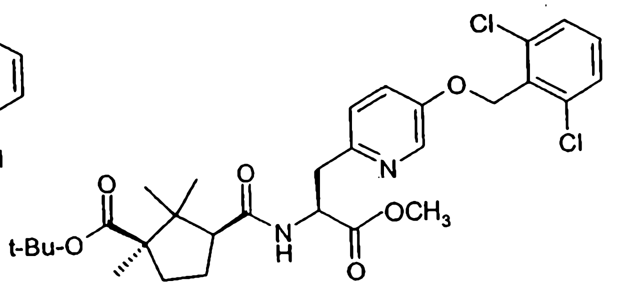
R is a carboxylic acid (-CO_2H) or an ester or amide derivative thereof;
and the salts, solvates and hydrates thereof,

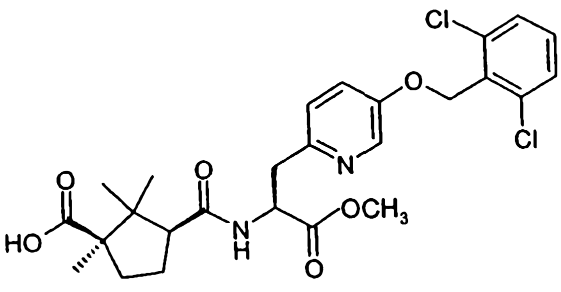
with the proviso that the compound is not

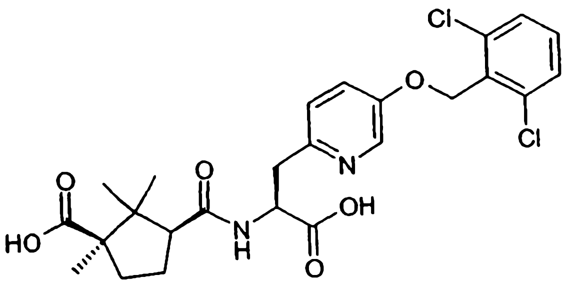












In a second aspect the present invention consists in a compound which is *N*-(*N′*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-y]propanoic acid;
N-(*N′*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid;
2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N′*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid.
and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diasteromers 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.

Six-membered nitrogen-containing aromatic groups represented by the group Az in compounds of the invention include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl and 1,2,3-triazinyl groups. Generally, each of said groups may be linked to the remainder of the compound of formula (1) through any available carbon atom in the ring represented by Az. Where desired, one or two additional substituents may be present on each Az group, for example one or two halogen atoms and/or straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro groups.

When the optional substituent on Az is an alkyl group it may be for example a straight or branched C_{1-6}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group. Alkoxy groups optionally present on Az include straight or branched C_{1-6}alkoxy groups such as methoxy or ethoxy groups. Halogen atoms include for example fluorine, chlorine, bromine or iodine atoms. When the optional substituent on Az is a haloalkyl or haloalkoxy group it may be for example a haloC_{1-6}alkyl or haloC_{1-6}alkoxy group containing one, two or three halogen atoms selected from fluorine, chlorine, bromine or iodine atoms. Particular examples of groups of this type include $-CF_3$, $-OCF_3$, $-CCl_3$, $-OCCl_3$, $-CHF_2$, $-OCHF_2$, $-CHCl_2$, $-OCHCl_2$, $-CH_2F$, $-OCH_2F$, $-CH_2Cl$ and $-OCH_2Cl$ groups.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include those $-CO_2Alk^5$, $-CONH_2$, $-CONHR^{12}$ and $-CON[R^{12}]_2$ groups described below in relation to the group R^6.

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3}alkylene chain. Particular examples include $-CH_2-$, $-CH(CH_3)-$ and $-(CH_2)_2-$.

When in the compounds of the invention L^1 is present 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-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CSN(R^8)-$, 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 Alk^1 and/or R^6 in compounds of formula (1) is 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.

Heteroaliphatic chains represented by Alk^1 and/or R^6 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^3 where L^3 is as defined above for L^1 when L^1 is a linker atom or group. Each L^3 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.

Particular examples of aliphatic chains represented by Alk^1 and R^6 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, -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 $-(CH_2)_2CC-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^3 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-L^3CH_2-$, $-CH_2L^3CH_2-$, $-L^3(CH_2)_2-$, $-CH_2L^3(CH_2)_2-$, $-(CH_2)_2L^3CH_2-$, $-L^3(CH_2)_3-$ and $-(CH_2)_2L^3(CH_2)_2-$ chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 and R^6 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 C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, 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 R^9 is a straight or branched alkyl group. Where two R^9 groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$ $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

Optionally substituted cycloaliphatic groups represented by R^1 and/or R^6 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} cycloalkenylgroups.

Optionally substituted heterocycloaliphatic groups represented by R^1 and/or R^6 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} heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^3 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^1 and/or R^6 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R^1 and/or R^6 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^3 atoms or groups.

Particular examples of R^1 and R^7 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups 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, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 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 R^1 and R^6 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups 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 $-(Alk)_vR^9$ groups in which Alk is a straight or branched C_{1-3}alkylene chain, v is zero or an integer 1 and R^9 is a -OH, -SH, $-N(R^{8a})_2$, -CN, $-CO_2R^{8a}$, $-NO_2$, $-CON(R^{8a})_2$, $-CSN(R^{8a})_2$, $-COR^{8a}$, $-CSN(R^{8a})_2$, $-N(R^{8a})COR^{8a}$, $-N(R^{8a})CSR^{8a}$, $-SO_2N(R^{8a})_2$, $-N(R^{8a})SO_2R^{8a}$, $-N(R^{8a})CON(R^{8a})_2$, $-N(R^{8a})CSN(R^{8a})$ or $-N(R^{8a})SO_2N(R^{8a})_2$ group in which R^{8a} is an atom or group as defined herein for R^8. Additionally, when R^6 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^4)_p(Alk^3)_qR^{10}$ in which L^4 is -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^8)-$, $-CSN(R^8)-$, $-SON(R^8)-$ or $SO_2N(R^8)-$; p is zero or an integer 1; Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{10} 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^3 include those optionally substituted chains described above for Alk^1.

Cycloaliphatic, heterocycloaliphatic, polycyloaliphatic or polyheterocycloaliphatic groups represented by R^{10} include those groups just described for R^1 and R^6. Optional substituents which may be present on these groups include those described above in relation to Alk^1 aliphatic and heteroaliphatic chains.

Optionally substituted aromatic or heteroaromatic groups represented by R^{10} include those aromatic and heteroaromatic groups generally and specifically described below for R^1 and/or R^6.

In the compounds of formula (1), optionally substituted aromatic groups represented by the groups R^1, R^6 and/or R^{10} include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups .

Optionally substituted heteroaromatic groups, represented by the groups R^1, R^6 and/or R^{10} in compounds of formula (1) 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 nine- 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 optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, 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, isobenzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, 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 R^1 include one, two, three or more of the substituents just described for R^1 cycloaliphatic groups.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^1, R^6 and/or R^{10} include one, two, three or more substituents, each selected from an atom or group R^{11} in which R^{11} is $-R^{11a}$ or $-Alk^4(R^{11a})_m$, where R^{11a} 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, $-COR^{12}$ [where R^{12} is an $-Alk^4(R^{11a})_m$, aryl or heteroaryl group], $-CSR^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-SO_2NH_2$, $-SO_2NHR^{12}$ $SO_2N(R^{12})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{12}$, $-CSNHR^{12}$, $-CON[R^{12}]_2$, $-CSN(R^{12})_2$, $-N(R^8)SO_2R^{12}$, $-N(SO_2R^{12})_2$, $-N(R^8)SO_2NH_2$, $-N(R^8)SO_2NHR^{12}$, $-N(R^8)SO_2N(R^{12})_2$, $-N(R^8)COR^{12}$, $-N(R^8)CON(R^{12})_2$, $-N(R^8)CSN(R^{12})_2$, $-N(R^8)CSR^{12}$, $-N(R^8)C(O)OR^{12}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^8)-$, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^8)SO_2NHet^1$, $-N(R^8)CONHet^1$, $-N(R^8)CSNHet^1$, $-SO_2N(R^8)Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^8)-$, -C(O)- or -C(S)- groups], $-CON(R^8)Het^2$, $-CSN(R^8)Het^2$, $-N(R^8)CON(R^8)Het^2$, $-N(R^8)CSN(R^8)Het^2$, aryl or heteroaryl group; Alk^4 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 $-N(R^{13})-$ groups [where R^{13} 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^8 or R^{12} groups are present in one of the above substituents, the R^8 or R^{12} groups may be the same or different.

When in the group $-Alk^4(R^{11a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{11a} may be present on any suitable carbon atom in -Alk^4. Where more than one R^{11a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^4. Clearly, when m is zero and no substituent R^{11a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{11a} is a substituted amino group it may be for example a group -NHR^{12} [where R^{12} is as defined above] or a group -$N(R^{12})_2$ wherein each R^{12} group is the same or different.

When R^{11a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{11a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{12} or a -SR^{12} or -SC(=NH)NH_2 group respectively.

Esterified carboxyl groups represented by the group R^{11a} include groups of formula -CO_2Alk^5 wherein Alk^5 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; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxy-propyl group. Optional substituents present on the Alk^5 group include R^{11a} substituents described above.

When Alk^4 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 $-N(R^8)-$ groups.

Aryl or heteroaryl groups represented by the groups R^{11a} or R^{12} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^6. 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^{11} 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 substituents described above in relation to Alk^1 chains.

Particularly useful atoms or groups represented by R^{11} 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, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, 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_{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 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. 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, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^6$ [where Alk^6 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, 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. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{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, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino 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, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{11} 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^{11} 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^1, R^6 and/or R^{10}.

Straight or branched alkyl groups represented by R^7, R^8 and/or R^9 in compounds of the invention include straight or branched C_{1-6}alkyl e.g. C_{1-3}alkyl groups such as methyl or ethyl groups. Each R^8 group may be optionally substituted, for example by one or more atoms or groups of the types described previously as optional Alk^1 substituents.

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 isethionates, 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.

Generally in the compounds of the invention the group R is preferably a $-CO_2H$ group.

Alk^2 in compounds of formula (1) is preferably a $-CH_2-$ chain and m is preferably an integer 1.

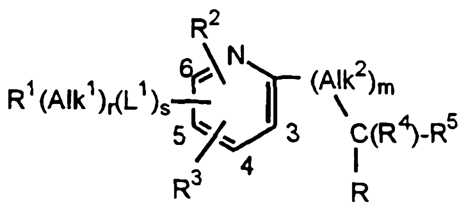
R^4 in compounds of the invention is preferably a hydrogen atom.

In general in compounds of formula (1) $-(Alk^1)_r(L^1)_s-$ is preferably $-CH_2O-$, $-S(O)_2O-$ or $-CON(R^8)-$, particularly -CONH-.

The group R^1 in compounds of formula (1) is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substitued phenyl, pyridyl or pyrimidinyl groups. Particularly useful substituents include one or two R^{11} atoms or groups as generally or particularly described herein. Especially useful substituents of this type include one or two halogen atoms or alkyl, alkoxy, haloalkyl, or haloalkoxy groups as described herein.

The group Az in the compounds according to the invention may in particular be an optionally substituted pyridyl group.

Thus, one particular class of compounds of the invention may have the formula (1a):



(1a)

where R^1, Alk^1, r, L^1, s, Alk^2, m, R, R^4 and R^5 are as defined for formula (1) and R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group; and the salts, solvates and hydrates thereof.

Particular halogen atoms, alkyl, haloalkyl, alkoxy or haloalkoxy groups represented by R^2 and/or R^3 include those atoms and groups described previously in relation to optional Az substituents.

One particular class of compounds of formula (1a) is that wherein the $R^1(Alk^1)_r(L^1)_s$ group is present at the 5-position of the pyridyl ring as shown.

Particularly useful classes of compounds of formula (1) and (1a) are those wherein R^5 is a -NHCOR^6 or -NHCSR^6 group.

In general in compounds according to the invention R^6 may especially be an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted pyridyl groups. Optional substituents on these groups include in particular R^{11} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^4)_p(Alk^3)_qR^{10}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful $-(L^4)_p(Alk^3)_qR^{10}$ groups include those in which L^3 is a -CO- group. Alk^3 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^{10} is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

Particularly useful compounds according to the invention are:

N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-y]propanoic acid;

N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid;

2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid;

and the salts, solvates and hydrates thereof

Compounds according to the invention are potent and selective inhibitors of the binding of $\alpha 4$ integrins to their ligands. 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. The invention extends to such uses and to the use of the compounds for preparing a medicament for treating these diseases and disorders. Particular 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.

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.

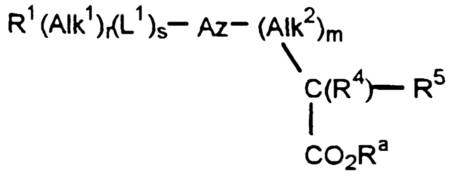
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane,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

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 R, R^1-R^5, L^1, Az, Alk^1, Alk^2, m, r and s 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.

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 (2):

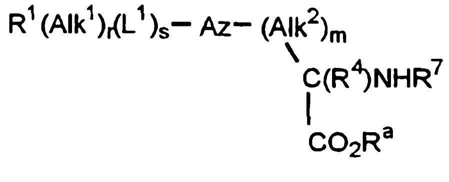


(2)

where R^a is an alkyl group, for example a C_{1-6}alkyl group such as a methyl or ethyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^a, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium 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 around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) in which R^5 is a $-N(R^7)CO(CH_2)_tR^6$ group may be prepared by coupling an amine of formula (3):



(3)

or a salt thereof with an acid $R^6(CH_2)_tCO_2H$ or an active derivative thereof. Active derivatives of acids include anhydrides, esters and halides.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert 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 a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

Where an acid $R^6(CH_2)_tCO_2H$ is used, the reaction may additionally be performed 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 reaction with the amine of formula (2).

Esters of formula (2) in which R^5 is a $-N(R^7)CS(CH_2)_tR^6$ groups may be preapred by treating a corrsponding ester in which R^5 is a $-N(R^7)CO(CH_2)_tR^6$ 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.

This reaction may not be particularly suitable with starting materials in which other carbonyl groups are present, for example in L^1 and/or R^6, and which might undesirably participate in the reaction. To avoid this the reaction with the thiation reagent may be performed earlier in the synthesis of the compound of the invention with an intermediate in which other carbonyl groups are absent and any required carbonyl groups then subsequently introduced by for example acylation as generally described hereinafter.

The amines of formula (3) 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. Additionally, although many of the acid intermediates $R^6(CH_2)_tCO_2H$ for use in the coupling reaction described above are known, other desired acids can be derived therefrom using these standard synthetic methods.

Thus, for example compounds of formulae (1), (2) and (3) and acids $R^6(CH_2)_tCO_2H$ may be prepared by alkylation, arylation or heteroarylation. In one example compounds containing a L^1H or L^4H group may be alkylated or arylated using a reagent $R^1(Alk^1)_rX$, or $R^{10}(Alk^3)_qX$ in which X 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-toluenesulphonyloxy group.

The alkylation or arylation 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, 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.

In a second example, intermediate amines of formula (3) may be prepared by alkylation of a glycinate, for example N-(diphenylmethylene)glycinate with a halide $R^1(Alk^1)_r(L^1)_sAzCH_2Hal$ (where Hal is a halogen atom such as a bromine or iodine atom) in the presence of a strong base, for example a hindered, non-nucleophilic base such as lithium diisopropylamide in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran at a low temperature e.g. around -70°C. The intermediate halide starting materials for this process are either known compounds or may be prepared from readily available compounds using methods analogous to the preparation of the known starting materials [see for example Myers, A.G. and Gleason, J.L., J.Org. Chem (1996), 61, 813-815].

In another example, compounds of formulae (1), (2) and (3) containing a L^1H group (where L^1 is for example a -NH- group) and acids $R^6(CH_2)_tCO_2H$ may be functionalised by acylation or thioacylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$, [wherein L^1 is a -C(O)-, -C(S)-, $-N(R^8)C(O)$ or $-N(R^8)C(S)-$ group], $R^{10}(Alk^3)_qCOX$ or $R^{10}(Alk^3)_qNHCOX$ in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, 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, or by reaction with $R^1(Alk^1)_rCO_2H$ or $R^{10}(Alk^3)_qCO_2H$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an -OH group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is -S(O)- or $-SO_2-$ and Hal is a halogen atom such as a 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, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO-$ group.

In a further example, ester groups $-CO_2Alk^5$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^5 using the reactants and conditions described above for the hydrolysis of esters of formula (2).

In another example, $-OR^{12}$ groups [where R^{12} represents an alkyl group such as methyl group] in compounds of formulae (1) or (2) 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 $-OCH_2R^{12}$ group (where R^{12} 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 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.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. 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 formulae (1) or (2) 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^3 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 suit able 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.

The following Examples illustrate the invention. All temperatures are in ^oC. All ^{1}Hnmr data is at 300mHz and at 300^oK unless otherwise stated. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)3-ethycarbodiimide;

DMF - dimethylformamide;	DMSO - dimethylsulphoxide;
HOBT - 1-hydroxybenzotriazole;	THF - tetrahydrofuran;
DCM - dichloromethane;	MeOH - methanol;
LDA - lithium diisopropylamide	EtOAc - ethyl acetate;
NMM - N-methylmorpholine;	EtOH - ethanol;
pyr - pyridine;	Ar - aryl;
Me - methyl;	thiopro - thioproline;
Et_2O - diethyl ether	

INTERMEDIATE 1

Ethyl N-(diphenylmethylene)-2-amino-3-(5-benzenesulphonyloxy-pyrid-2-yl)propionate

A solution of ethyl *N*-(diphenylmethylene)glycinate (1.71g, 6.40mmol) in dry THF (10ml) was added to a stirred solution of LDA (2M in heptane/ THF/ethylbenzene, 3.20ml, 6.40mmol) in dry THF (10ml) at -70° under nitrogen. After stirring at this temperature for 0.75h, a solution of 5-benzenesulphonyloxy-2-bromomethyl-pyridine [2.00g, 6.01mmol; prepared as described by Myers *et al*, J.Org.Chem. (1996), 61, 813] in dry THF (10ml) was added. The reaction mixture was stirred at -70° for 1h then at room temperature for 18h. The reaction was quenched with water (10ml) then partitioned between EtOAc (70ml) and brine (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude proudct as a dark oil. Purification by flash chromatography (silica, 60% to 75% Et_2O/ hexane; applied as DCM solution) afforded the title compound as a tan-coloured solid (2.25g, 72%). δH ($CDCl_3$) 8.02 (1H, d, J 2.8Hz, pyr-H(6), 7.72 (2H, d, J ~8Hz, ortho-Ar-H), 7.59 (1H, t, J ~8Hz, para-Ar-H), 7.50 (2H, dd, J 8.4, 1.4Hz, phenyl-H), 7.40-7.27 (8H, ms, Ar and phenyl-H), 7.19 (1H, dd, J 8.5, 2.8Hz, pyr-H(4), 7.11 (1H, d, J 8.5Hz, pyr-H(3), 6.67 (2H, br d, J ~8Hz, phenyl-H), 4.50 (1H, dd, J 9, 4.6Hz, CH-α), 4.24-4.10 (2H, sym.m. CH_2CH_3), 3.50-3.33 (2H, m, pyr-CH_2), 1.24 (3H, t, J 7.2Hz, CH_2CH_3); m/z (ESI) 515 (MH^+).

INTERMEDIATE 2

Ethyl 2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propionate

A solution of Intermediate 1 (1.9g, 3.7mmol) in 10% aqueous HCl (5ml) and ethanol (120ml) was stirred at room temperature for 1.5h. Most of the solvent was removed *in vacuo* and the residue partitioned between half-saturated aqueous $NaHCO_3$ (50ml) and EtOAc (80ml). The phases were separated and the aqueous layer re-extracted with EtOAc (4 x 40ml) and evaporated *in vacuo*. The obtained yellow oil was chromatographed (silica; EtOAc) to afford the title compound as a colourless oil (1.15g, 78%). δH ($CDCl_3$) 8.04 (1H, d, J 2.8Hz, pyr-H(6)), 7.80 (2H, d, J ~8Hz, ortho-Ar-H), 7.65 (1H, t, J ~8Hz, para-Ar-H), 7.51 (2H, t, J ~8Hz, meta-Ar-H), 7.31 (1H, dd, J 8.5, 2.8Hz, pyr-H(3)), 7.12 (1H, dd, J 8.5Hz, pyr-H(3)), 4.10 (2H, q, J 7.1Hz, CH_2CH_3), 3.86 (1H, dd, J 7.9, 4.9Hz, CH-α), 3.19 (1H, dd, J 14.4, 4.9Hz, pyr-CH_AH_B), 2.99 (1H, dd, J 14.4, 7.9Hz, pyr-CH_AH_B), 1.66 (2H, br s, NH_2), 1.17 (3H, t, J 7.1Hz, CH_2CH_3); m/z (ESI) 351 (MH^+).

INTERMEDIATE 3

Ethyl *N, N*-Di-(2,6-dichlorobenzoyl)-6-amino-pyridine-3-carboxylate

2,6-Dichlorobenzoylchloride (7.5g, 5.2ml, 26.1mmol) was added to a stirred slution of ethyl 6-aminonicotinate (4.0g, 24.1mmol) and NMM (3.65g, 3.97ml, 36.13mmol) in dry DCM (60ml) and stirred at room temperature for 5 days. The phases were separated and the aqueous layer re-extracted with DCM (2 x 50ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (40ml) and brine (20ml), dried ($MgSO_4$) and evaporated *in vacuo* to afford the crude product as a mixture of the mono-benzoylated and di-benzoylated products. Chromatography (silica; 0.5—>1.5% EtOH/DCM) afforded the less polar title compound as a pale yellow viscous oil (6.3g, 51%). δH ($CDCl_3$) 8.97 (1H, d, with fine coupling), 8.31 (1H, d, J 8.2Hz with fine coupling), 7.72 (1H, d, J 8.2Hz), 7.40-7.00 (6H, broad symmetric peak), 4.37 (2H, q, J 7.2Hz) and 1.37 (3H, t, J 7.2Hz); m/z (ESI, 60V), 511 (MH^+).

INTERMEDIATE 4

***N,N*-Di-(2,6-Dichlorobenzoyl)-6-amino-3-(hydroxymethyl)pyridine**

Lithium aluminium hydride (1M in THF, 5.66ml, 22.54mmol of hydride) was added dropwise to a stirred ice-bath cooled solution of Intermediate 3 (5.25g, 10.54mmol) in dry THF (60ml) and stirred under nitrogen for 1h. The reaction was quenched withEtOAc (5ml) and partitioned between 10% aqueous NH_4Cl (60ml) and EtOAc (100ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained yellow foam was chromatographed (silica; 2—>4% MeOH/DCM) affording the title compound as a white foam (4.98g). δH ($CDCl_3$) 8.32 (1H, d, J 2.3Hz), 7.71 (1H, dd, J 8.1, 2.3Hz), 7.62 (1H, d, J 8.1Hz), 7.50-6.95 (6H, broad peak), 4.63 (2H, d, J 5.3Hz) and 2.09 (1H, J 5.7Hz); m/z (ESI, 60V), 469 (MH^+).

INTERMEDIATE 5

***N,N*-(Dichlorobenzoyl)-6-amino-3-chloromethyl-pyridine**

Hydrogen chloride gas was bubbled through a stirred solution of Intermediate 4 (2.5g, 5.30mmol) in dry DCM (50ml) for 15 seconds. Thionyl chloride (525μl, 858mg, 7.21mmol) was added and the reaction stirred for 2h at room temperature. The volatiles were removed *in vacuo* and the residue partitioned between saturated aqueous $NaHCO_3$ (40ml) and DCM (75ml). The phases were separated and the aqueous layer re-extracted with DCM (2 x 20ml). The combined organic extracts were washed with brine (15ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a white foam (2.33g, 90%) δH ($CDCl_3$) 8.37 (1H, d, J 2.3Hz), 7.75 (1H, dd, J 8.2, 2.3Hz), 7.64 (1H, d, J 8.2Hz), 7.48-6.92 (6H, broad peak) and 4.49 (2H, s). m/z (ESI, 60V), 487 (MH^+).

INTERMEDIATE 6

Ethyl *N*-(diphenylmethylene)-2-amino-3-[*N'*,*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

LDA (2M in heptane/THF/ethylbenzene, 2.59ml, 5.18mmol) was added to a stirred solution of ethyl (N-diphenylmethylene)glycinate (1.32g, 4.94mmol) in dry THF (20ml) at -70° and stirred at this temperature under N_2 for 0.75h. A solution of Intermediate 5 (2.30g, 4.70mmol) in dry THF (20ml) was added, and the reaction mixture stirred at -70° for 0.5h and at room temperature for 6h. The reaction was partitioned between EtOAc (60ml) and water (40ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a dull yellow oil. Chromatography (silica; 50% Et_2O/hexane; applied in DCM) afforded the title compound as a pale yellow foam (1.47g, 41%) δH ($CDCl_3$) 8.16 (1H, d, J 1.9Hz), 7.56-6.50 (18H, various m's), 4.16 (1H, obscured m), 4.15 (2H, q, J 7.1Hz) and 1.25 (3H, t, J 7.1Hz); m/z (ESI), 60V) 718 (MH^+).

INTERMEDIATE 7

Ethyl-2-amino-3-[*N*,*N*-dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

A solution of Intermediate 6 (1.40g) and ethanol (50ml) was stirred at room temperature for 1h. The volume of reaction mixture was reduced *in vacuo* by about half neutralized with solid $NaHCO_3$, then evaporated *in vacuo* to near dryness. The residue was partitioned between EtOAc(70ml) and water (40ml), the phases separated and the aqueous layer re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* The obtained yellow oil was chromatographed (silica; 3% MeOH/DCM) to afford the title compound as a white foam (0.87g, 81%). δH ($CDCl_3$) 8.23 (1H, s), 7.57 (1H s), 7.56 (1H, s), 7.48-6.92 (6H, broad peak), 4.11 (2H, q, J 7.1Hz), 3.60 (1H, dd, J 7.4, 5.6Hz), 2.96 (1H, dd, J 13.8, 5.6 Hz), 2.81 (1H, dd, J 13.8, 7.4Hz), 1.31 (2H, br s) and 1.23 (3H, J 7.1HZ); m/z (ESI, 60V) 554 (MH^+).

INTERMEDIATE 8

Ethyl 2-amino-3-[*N*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

Sodium metal (61mg, 2.65mmol) was added to anhydrous ethanol (20ml) and stirred under N_2 for 0.5h. Intermediate 7 (490mg, 0.88mmol) was added and the reaction mixture heated under reflux for 6h. The volatiles were removed *in vacuo* and the residue treated with EtOH (50ml). HCl gas was bubbled through for a short time and the reaction mixture allowed to stand at room temperature for 18h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (70ml) and saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous layer re-extracted with ethyl acetate (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed (silica; 5% MeOH/DCM) affording the title compound as a white foam (240mg, 71%). δH ($CDCl_3$) 9.75 (1H, s), 8.33 (1H, d, J 5.4Hz), 7.62-7.60 (2H, m's), 7.35-7.30 (3H, m's), 4.17 (2H, q, J 7.2Hz), 3.60 (1H, dd, J 7.6, 6.4Hz), 2.93 (1H, dd, J 13.8, 6.4Hz), 2.72 (1H, dd, J 13.8, 7.6Hz), 1.55 (2H, br s) and 1.26 (3H, t, J 7.2Hz); m/z (ESI, 60V) 382 (MH^+).

EXAMPLE 1

Ethyl *N*-(*N'*-acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxy-pyrid-2-yl)propionate

HOBT (570mg, 4.22mmol), *N*-acetyl-*D*-thioproline (682mg, 3.90mmol) and EDC (750mg, 3.90mmol) were added sequentially to a stirred solution of Intermediate 2 (1.24g, 3.54mmol) in dry DMF (20ml) and stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (75ml) and 10% aqueous Na_2CO_3 (40ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (silica, 3 - 5% methanol/DCM) to afford the title compound as a near colourless glass (1.46g, 81%). δH ($CDCl_3$; approx: 1:1 mixture of diastereoisomers and rotameric species): 8.4-8.35, 8.1-8.02, 7.81-7.76, 7.71-7.45, 7.42-7.25 and 7.15-7.08 (9H, m's, CONH, pyr-H and Aryl-H), 5.10-4.31 (4H, ms, α-CHx2 and NCH_2S), 4.15-4.01 (2H, m, CH_2CH_3), 3.41-3.02 (4H, m, CH_2-pyr and CH_2S), 2.13, 2.10, 2.08 and 1.95 (3H, singlets, NCOMe) and 1.12 (3H, m, CH_2CH_3); m/z (ESI) 508 (MH^+).

EXAMPLE 2

_N_-(_N'_-Acetyl-_D_-thioproline)-2-amino-3-(5-hydroxypyrid-2-yl)propanoic acid

The compound of Example 1 (1.2g, 2.4mmol) was treated with a solution of $LiOH.H_2O$ (220mg, 5.2mmol) in dioxan (10ml), water (10ml) and methanol (5ml), and stirred at room temperature for 3.5h. The reaction mixture was acidified with acetic acid and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (120 - 100), methanol (20), acetic acid (3), H_2O (2)] affording the title compound (580mg, 72%, slightly contaminated with benzenesulphonic acid). δH (d^6 - DMSO; spectrum shows an approximate 1:1 mixture of diastereoisomers and rotameric species): 8.29, 8.09, 7.98 and 7.83 (1H, doublets, CONH), 7.98 (1H, br s, pyr-H (6)), 7.02 (2H, br s, pyr-H (3 and 4)), 4.88-4.67 (2H, br m, CHαthiopro and NCH_AH_BS), 4.49-4.18 (2H, ms, CHα-CH_2pyr and NCH_AH_BS), 3.37-2.82 (2H, br m, CCH_2S and CH_2-pyr) and 2.05, 1.88, 1.87 and 1.85 (3H, singlets, NCOMe); m/z (ESI) 340 (MH^+).

EXAMPLE 3

_N_-(_N'_-Acetyl-_D_-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-yl]propanoic acid

A mixture of the compound of Example 2 (450mg, 1.33mmol), 2,6-dichlorobenzyl bromide (669mg, 2.78mmol) and ceasium carbonate (1.34g, 4.11mmol) in dry DMF (10ml) was stirred at room temperature for 6h. The volatiles were removed *in vacuo* and the residue partitoned between EtOAc (70ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (silica; EtOAc) to afford the di-O-alkylated intermediate as a mixture of two diastereoisomers and as a colourless viscous oil (227mg, 26%). This material was treated with a solution of $LiOH.H_2O$ (17mg, 0.41mmol) in dioxan (4ml), water (3ml) and methanol (2ml) at room temperature for 1h. After adding a few drops of acetic acid, the volatiles were removed *in vacuo*. The residue was chromatographed [silica, DCM (200), methanol (20), acetic acid (3), H_2O (2)] to afford the product as a colourless oil. Freeze-drying from aqueous methanol afforded the title compound as a white amorphous solid (130mg, 76%). δH (d^6-DMSO, 390K) (approximately 1:1 mixture of diastereoisomers) 8.27 (1H, d, J 2.5Hz, pyr-H (6)), 7.88 (1H, br d, J ~8Hz, CONH), 7.52-7.39 (4H, ms, pyr-H and Ar-H), 7.21 (1H, dd, J 8.5, 2.5Hz, pyr-H (4)), 5.34 (2H, s, CH_2O), 4.81 (1H, dd, J 7.4, 3.8Hz, CHα-thiopro), 4.77 and 4.74 (1H, overlapping doublets, J 9.3Hz, SH_AH_BN), 4.69 (1H, br m, CHα-CH_2pyr), 4.37 and 4.34 (1H, overlapping doublets, J 9.3Hz, SH_AH_BN), 3.30-3.07 (3H, ms, CH_2pyr and CH_AH_BS), 3.04 (1H, dd, J 11.5, 3.8Hz, CH_AH_BS) and 1.99 and 1.98 (3H, singlets, NCOMe); m/z (ESI) 498 and 500 (MH^+). Found: C, 49.86; H, 4.20; N, 8.33. $C_{21}H_{21}Cl_2N_3O_5S.0.4\ H_2O$ requires C, 49.89; H, 4.35; N, 8.31%.

EXAMPLE 4

N-(N'-Acetyl-D-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid

The compound of Example 1 (400mg, 0.79mmol) was treated with a solution of $LiOH.H_2O$ (36mg, 0.86mmol) in dioxan (4ml), H_2O (3ml) and ethanol (2ml) for 1.5h at room temperature. A few drops of acetic acid were added and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (200), methane (20), acetic acid (3), H_2O (2)) to afford the product as a colourless oil. This was freeze-dried from aqueous methanol to afford the title compound as a white amorphous solid (240mg, 64%). δH (d^6-DMSO, 390K; approximately 1:1 mixture of diasteroisomers) 8.17 (1H, singlet with fine couplings, pyr-H (6)), 7.90-7.79 (4H, ms, Ar-H and NHCO), 7.68 (2H, apparent J ~8Hz, Ar-H), 7.43 (1H, dd, J 8.6, 2.8Hz, pyr-H (4)), 7.30 (1H, dd, J 8.6, 3.2Hz, pyr-H (3)), 4.79

(1H, overlapping m, C<u>H</u>αCHpyr), 4.75 (1H, apparent <u>J</u> ~9Hz, $NC\underline{H}_AH_BS$), 4.68 (1H, overlapping m, C<u>H</u>αthiopro), 4.38 (1H, apparent <u>J</u> ~9Hz, $NCH_A\underline{H}_BS$), 3.33-2.98 (4H, ms, $C\underline{H}_2$pyr and $CC\underline{H}_2S$) and 1.99 and 1.98 (3H, singlets, NCO<u>M</u>e); <u>m/z</u> (ESI) 480 (MH^+); Found: C, 48.33; H, 4.30; N, 8.34. $C_{20}H_{21}N_3O_7S_2.H_2O$ requires C, 48.28; H, 4.66; N, 8.45%.

<u>EXAMPLE 5</u>

<u>Ethyl 2-[*N*-(2-chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate</u>

2-Chloronicotinoyl chloride (110mg, 0.63mmol) was added to a stirred solution of Intermediate 8 (240mg, 0.63mmol) and pyridine (50mg, 50μl, 0.63mmol) in dry DCM (5ml), and the reaction stirred under nitrogen fof 2h. The reaction mixture was partitioned between DCM (100ml) and saturated aqueous $NaHCO_3$ (10ml). The phases were separated and the organic layer washed with brine (5ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained white foam was chromatographed (silica, 2% MeOH/DCM) affording the <u>title compound</u> as a white amorphous solid (145mg, 44%) δH ($CDCl_3$) 9.79 (1H, s), 8.35 (1H, dd, <u>J</u> 4.8, 2.0Hz), 8.23 (1H, d, <u>J</u> 8.5Hz), 7.96 (1H, d, <u>J</u> 8.0Hz), 7.91 (1H, dd, <u>J</u> 7.6, 2.0Hz), 7.37 (1H,dd, <u>J</u> 8.5, 2.3Hz), 7.34-7.21 (5H, m), 5.05 (1H, symmetrical m), 4.02 (2H, q, <u>J</u> 7.1Hz), 3.11-2.95 (2H, m) and 1.24 (3H, t, <u>J</u> 7.1Hz); <u>m/z</u> (ESI, 60V), 521 (MH^+).

<u>EXAMPLE 6</u>

<u>2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid</u>

The compound of Examaple 5 (135mg, 0.26mmol) was treated with a solution of $LiOH.H_2O$ (23mg, 0.55mmol) in dioxane (2ml), methanol (1ml) and water (2ml) at room temperature for 2h. A few drops of acetic acid were added and the volatiles removed *in vacuo*. The residue was treated with water and the obtained white solid collected by filtration, water-washed and sucked dry, affording the <u>title compound</u> as a white powder (101mg, 80%). δH (d^6-DMSO) 11.16 (1H, s), 8.98 (1H, d, <u>J</u> 8.2Hz), 8.45 (1H, dd, <u>J</u> 4.8, 1.9Hz), 8.26 (1H, d, <u>J</u> 1.9Hz), 8.14 (1H, d, <u>J</u> 8.5Hz), 7.79 (1H,dd, <u>J</u> 8.5,2.2Hz), 7.71 (1H, dd, <u>J</u> 7.5, 1.9Hz), 7.57-7.42 (4H, m's),4.71-4.63 (1H, symmetrical m), 3.20 (1H, dd, <u>J</u> 14.1, 4.8Hz) and 2.98 (1H, dd, <u>J</u> 14.1, 9.8Hz); <u>m/z</u> (ESI, 60V) 493 (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 methanol 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.

$\alpha IIb/\beta_3$ -dependent human platelet aggregation

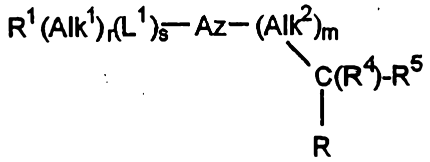
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 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 compounds of the invention 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 $.\alpha_4$ integrins.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of formula (1):



(1)

wherein

Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group;

$R^1$is an optionally substituted C_{6-12}aromatic or C_{1-9}heteroaromatic group;

$-(Alk^1)_r\ (L^1)_s-$ is a $-CH_2O-$, $-S(O)_2O-$ or $-CON(R^8)-$ group where R^8 is a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group;

Alk^2 is a straight or branched C_{1-3}alkylene chain;

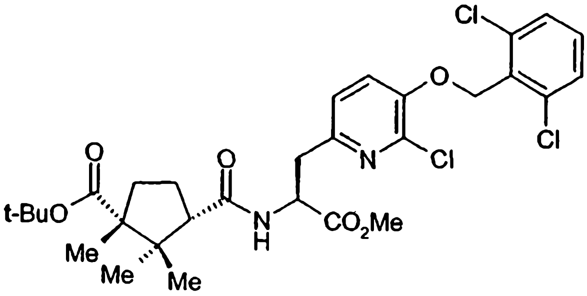
m is zero or the integer 1;

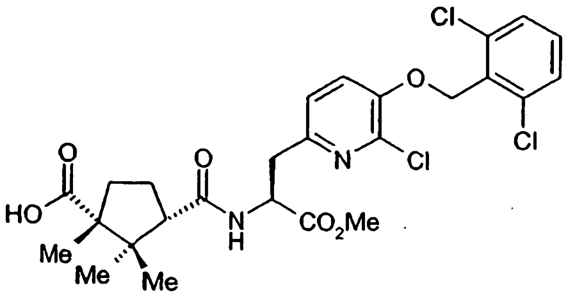
R^4 is a hydrogen atom or a methyl group;

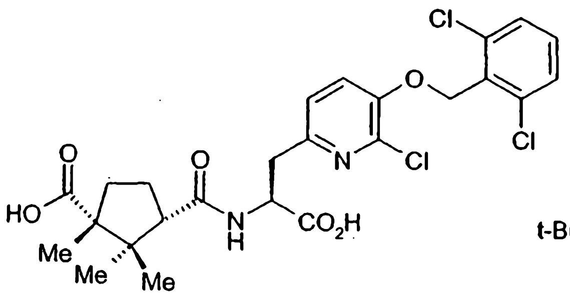
R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched C_{1-6}alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted C_{1-10}aliphatic, C_{1-10}heteroaliphatic, C_{3-10}cycloaliphatic, C_{7-10}polycycloaliphatic, C_{3-10}heterocycloaliphatic, C_{7-10}polyheterocycloaliphatic, C_{6-12}aromatic or C_{1-9}heteroaromatic group;

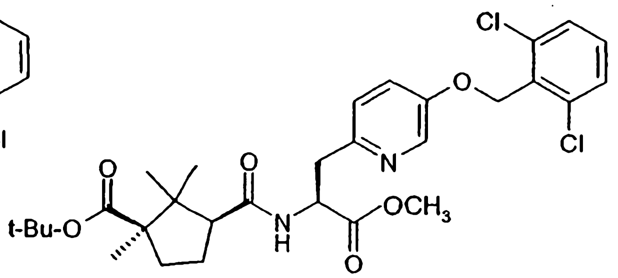
R is a carboxylic acid ($-CO_2H$) or an ester or amide derivative thereof;

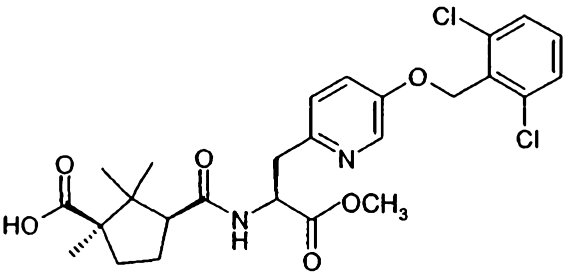
and the salts, solvates and hydrates thereof, with the proviso that the compound is not

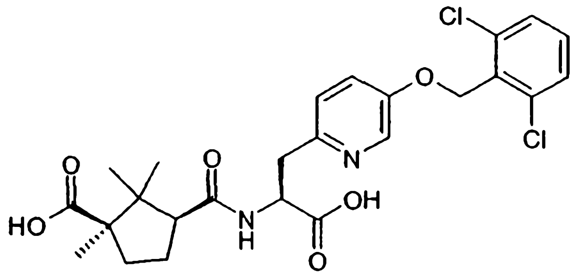












2. A compound according to Claim 1 wherein R is a $-CO_2H$ group.

3. A compound according to Claim 1 or Claim 2 wherein Alk^2 is a $-CH_2-$ chain, m is the integer 1 and R^4 is a hydrogen atom.

4. A compound according to any one of Claims 1 to 3 wherein $-(Alk^1)_r(L^1)_s-$ is a -CONH- group.

5. A compound according to any one of Claims 1 to 4 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.

6. A compound according to any one of Claims 1 to 5 wherein Az is an optionally substituted pyridyl group.

7. A compound according to any one of Claims 1 to 6 wherein R^5 is a $-NHCOR^6$ or $-NHCSR^6$ group.

8. A compound according to any one of Claims 1 to 7 wherein R^6 is an optionally substituted C_{3-10}cycloaliphatic, C_{3-10}heterocycloaliphatic, C_{6-12}aromatic or C_{1-9}heteroaromatic group.

9. A compound according to Claim 8 wherein R^6 is an optionally substituted pyrrolidinyl, thiazolidinyl, phenyl or pyridyl group.

10. A compound which is

N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-yl] propanoic acid;

N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid;

2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl] propionic acid;

and the salts, solvates and hydrates thereof.

11. A pharmaceutical composition comprising a compound according to any of Claims 1 to 10 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

12. A compound as hereinbefore described with reference to the Examples 1-6.

Dated this eighth day of August 2003

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