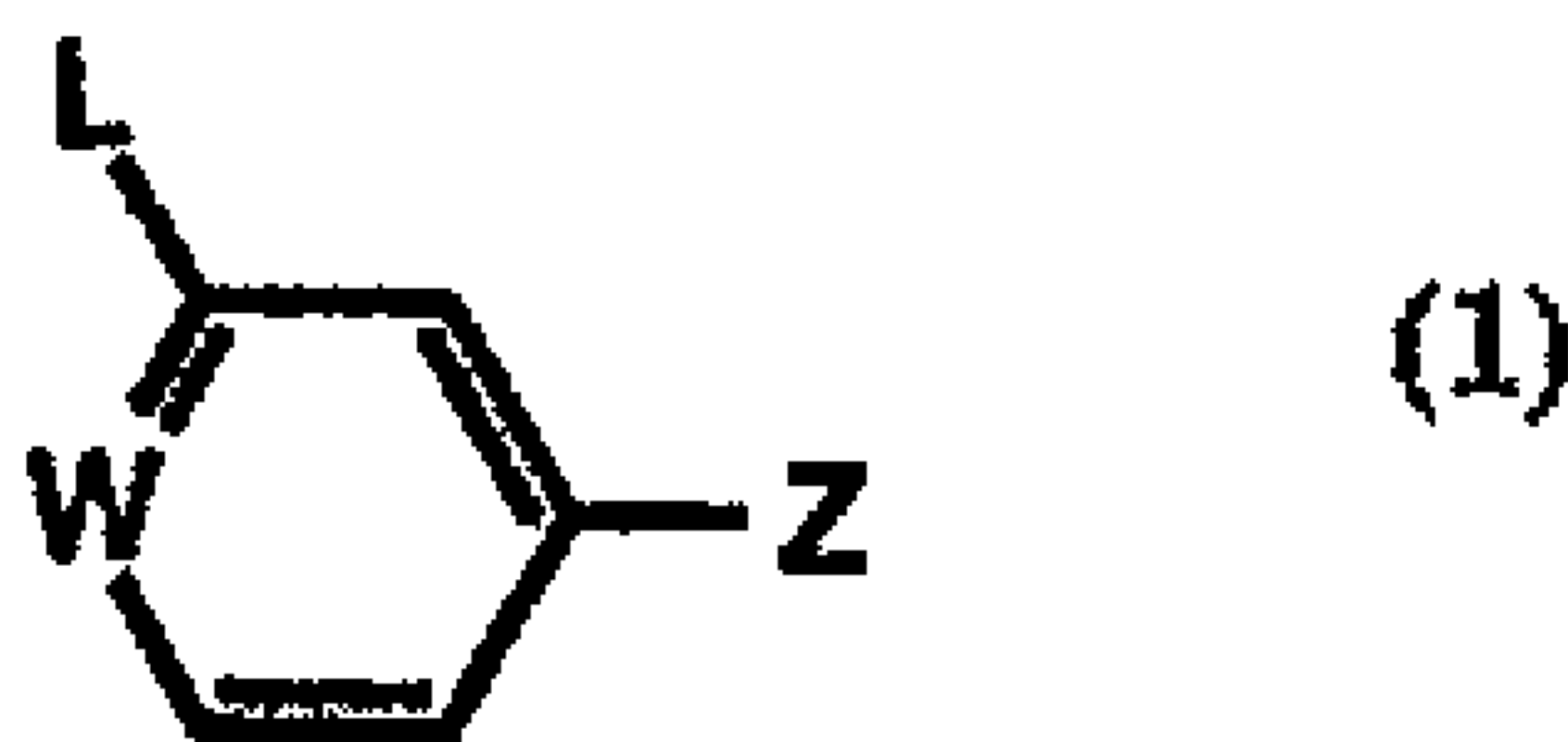




(86) Date de dépôt PCT/PCT Filing Date: 1995/06/22
(87) Date publication PCT/PCT Publication Date: 1995/12/28
(45) Date de délivrance/Issue Date: 2006/02/14
(85) Entrée phase nationale/National Entry: 1996/12/11
(86) N° demande PCT/PCT Application No.: GB 1995/001466
(87) N° publication PCT/PCT Publication No.: 1995/035284
(30) Priorité/Priority: 1994/06/22 (9412573.9) GB

(51) Cl.Int./Int.Cl. *C07D 213/30* (2006.01),
C07D 213/89 (2006.01), *A61K 31/44* (2006.01),
A61K 31/395 (2006.01)
(72) Inventeurs/Inventors:
HEAD, JOHN CLIFFORD, GB;
WARRELOW, GRAHAM JOHN, GB;
ALEXANDER, RIKKI PETER, GB
(73) Propriétaire/Owner:
CELLTECH THERAPEUTICS LIMITED, GB
(74) Agent: KIRBY EADES GALE BAKER

(54) Titre : DERIVES PHENYLE TRISUBSTITUES UTILISES COMME INHIBITEURS DE PDE IV
(54) Title: TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS



(57) **Abrégé/Abstract:**

Compounds of general formula (1) (see formula 1) are described wherein =W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or -XR^a group where X is -O-, -S(O)_m- [where m is zero or an integer of value 1 or 2], or -N(R^b)- where R^b is a hydrogen atom or an optionally substituted alkyl group or, (2) =N; L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]₀CH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂ R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different are as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group, or R¹ and R² together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1; Z is (1) a group -C(R³)(R⁴)C(R⁵)(R⁶)(R⁷) or -C(R⁴)=C(R⁵)(R⁶) where R³ is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group; R⁴ is a group selected from -X^a L¹ R¹² [where X^a is as defined above for X, L¹ is a linker group and R¹² is a hydrogen atom or a cycloaliphatic, heterocycloaliphatic, or monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms], -Alk¹ R¹² [where Alk¹ is an optionally substituted straight or branched alkenyl or alkynyl chain optionally containing one or more -O- or -S- atoms or -N(R^b)-, carbocyclic or heteroatom-containing groups], -CH₂ L¹ R^{12a} [where R^{12a} is as defined for R¹² but is not a hydrogen atom]; -X^a R^{12a}; or -C(X^b) R^{12a} [where X^b is an oxygen or sulphur atom]; R⁵ is a -(CH₂)_p Ar group where p is zero or an integer 1, 2 or 3 and, Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms R⁶ is a hydrogen or a fluorine atom or an optionally substituted alkyl group; R⁷ is a hydrogen or a fluorine atom or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; or Z is (2) a group -C(R⁴)C(R⁵)(R⁶)(R⁷) where R⁴ is a group =CH₂, or CH(L¹)_n-R¹²; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. Compounds according to the invention are phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of disease such as asthma where an unwanted inflammatory response or muscular spasm is present.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

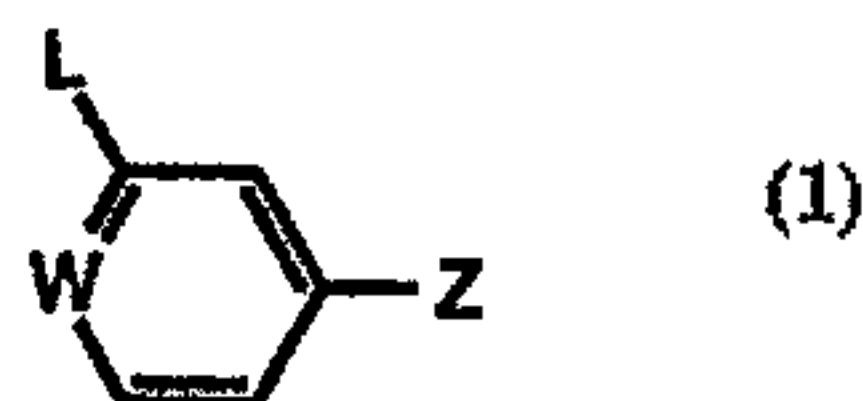
(51) International Patent Classification ⁶ : C07D 213/30, A61K 31/44, C07D 213/32, 213/38		A1	(11) International Publication Number: WO 95/35284
			(43) International Publication Date: 28 December 1995 (28.12.95)
(21) International Application Number: PCT/GB95/01466		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 22 June 1995 (22.06.95)		Published With international search report. 2192644	
(30) Priority Data: 9412573.9 22 June 1994 (22.06.94) GB			
(71) Applicant: CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).			
(72) Inventors: HEAD, John, Clifford ; Flat 2A, 8 Claremont Road, Windsor, Berkshire SL4 3AX (GB). WARRELOW, Graham, John ; Oakside, 4 Wieland Road, Northwood, Middlesex HA6 2QU (GB). ALEXANDER, Rikki, Peter ; 14 Carrington Road, High Wycombe, Bucks HP12 3HY (GB).			
(74) Agent: SKAILES, Humphrey, John ; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).			

(54) Title: TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS

(57) Abstract

Compounds of general formula (1) are described wherein =W- is (1) =C(Y)- where Y is a halogen atom, or

an alkyl or -XR^a group where X is -O-, -S(O)_m- [where m is zero or an integer of value 1 or 2], or -N(R^b)- where R^b is a hydrogen atom or an optionally substituted alkyl group or, (2) =N; L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]_nCH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different are as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group, or R¹ and R² together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1; Z is (1) a group -C(R³)(R⁴)C(R⁵)(R⁶)(R⁷) or -C(R⁴)=C(R⁵)(R⁶) where R³ is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group; R⁴ is a group selected from -X^aL¹R¹² [where X^a is as defined above for X, L¹ is a linker group and R¹² is a hydrogen atom or a cycloaliphatic, heterocycloaliphatic, or monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms], -Alk¹R¹² [where Alk¹ is an optionally substituted straight or branched alkenyl or alkynyl chain optionally containing one or more -O- or -S- atoms or -N(R^b)-, carbocyclic or heteroatom-containing groups], -CH₂L¹R^{12a} [where R^{12a} is as defined for R¹² but is not a hydrogen atom]; -X^aR^{12a}; or -C(X^b)R^{12a} [where X^b is an oxygen or sulphur atom]; R⁵ is a -(CH₂)_pAr group where p is zero or an integer 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; R⁶ is a hydrogen or a fluorine atom or an optionally substituted alkyl group; R⁷ is a hydrogen or a fluorine atom or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; or Z is (2) a group -C(R⁴)C(R⁵)(R⁶)(R⁷) where R⁴ is a group =CH₂, or =CH(L¹)_n-R¹²; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. Compounds according to the invention are phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of disease such as asthma where an unwanted inflammatory response or muscular spasm is present.



TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS

- 5 This invention relates to a novel series of tri-substituted phenyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

10 Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of adenosine 3', 5'-cyclic monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell
15 surface receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family have been described (PDE I-VII) the distribution of which varies from tissue to
20 tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues, [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnyder (1990) TIPS, 11: 150-155 and Nicholson et al (1991) TIPS, 12: 19-27].

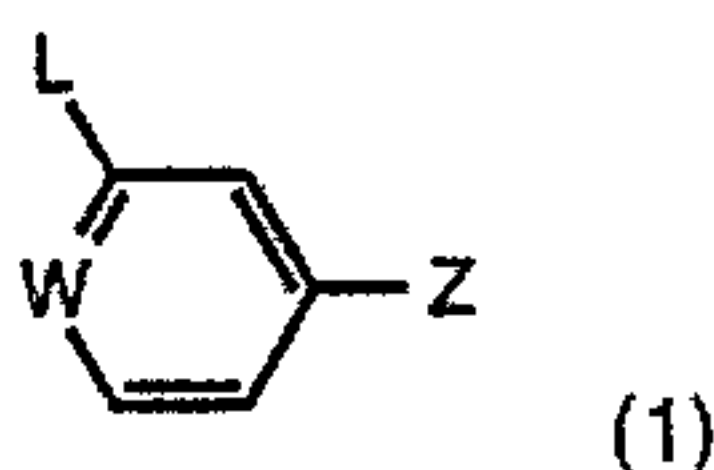
25 There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV plays a major role in the hydrolysis of cAMP. It can be expected,
30 therefore, that selective inhibitors of PDE IV would have therapeutic effects in inflammatory diseases such as asthma, by achieving both anti-inflammatory and bronchodilator effects.

35 The design of PDE IV inhibitors has met with limited success to date, in that many of the potential PDE IV inhibitors which have been synthesised have lacked potency and/or have been capable of inhibiting more than one

type of PDE isoenzyme in a non-selective manner. Lack of a selective action has been a particular problem given the widespread role of cAMP in vivo and what is needed are potent selective PDE IV inhibitors with an inhibitory action against PDE IV and little or no action against other PDE isoenzymes.

We have now found a novel series of trisubstituted phenyl derivatives, members of which are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the isolated PDE IV enzyme and also elevate cAMP in isolated leukocytes. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma.

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



wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or -XR^a group where X is -O-, -S(O)_m- [where m is zero or an integer of value 1 or 2], or -N(R^b)- [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]_nCH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different are as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group,

or R¹ and R² together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1;

Z is (1) a group -C(R³)(R⁴)C(R⁵)(R⁶)(R⁷) or -C(R⁴)=C(R⁵)(R⁶) where R³ is
5 a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group;

R⁴ is a group selected from -X^aL¹R¹² [where X^a is as defined above for X, L¹ is a linker group and R¹² is a hydrogen atom or a cycloaliphatic, heterocycloaliphatic, or monocyclic or bicyclic aryl group optionally
10 containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms], -Alk¹R¹² [where Alk¹ is an optionally substituted straight or branched alkenyl or alkynyl chain optionally containing one or more -O- or -S- atoms or -N(R^b)-, carbocyclic or heteroatom-containing groups], -CH₂L¹R^{12a} [where R^{12a} is as defined for R¹² but is not a hydrogen atom];
15 -X^aR^{12a}; or -C(X^b)R^{12a} [where X^b is an oxygen or sulphur atom];

R⁵ is a -(CH₂)_pAr group where p is zero or an integer 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

R⁶ is a hydrogen or a fluorine atom or an optionally substituted alkyl
20 group;

R⁷ is a hydrogen or a fluorine atom or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group;

or Z is (2) a group -C(R⁴)C(R⁵)(R⁶)(R⁷) where R⁴ is a group =CH₂, or
25 =CH(L¹)_n-R¹²;

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

It will be appreciated that certain compounds of formula (1) may have one or more chiral centres, depending on the nature of the groups L¹, R¹, R²,
30 R³, R⁴, R⁵, R⁶ and R⁷. 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, diastereomers and mixtures thereof, including racemates.

35 Compounds of formula (1) wherein L is a -C(R¹¹)=C(R¹)(R²) group and/or Z is the group -C(R⁴)=C(R⁵)(R⁶), may exist as geometric isomers

depending on the nature of the groups R^1 , R^2 , R^4 , R^5 , R^6 and R^{11} and the invention is to be understood to extend to all such isomers and mixtures thereof.

- 5 In the compounds of formula (1), when $=W-$ is $=C(Y)-$ and Y is a halogen atom Y may be for example a fluorine, chlorine, bromine or iodine atom.

When W in the compounds of formula (1) is a group $=C(Y)-$ and Y is $-XR^a$, R^a may be, for example, a hydrogen atom or an optionally substituted
10 straight or branched alkyl group, for example, an optionally substituted C_{1-6} alkyl group, such as a methyl, ethyl, n-propyl or i-propyl group. Optional substituents which may be present on R^a groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms. Particular R^a groups include for example $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CHCl_2$, $-CF_3$ or $-CCl_3$ groups.

15

When $=W-$ in the compounds of formula (1) is a group $=C(Y)-$ where $-Y$ is $-N(R^b)$, $=W-$ may be a $=C(NH_2)-$, $=C(NHCH_3)-$ or $=C(NHC_2H_5)-$ group.

20 In compounds of formula (1), X may be an oxygen or a sulphur atom, or a group $-S(O)-$, $-S(O)_2-$, $-NH-$ or C_{1-6} alkylamino, for example a C_{1-3} alkylamino, e.g. methylamino $[-N(CH_3)-]$ or ethylamino $[-N(C_2H_5)-]$ group.

Alkyl groups represented by Y , R , R^1 , R^2 , or R^b in the compounds of formula (1) include optionally substituted straight or branched C_{1-6} alkyl
25 groups optionally interrupted by one or more X atoms or groups. Particular examples include C_{1-3} alkyl groups such as methyl or ethyl groups. Optional substituents on these groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C_{1-6} alkoxy e.g. C_{1-3} alkoxy such as
30 methoxy or ethoxy or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$ or $-CN$ groups.

Alkenyl groups represented by R , R^1 or R^2 in the compounds of formula (1) include optionally substituted straight or branched C_{2-6} alkenyl groups optionally interrupted by one or more X atoms or groups. Particular
35 examples include ethenyl, propen-1-yl and 2-methylpropen-1-yl groups.

Optional substituents include those described above in relation to alkyl groups represented by the groups R¹ or R².

Alkynyl groups represented by R¹ or R² in compounds of formula (1) include optionally substituted straight or branched C₂₋₆alkynyl groups optionally interrupted by one or more X atoms or groups. Particular examples include ethynyl and propyn-1-yl groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R¹ or R².

10

When R¹ or R² in compounds of formula (1) is an alkoxy or alkylthio group it may be for example an optionally substituted straight or branched C₁₋₆alkoxy or C₁₋₆alkylthio group optionally interrupted by one or more X atoms or groups. Particular examples include C₁₋₃alkoxy, e.g. methoxy or ethoxy, or C₁₋₃alkylthio e.g. methylthio or ethylthio groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R¹ or R².

15

When R¹ and R² together with the carbon atom to which they are attached in the compounds of formula (1) are linked to form a cycloalkyl or cycloalkenyl group, the group may be for example a C₃₋₈cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃₋₈cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl such as methyl or ethyl, hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

25

30

When R in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C₃₋₈cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃₋₈cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclo-

35

pentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms,
5 straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl such as methyl or ethyl, hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

When the group R⁷ in compounds of formula (1) is an OR^c group it may be for example a hydroxyl group; or a group -OR^c where R^c is an
10 optionally substituted straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl or ethyl group, a C₂₋₆alkenyl group such as an ethenyl or 2-propen-1-yl group, a C₁₋₃alkoxyC₁₋₃alkyl group such as a methoxymethyl, ethoxymethyl or ethoxyethyl group, a C₁₋₆alkanoyl, e.g. C₁₋₃alkanoyl group such as an acetyl group, or a formyl [HC(O)-],
15 carboxamido (CONR¹²R^{12a}) or thiocarboxamido (CSNR¹²R^{12a}) group, where R¹² and R^{12a} in each instance may be the same or different and is each a hydrogen atom or an optionally substituted straight or branched C₁₋₆alkyl, e.g. C₁₋₃alkyl group such as methyl or ethyl group. Optional substituents which may be present on such R^c, R¹² or R^{12a} groups
20 include those described below in relation to the alkyl groups R⁶ or R⁷.

Alkyl groups represented by R³, R⁶ or R⁷ in compounds of formula (1) include optionally substituted straight or branched C₁₋₆ alkyl groups, e.g. C₁₋₃ alkyl groups such as methyl, ethyl, n-propyl or i-propyl groups.
25 Optional substituents which may be present on these groups include one or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

When R¹ or R² is a -CO₂R⁸, -CONR⁹R¹⁰ or CSNR⁹R¹⁰ group it may be for example a -CO₂H, -CONH₂ or -CSNH₂ group or a group -CO₂R⁸,
30 -CONR⁹R¹⁰, -CSNR⁹R¹⁰, -CONHR¹⁰, or -CSNHR¹⁰ where R⁸, R⁹ and R¹⁰ where present is a C₁₋₃alkyl group such as methyl or ethyl group, a C₆₋₁₂aryl group, for example an optionally substituted phenyl, or a 1- or 2-naphthyl group, or a C₆₋₁₂aryl C₁₋₃alkyl group such as an optionally
35 substituted benzyl or phenethyl group. Optional substituents which may

be present on these aryl groups include R^{13} substituents discussed below in relation to the group Ar.

- When R^4 in compounds of formula (1) contains a L^1 linker group, L^1 may be any divalent linking group. Particular examples of L^1 groups include groups of formula $-(Alk^2)_r(X^a)_s(Alk^3)_t-$ where Alk^2 and Alk^3 is each an optionally substituted straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain optionally containing one or more, e.g. one, two or three heteroatoms or carbocyclic or heteroatom-containing groups, X^a is as defined previously, r is zero or the integer 1, t is zero or the integer 1 and s is zero or the integer 1, provided that when one of r , s , or t is zero at least one of the remainder is the integer 1; and when L^1 is adjacent to $-X^a$ and s is the integer 1, r is also the integer 1.
- The heteroatoms which may interrupt the Alk^2 or Alk^3 chains include for example $-O-$ or $-S-$ atoms. Carbocyclic groups include for example cycloalkyl, e.g. cyclopentyl or cyclohexyl, or cycloalkenyl e.g. cyclopentenyl or cyclohexenyl, groups. Particular heteroatom-containing groups which may interrupt Alk^2 or Alk^3 include oxygen-, sulphur- or nitrogen-containing groups such as $-S(O)-$, $-S(O)_2-$, $-N(R^b)-$, $-C(O)-$, $-C(S)-$, $-C(NR^b)-$, $-CON(R^b)-$, $-CSN(R^b)-$, $-N(R^b)CO-$, $-N(R^b)CS-$, $-SON(R^b)-$, $-SO_2N(R^b)-$, $-N(R^b)SO-$, $-N(R^b)SO_2-$, $-N(R^b)SO_2N(R^b)-$, $-N(R^b)SON(R^b)-$, $-N(R^b)CON(R^b)-$ or $-N(R^b)CSN(R^b)$ groups. It will be appreciated that when the chains Alk^2 or Alk^3 contain two or more heteroatoms, carbocyclic or heteroatom-containing groups, such atoms or groups may be adjacent to one another, for example to form a group $-N(R^b)-C(NR^b)-N(R^b)-$ or $-O-CONH-$.

- Optional substituents which may be present on Alk^2 or Alk^3 chains include those described above in relation to the group R^1 when it is an alkyl group.

- In the group L^1 particular examples of Alk^2 or Alk^3 when present include optionally substituted methylene, ethylene, propylene, butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chains, optionally containing

one, two or three heteroatoms, carbocyclic or heteroatom-containing groups as described above.

Particular examples of linking groups L^1 include the groups $-\text{CH}_2-$,
5 $-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{CH}_2\text{SCH}_2-$, $-\text{CH}_2\text{N}(\text{R}^b)\text{CH}_2-$, $-\text{CH}=\text{CH}-$,
 $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{N}(\text{R}^b)-$, $-\text{CH}_2\text{OCH}_2\text{O}-$, $-\text{CH}_2\text{COCH}_2-$,
 $-(\text{CH}_2)_2\text{COCH}_2-$, or $-\text{CH}_2\text{CON}(\text{R}^b)-$.

Particular R^4 groups include $-\text{X}^a\text{Alk}^2\text{R}^{12}$ eg. $\text{OAlk}^2\text{R}^{12}$, $\text{OAlk}^2\text{X}^a\text{R}^{12}$,
10 $-\text{CH}_2\text{Alk}^2\text{X}^a\text{Alk}^3\text{R}^{12a}$, or $-\text{OR}^{12a}$ groups.

The group R^{12} or R^{12a} when present in R^4 may be a C_{3-8} cycloaliphatic, or a C_{3-8} heterocycloaliphatic group. Cycloaliphatic groups include for example optionally substituted C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl groups,
15 such as optionally substituted cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexadien-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl groups. Heterocycloaliphatic groups include for example optionally substituted C_{3-8} cycloalkyl or C_{3-8}
20 cycloalkenyl groups containing one, two or more $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^b)-$ groups, such as an optionally substituted pyrrolidinyl, dioxolanyl, e.g. 1,3 dioxolanyl, imidazolidinyl, pyrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, 3-pyrrolinyl, 2-imidazolinyl, or 2-pyrazolinyl group. Optional substituents
25 which may be present on cycloaliphatic or heterocycloaliphatic groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C_{1-6} alkyl, e.g. C_{1-3} alkyl such as methyl or ethyl, hydroxyl or C_{1-3} alkoxy e.g. C_{1-3} alkoxy such as methoxy or ethoxy groups.

30

Alternatively, R^{12} or R^{12a} may be a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms as described more fully below.

35 When an Alk^1 chain is present in the group R^4 it may be an optionally substituted straight or branched C_{2-6} alkenyl or C_{2-6} alkynyl chain

optionally containing one, two or more -O- or -S- atoms or -N(R^b)-, carbocyclic or heteroatom-containing groups. Particular examples of such chains include those described previously in relation to the chains Alk² or Alk³.

5

Monocyclic or bicyclic aryl groups represented by the groups R⁵, R¹² or R^{12a} in compounds of formula (1) include for example C₆₋₁₂ optionally substituted aryl groups, for example optionally substituted phenyl, 1- or 2-naphthyl, indenyl or isoindenyl groups.

10

When the monocyclic or bicyclic aryl group contains one or more heteroatoms it may be a C₁₋₉ for example a C₃₋₉ optionally substituted heteroaryl group containing for example one, two, three or more heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms.

15

20 Examples of heteroaryl groups represented by R⁵, R¹² or R^{12a} include 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, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, 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 and 5,6,7,8-tetrahydroisoquinolinyl.

25

30

The heteroaryl group represented by R⁵, R¹² or R^{12a} may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heteroaryl group is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group, and, similarly, when it is a furyl group it may be a 2-furyl or 3-furyl group.

35

When in compounds of formula (1) the heteroaryl group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for example N-alkyl quaternary salts and the invention is to be understood to
 5 extend to such salts. Thus for example when the group Ar is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

The aryl or heteroaryl groups represented by R^5 , R^{12} or R^{12a} in
 10 compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R^{13}]. The substituent R^{13} may be selected from an atom or group R^{14} or $-Alk^4(R^{14})_m$ wherein R^{14} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl ($-OH$), substituted hydroxyl, cycloalkyl, cycloalkoxy, formyl [$HC(O)-$], carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-C(O)R^{8a}$ [where
 15 R^{8a} is as defined above for R^8], $-CHO$, $-SO_3H$, $-SO_2R^{8a}$, $-SO_2NH_2$, $SO_2N(R^{8a})(R^{9a})$, (where R^{9a} is as described above for R^{8a} and may be the same as or different to R^{8a}), $-CONH_2$, $-CON(R^{8a})(R^{9a})$, $-NHSO_2R^{8a}$, $-N(R^{8b})SO_2R^{8a}$, $-N[SO_2R^{8a}]_2$, $-NHSO_2N(R^{8a})(R^{9a})$,
 20 $-N(R^{8b})SO_2N(R^{8a})(R^{9a})$ (where R^{8b} is as described for R^{8a} and may be the same as or different to R^{8a}), $-NHCONH_2$, $-NHCON(R^{8a})(R^{9a})$, $-N(R^{8b})CONH_2$, $-N(R^{8b})CON(R^{8a})(R^{9a})$, $-NHCSNH_2$, $-NHCSN(R^{8a})(R^{9a})$, $-N(R^{8b})CSN(R^{8a})(R^{9a})$, $-N(R^{8b})CSNH_2$, $-NHCSNH(R^{8a})$, $-N(R^{8a})CSNH(R^{8b})$, $-NHC(O)H$, $-N(R^{8b})C(O)H$, $-NHC(O)R^{8a}$,
 25 $-N(R^{8b})C(O)R^{8a}$, $-N[C(O)R^{8a}]_2$, $-N[CHO]_2$, $-NHCO_2H$, $-NHC(O)OR^{8a}$, $-N(R^{8b})C(O)OR^{8a}$, $-N(R^{8b})CO_2H$, $-N[C(O)H]SO_2H$, $-N[C(O)H]SO_2R^{9a}$, $-N[C(O)R^{8a}]SO_2H$, $-N[C(O)R^{8a}]SO_2R^{9a}$, $-C(S)H$, $-C(S)R^{8a}$, $-C(S)NH_2$, $-C(S)NH(R^{8a})$, $C(S)N(R^{8a})(R^{9a})$, $-NHC(S)H$, $-N(R^{8b})C(S)H$, $-N[C(S)H]_2$, $-NHC(S)R^{8a}$, $-N(R^{8b})C(S)R^{8a}$, $-N[C(S)R^{8a}]_2$, $-N[C(S)H]SO_2H$,
 30 $-N[C(S)R^{8a}]SO_2H$, $-N[C(S)H]SO_2R^{9a}$, or $-N[C(S)R^{8a}]SO_2R^{9a}$ 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 $-S(O)_z-$, [where z is an integer 1 or 2] or $-N(R^7)-$ groups; and m is zero or an integer 1, 2 or 3.

When in the group $-\text{Alk}^4(\text{R}^{14})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{14} may be present on any suitable carbon atom in $-\text{Alk}^4$. Where more than one R^{14} substituent is present these may be the same or different and may be present on the same or different carbon atom in Alk^4 . Clearly, when m is zero and no substituent R^{14} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{14} is a substituted amino group it may be a group $-\text{NH}[\text{Alk}^4(\text{R}^{15})_m]$ [where Alk^4 and m are as defined above and R^{15} is as defined above for R^{14} but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group $-\text{N}[\text{Alk}^4(\text{R}^{15})_m]_2$ wherein each $-\text{Alk}^4(\text{R}^{15})_m$ group is the same or different.

When R^{14} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{14} is a cycloalkoxy group it may be for example a C_{5-7} cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R^{14} is a substituted hydroxyl or substituted thiol group it may be a group $-\text{OAlk}^1(\text{R}^{15})_m$ or $-\text{SAlk}^4(\text{R}^{15})_m$ respectively, where Alk^4 , R^{15} and m are as just defined.

Esterified carboxyl groups represented by the group R^{14} include groups of formula $-\text{CO}_2\text{Alk}^5$ 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} aryl C_{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} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or

benzoyloxypropyl group. Optional substituents present on the Alk⁵ group include R¹³ substituents described above.

- When Alk⁴ is present in or as a substituent R¹³ it may be for example a
- 5 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(R⁷)- groups.
- 10 Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆ hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C₁₋₆alkylthiol e.g. methylthiol or ethylthiol,
- 15 C₁₋₆alkoxy, e.g. methoxy or ethoxy, C₅₋₇ cycloalkyl, e.g. cyclopentyl, C₅₋₇ cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl
- 20 (-CO₂H), -CO₂Alk⁵ [where Alk⁵ is as defined above], C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, arylaminosulphonyl, e.g. optionally substituted phenylaminosulphonyl, aralkylaminosulphonyl, e.g. optionally substituted benzylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, arylaminocarbonyl, e.g. phenylaminocarbonyl, sulphonylamino (-NHSO₂H),
- 30 C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, arylaminosulphonylamino,
- 35

2192644

13

e.g. phenylaminosulphonylamino C₁₋₆alkanoylamino, e.g. acetylamino, C₁₋₆ alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl or C₁₋₆ alkoxy-carbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxy-carbonylamino, thiocarboxamido (-CSNH₂), C₁₋₆ alkylaminothiocarbonyl, 5 e.g. methylaminothiocarbonyl or ethylaminothiocarbonyl, C₁₋₆dialkylaminothiocarbonyl, e.g. dimethylaminothiocarbonyl or diethylaminothiocarbonyl, phenylaminothiocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or 10 diethylaminocarbonylamino, aminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆ dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino, or diethylaminothiocarbonylamino, aminocarbonylC₁₋₆ alkylamino, e.g. aminocarbonylmethylamino or aminocarbonylethylamino, 15 aminothiocarbonylC₁₋₆alkylamino e.g. aminothiocarbonylmethylamino or aminothiocarbonylethylamino, formylaminoC₁₋₆ alkylsulphonylamino, e.g. formylaminomethylsulphonylamino or formylaminoethylsulphonylamino, thioformylaminoC₁₋₆alkylsulphonylamino, e.g. thioformylaminomethylsulphonylamino or thioformylethylsulphonylamino, C₁₋₆acylaminosulphonylamino, e.g. acetylaminosulphonylamino, C₁₋₆thioacylaminosulphonylamino, e.g. thioacetylaminosulphonylamino groups. 20

Where desired, two R¹³ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₂₋₆alkylenedioxy group such as 25 ethylenedioxy.

It will be appreciated that where two or more R¹³ substituents are present, these need not necessarily be the same atoms and/or groups. The R¹³ substituents may be present at any ring carbon atom away from that 30 attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by R⁵, R¹² or R^{12a} any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

In the compounds of formula (1), when an ester group is present, for example a group $-\text{CO}_2\text{Alk}^5$ this may advantageously be a metabolically labile ester.

- 5 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.

10

- 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, 15 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 20 magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

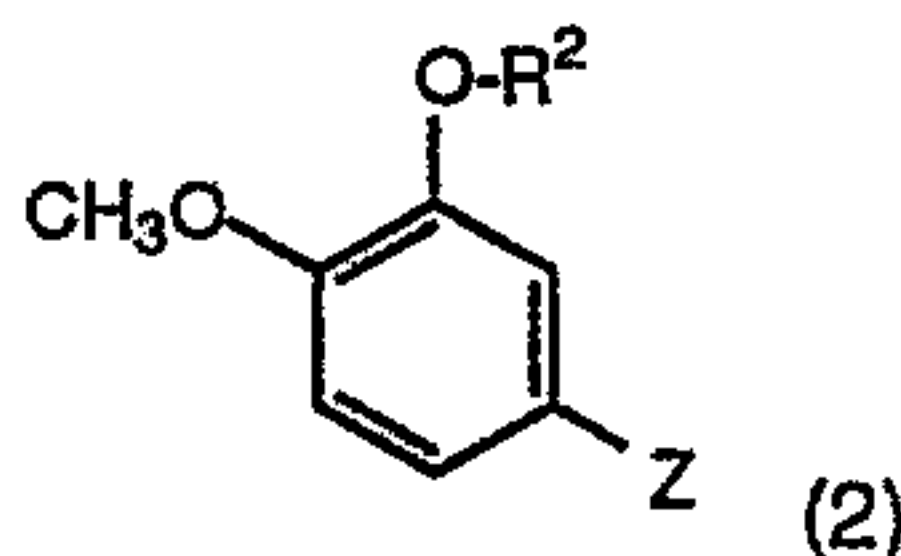
- Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or aminos, which are convertible in vivo by 25 metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

- Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition 30 pharmaceutically acceptable salts.

- In the compounds of formula (1), the group $-\text{W}=$ is preferably a group $-\text{C}(\text{Y})=$ where Y is a group X^aR^1 , where $-\text{X}^a-$ is $-\text{O}-$, especially where R^1 is an optionally substituted ethyl group or, especially, an optionally 35 substituted methyl group. Especially useful substituents which may be present on R^1 groups include one, two or three fluorine or chlorine atoms.

The group X in compounds of formula (1) is preferably -O-.

5 A particularly useful group of compounds of formula (1) has the formula (2):



10 where R² is an optionally substituted cycloalkyl group; Z is as defined for formula (1); and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

15 The group R³ in compounds of formulae (1) or (2) is preferably a hydrogen atom or a C₁₋₃ alkyl group, particularly a methyl group.

R⁴ in the compounds of formulae (1) or (2) is preferably (1) a X^aL¹R¹² group, particularly where X^a is an oxygen atom, L¹ is Alk² and R¹² is a hydrogen atom or an aryl group, or (2) is a -X^aR^{12a} group, particularly where R^{12a} is a cycloaliphatic group.

20 Particular examples of such R⁴ groups include optionally substituted alkoxy, cycloalkoxy, cycloalkylalkoxy, phenoxy or phenalkoxy groups. Such groups include optionally substituted ethoxy, n-propoxy, i-propoxy, n-butoxy, methoxyethoxy, cyclopentyloxy, cyclohexyloxy, cyclopentyl-methoxy, cyclopentylethoxy, cyclohexylmethoxy, cyclohexylethoxy, 25 phenoxy, benzyloxy and phenethyloxy groups.

30 R⁵ in the compounds of formulae (1) or (2) is preferably an optionally substituted phenyl group, particularly a phenyl group optionally substituted by one, two or more R¹³ groups, and is especially a 2- or 3-monosubstituted or 2,6-disubstituted phenyl group. Particular substituents include-halogen atoms, especially fluorine or chlorine atoms, and nitro,

amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{8a}, -NHCONHR^{8a} and -NHSO₂R^{8a} groups.

5 Particular R⁵ groups include 2-nitrophenyl, 2-aminophenyl, 2-haloalkylphenyl, e.g. 2-trifluoroalkylphenyl, 2-halophenyl, e.g. 2-fluorophenyl, 2-chlorophenyl, or 2-bromophenyl, 3-halophenyl, e.g. 3-fluorophenyl, 2,6-dihalophenyl, e.g. 2,6-difluorophenyl, or 2,6-dichlorophenyl, and 2, 6-dialkoxyphenyl, e.g. 2, 6-dimethoxyphenyl.

10 Other particularly useful R⁵ groups in compounds of formulae (1) and (2) include 2-,3- and 4-pyridinyl, thienyl, e.g. 2-thienyl or pyrimidinyl, especially 2-pyrimidinyl, groups, optionally substituted by one, two or more R¹³ groups, especially halogen atoms, e.g. fluorine or chlorine atoms, nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{8a}, -NHCONHR^{8a} or
15 -NHSO₂R^{8a} groups.

Particularly useful compounds according to the invention are:

- (±)-4-[2-Benzoyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propyloxyethyl]pyridine;
20 (±)-4-[2-Cyclopentyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl] - pyridine;
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-butyloxy)ethyl]pyridine;
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methylpropyloxy)ethyl] - pyridine;
25 (±)-4-[2-Cyclohexylmethoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl] - pyridine;
(±)-3,5-Dichloro-4-[2-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
(±)-3,5-Dichloro-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1-butyloxy) - ethyl]pyridine
30 (±)-3,5-Dichloro-4-[2-cyclopentyloxy-4-methoxyphenyl)-2-methoxyethoxy-ethyl]pyridine;
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-ethoxyethyl]pyridine;
4-[2(R)-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylbut-3-enyl]pyridine;
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propylthioethyl]pyridine.
35 and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

Compounds according to the invention are selective and potent orally active inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

5

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human or animal diseases where an unwanted inflammatory response or muscular spasm (for example bladder or alimentary smooth muscle spasm) is present and where the elevation
10 of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung
15 associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis,
20 atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and arteriosclerosis.

Compounds of the invention also suppress neurogenic inflammation
25 through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

Compounds according to the invention may also elevate cAMP in
30 lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

Compounds according to the invention have also been found to reduce
35 gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

Compounds of the invention suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention suppress inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteoarthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention ameliorate these symptoms with a consequent enhancement of quality of life.

Compounds of the invention also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

Compounds of the invention suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

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. Forms suitable for oral administration are particularly useful.

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 for adult or paediatric use and/or 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 of 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
5 suitable gas or mixture of gases.

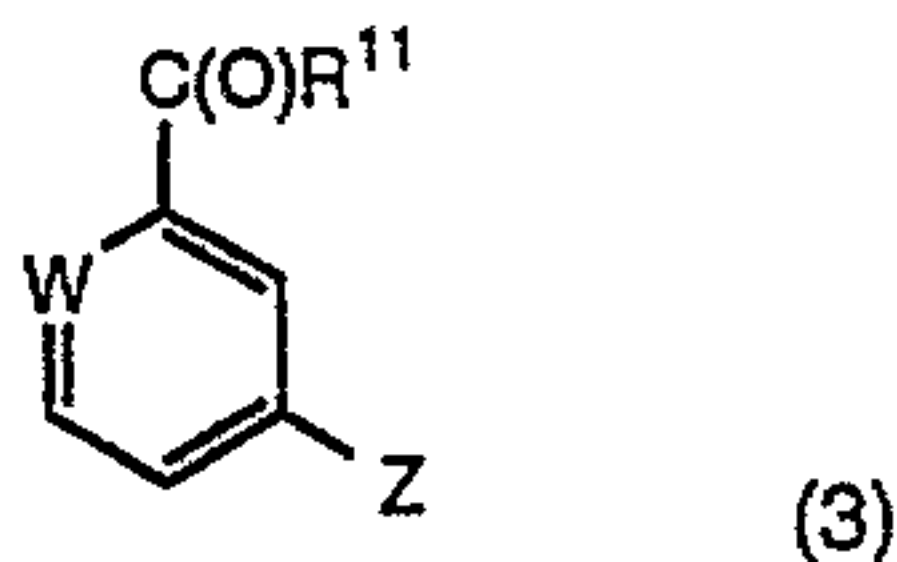
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the
10 active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the
15 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.
20 around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. The symbols L, R², R³, R⁴, R⁵, R⁶, R⁷, W, Z and X,
25 when used in the formulae below 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, carboxy or aldehyde groups, where these are desired in the final product, to avoid
30 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, 1981.]

35 Thus, according to a further aspect of the invention, compounds of general formula (1) where L is a -C(R¹¹)=C(R¹)(R²) group in which R¹¹ is a

hydrogen atom or a methyl group, may be prepared by coupling a compound of formula (3)



5

where R^{11} is as described above with an olefination agent.

Particular examples of olefination agents include phosphonium salts such as compounds $(R^1)(R^2)CHP(D)_3Hal$ where Hal is a halogen atom, such as a bromine atom, and D is an optionally substituted alkyl, e.g. methyl, or aryl, especially phenyl, group; phosphoranes $(R^1)(R^2)C=P(D)_3$; phosphonates $(DO)_2P(O)CH(R^1)(R^2)$; or silane derivatives, for example compounds of formula $(D)_3SiC(R^1)(R^2)$, e.g. trialkylsilanes such as $(CH_3)_3SiC(R^1)(R^2)$.

15

Bases for use in the above reaction include organometallic bases, for example, an organolithium compound such as an alkyllithium e.g. n-butyllithium, a hydride, such as sodium or potassium hydride or an alkoxide, such as a sodium alkoxide, e.g. sodium methoxide.

20

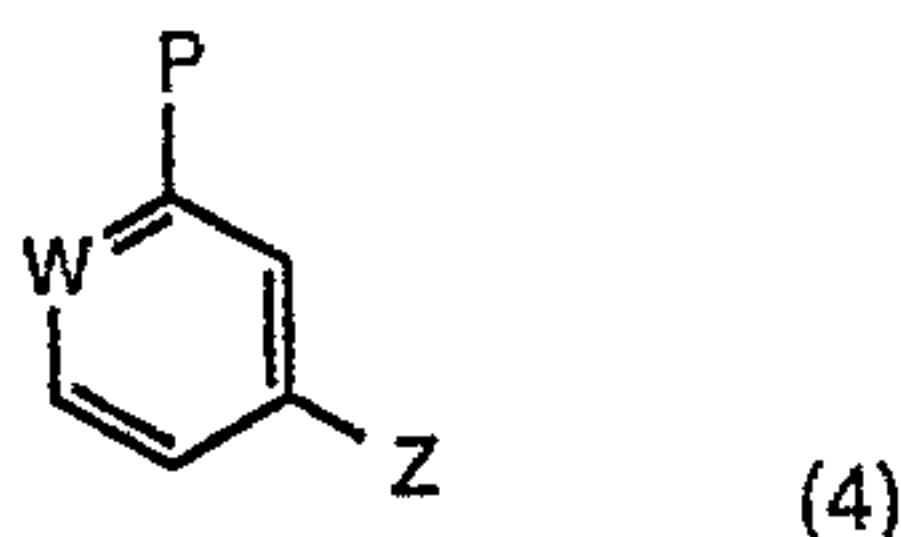
The reaction may be performed in a suitable solvent, for example a polar aprotic solvent, such as an alkyl sulphoxide, e.g. methyl sulphoxide, an amide such as N,N-dimethylformamide or hexamethylphosphorous triamide; a non-polar solvent, such as an ether, e.g. tetrahydrofuran or diethyl ether or an aromatic solvent such as benzene, toluene or xylene; or a polar protic solvent, such as an alcohol, for example ethanol. Preferably the reaction is carried out at a low temperature, for example from around $-78^\circ C$ to around room temperature.

25

The olefination agents used in this reaction are either known compounds or may be prepared from known starting materials using reagents and conditions similar to those used to prepare the known compounds. For

30

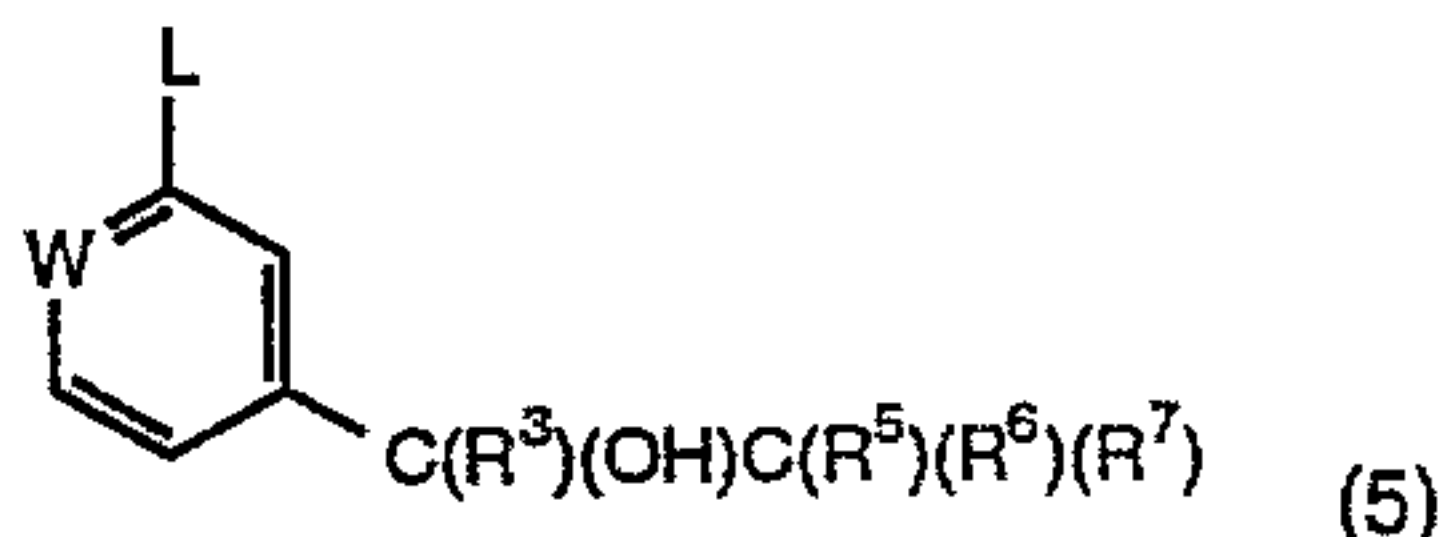
- example, a phosphorane may be prepared in situ by reaction of a phosphonium salt with a base of the type described above. In another example, a phosphonate may be prepared by reacting a halide $(R^1)(R^2)CHHal$ with a phosphite $(DO)_3P$, as described in the Arbuzov reaction.
- 5 Silane derivatives may be prepared by reaction of a halosilane $(D)_3SiHal$ with a base, such as lithium diisopropylamide, in a solvent, such as an ether, for example a cyclic ether, e.g. tetrahydrofuran, at low temperature, e.g. $-10^\circ C$.
- 10 According to a further aspect of the invention compounds of formula (1) where L is a group $-C(R)=CR^2$ and R^2 is an optionally substituted alkyl, alkenyl or alkynyl group may also be prepared by reaction of an intermediate of formula (3) with an organometallic reagent, followed by dehydration of the resulting alcohol.
- 15 Examples of organometallic reagents include organolithium R^2Li or organomagnesium R^2MgHal reagents. The reaction with the organometallic reagent may be performed in a solvent such as an ether, such as diethyl ether or for example a cyclic ether such as tetrahydrofuran, at a low
- 20 temperature for example $-10^\circ C$ to room temperature. The dehydration may be performed using an acid, for example an organic acid such as p-toluene sulphonic acid or trifluoroacetic acid, in the presence of a base, such as an amine, e.g. triethylamine.
- 25 Intermediates of formula (3) where R^{11} is a methyl group, may be prepared by reacting an intermediate of formula (3) where R^{11} is a hydrogen atom with an organometallic reagent, such as methyllithium or CH_3MgHal , using the conditions just described followed by oxidation of the resulting alcohol, using an oxidising agent, e.g. manganese dioxide.
- 30 Intermediates of formula (3) where R^{11} is a hydrogen atom may be prepared by deprotecting a protected aldehyde of formula (4)



where P is a protected aldehyde group, e.g. a dioxanyl group, using acid hydrolysis e.g. by reaction with trifluoroacetic acid or p-toluene sulphonic acid, in the presence of a solvent, e.g. acetone, or a mixture of solvents, e.g. chloroform and water.

Intermediates of formula (4) may be prepared using the following general reactions, where L is a -XR group, involving manipulation and synthesis of the group Z, from, for example, a compound where Z is a halogen atom. The protected aldehyde group P may be formed at the beginning of such a synthesis by reaction of a compound where P is -CHO with an aldehyde protecting group, using for example a suitable diol, e.g. 1,3-propanediol, in the presence of an acid catalyst, e.g. 4-toluenesulphonic acid, in a solvent, such as an aromatic solvent, e.g. toluene, at an elevated temperature such as the reflux temperature.

According to a further aspect of the invention a compound of formula (1) where Z is $-C(R^3)(R^4)C(R^5)(R^6)(R^7)$ and R^4 is a $-OL^1R^{12}$ or OR^{12a} group may be prepared by reaction of an alcohol of formula (5)



where L is as defined for compounds of formula (1) with a reagent $R^{12}L^1L^2$ or $R^{12a}L^2$, where L^2 is a leaving group, such as a halogen atom, e.g. a chlorine or iodine atom, using a base at an elevated temperature, if necessary in the presence of a catalyst, e.g. tetrafluoroboric acid (BF_4).

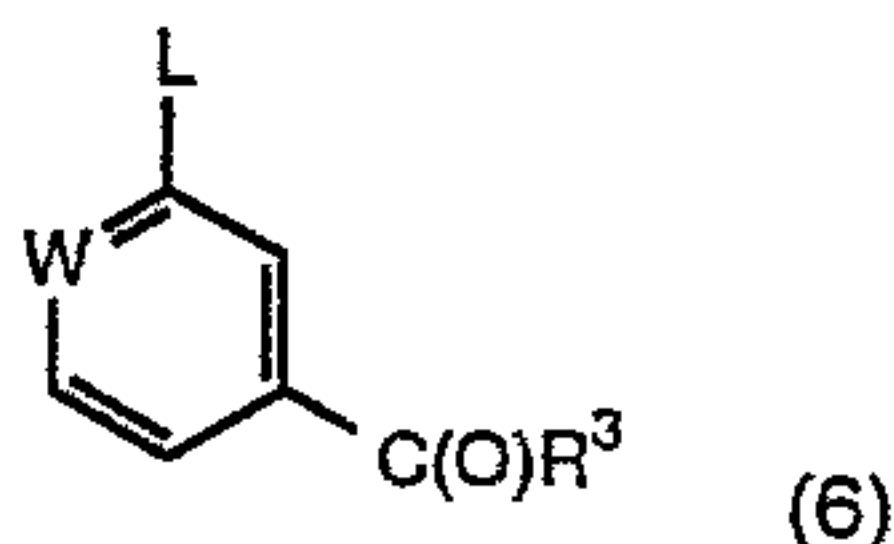
Suitable bases include inorganic bases, for example alkali and alkaline earth metal bases, e.g. hydroxides, such as potassium hydroxide, an organometallic bases, such as n-butyllithium, and hydride such as lithium hydride and sodium hydride. The reaction may be performed in an inert organic solvent, for example methylsulphoxide.

Compounds of formula (1) where Z and L are as just defined may also be prepared by dehydration of an alcohol of formula (5) and an alcohol of formula $R^{12}L^1OH$.

The reaction may be performed in the presence of an acid catalyst, e.g. sulphuric acid, or in the presence of an activator e.g. diethyl azodicarboxylate ($EtO_2C-N=N-CO_2Et$) and a phosphine, such as triphenylphosphine, in the presence of an organic base such as triethylamine, in a solvent such as tetrahydrofuran at an elevated temperature e.g. the reflux temperature [see for example Mitsunobu, O., Synthesis, (1981), 1].

In another example of a process according to the invention compounds of formula (1) as just described may be prepared by reaction of an alcohol of formula (5) with an oxonium ion $(R^{12})_3O^+$. Oxonium anions $(R^{12})_3O^+$ may be formed by treating a compound $R^{12}X$ (where X is a halogen atom) with an ether $(R^{12})_2O$, in the presence of a silver salt, such as silver tetrafluoroborate ($AgBF_4$) or silver hexafluoroantimonate ($AgSbF_6$).

Intermediates of formula (5) where R^3 is as defined for formula (1) but is not a fluorine atom may be prepared by reaction of a ketone or aldehyde of formula (6)



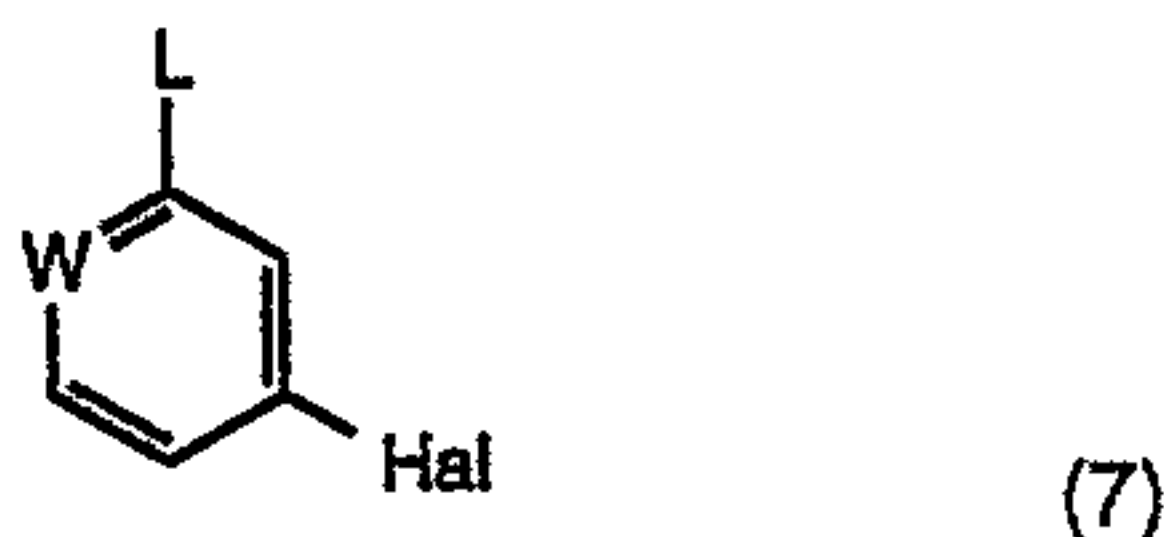
with an organometallic reagent $(R^7)(R^6)R^5CM$ [where M is a metal atom, for example a lithium atom] in a solvent such as an ether, e.g. a cyclic -

ether such as tetrahydrofuran, at a low temperature e.g. around -70°C to ambient temperature.

5 Reagents $(\text{R}^7)(\text{R}^6)\text{R}^5\text{CM}$ are either known compounds or may be prepared, preferably in situ during the above process, by reaction of a compound $\text{Alk}^6\text{CH}_2\text{M}$ or $[\text{Alk}^6]_2\text{NM}$ [where Alk^6 is an alkyl group such as a n-propyl or i-propyl group] with a compound $(\text{R}^7)(\text{R}^6)\text{R}^5\text{CH}$ using the just mentioned reaction conditions.

10 The reagents $(\text{R}^7)(\text{R}^6)\text{R}^5\text{CH}$ are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

15 Intermediates of formula (6) where R^3 is a hydrogen atom may be prepared by reacting a compound of formula (7)

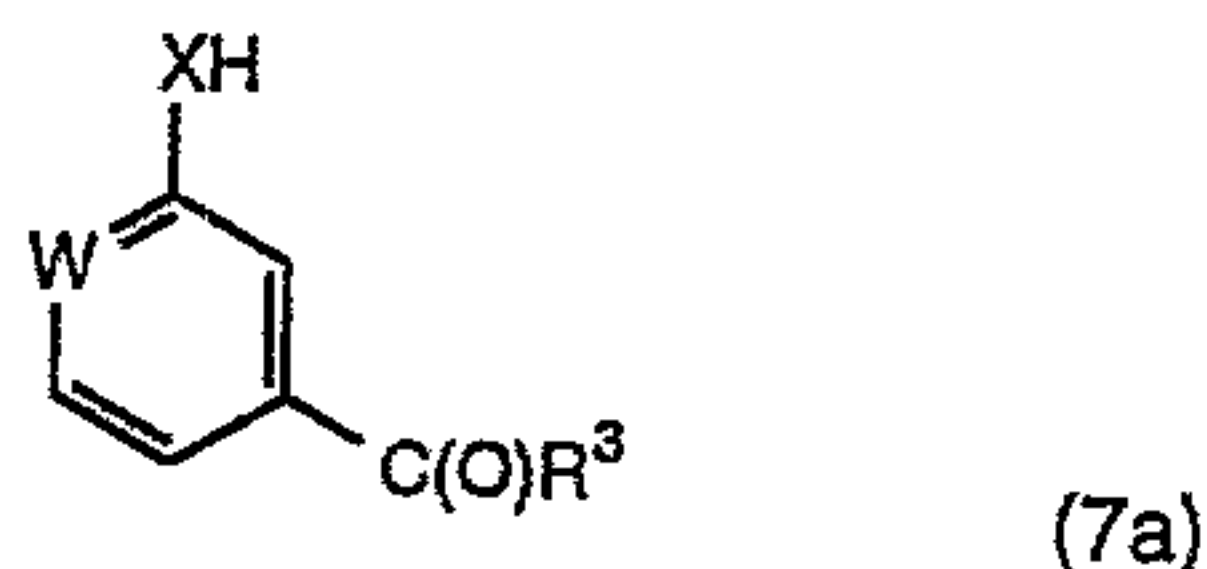


20 where Hal is a halogen atom, e.g. a bromine atom, with an organometallic reagent, such as n-butyllithium, in a solvent, such as an amide, e.g. dimethylformamide, at a low temperature, e.g. below -60°C .

25 Ketones of formula (6) where R^3 is an alkyl group may be prepared by reaction of an aldehyde of formula (6), with an organometallic compound, such as an organolithium compound R^3Li , or a Grignard R^3MgBr , in a solvent, such as tetrahydrofuran, at a low temperature, e.g. around -55°C to 0°C followed by oxidation of the resulting alcohol with an oxidising agent, such as manganese (IV) oxide.

30

Intermediates of formula (6) where L is a XR group may also be prepared by alkylation of a corresponding compound of formula (7a)

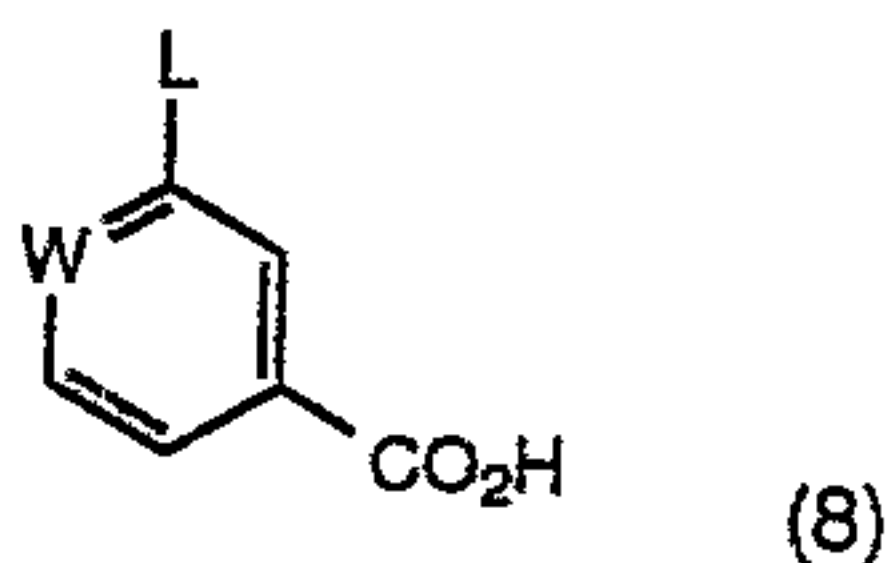


5 using a compound RHal [where Hal is a halogen atom such as a bromine or chlorine atom] where necessary in the presence of a base such as caesium or potassium carbonate or an alkoxide such as potassium t-butoxide, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide at ambient temperature or above e.g. around 40°C to 50°C.

10

Intermediates of formulae (7) and (7a) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

15 Intermediates of formula (6) wherein -W= is -N= and R³ is a hydrogen atom may be prepared from a compound of formula (8)

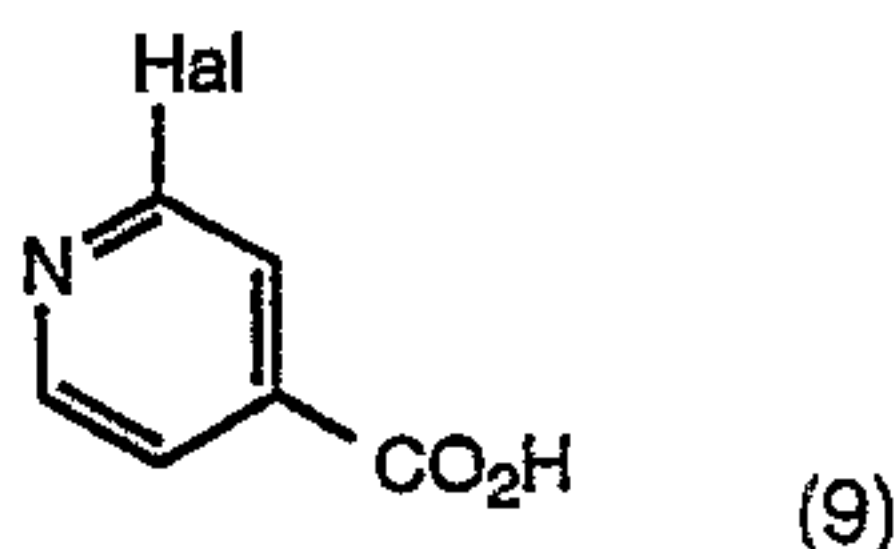


20 by successive reduction and oxidation.

The first reduction, for example by lithium aluminium hydride, affords the alcohol analogue. This, in turn is oxidised, for example by manganese dioxide, to yield the compound of formula (6).

25

Compounds of formula (8) wherein L is -XR and X is -O-, -S- or -NH-, may be prepared by reacting a halide of formula (9)



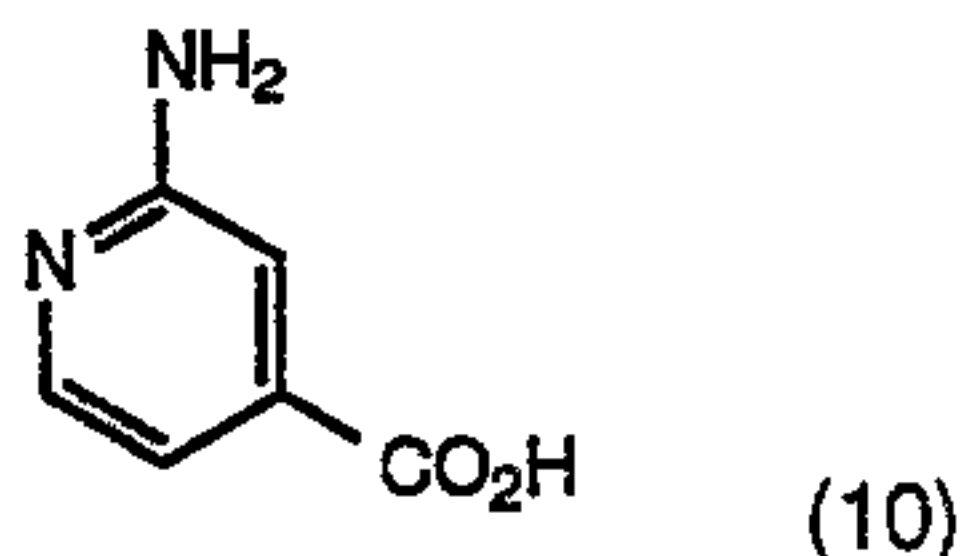
where Hal is a halogen atom, e.g. a bromine, chlorine or iodine atom with a compound RXH, where -X- is -O-, -S- or -NH- in the presence of a base.

5

Bases used in this reaction include hydrides, such as sodium hydride, or an organometallic base, such as butyllithium in a solvent, such as an amide, for example dimethylformamide at a temperature from room temperature to above, e.g. 80°C.

10

Intermediates of formula (9) may be prepared by reacting the known acid of formula (10)



15

with nitrous oxide (made *in situ* by reacting sodium nitrite with an acid, for example sulphuric acid or hydrobromic acid) to produce the diazonium salt. This in turn may be reacted with a haloacid, e.g. hydrobromic, hydrochloric or hydroiodic acid if necessary in the presence of the corresponding copper (I) halide (CuBr or CuI) or halogen Br₂, Cl₂ or I₂.

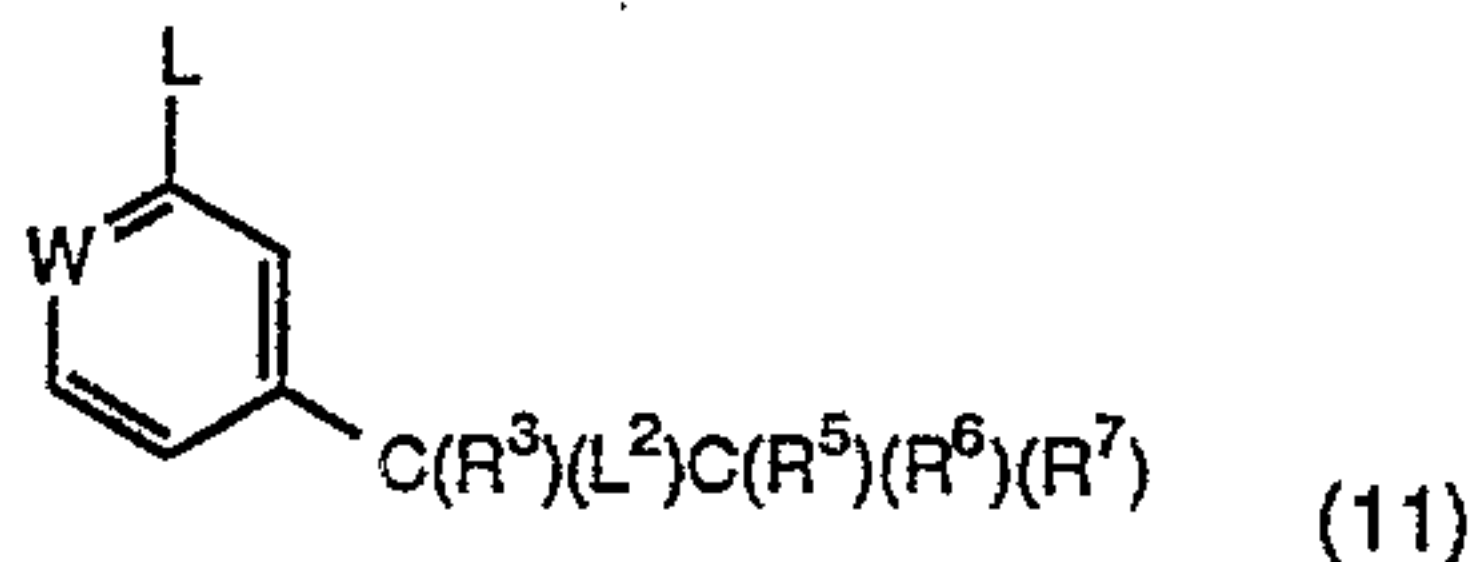
20

According to a further aspect of the invention a compound of formula (1) wherein Z is a group -C(R³)(R⁴)C(R⁵)(R⁶)(R⁷) where R⁴ is a -SL¹R¹² or -SR^{12a} group (where R^{12a} is an aryl group) may be prepared by reaction of an alcohol of formula (5), with (1) a compound R¹²L¹L², where L² is Hal in the presence of tetramethylthiourea Me₂NC(=S)NMe₂ followed by sodium hydride; or (2) a compound -SR^{12a} (where R^{12a} is an aryl group) in the presence of tributylphosphine (Bu₃P) and N-(arythiosuccinimide) in

25

an inert solvent, such as an aromatic solvent, e.g. benzene or xylene, at elevated temperature.

- 5 In yet another aspect of the invention, a compound of formula (1) where Z is a group $-C(R^3)(R^4)C(R^5)(R^6)(R^7)$, where R^4 is $-SL^1R^{12}$ or $-SR^{12a}$ may be prepared by reacting a compound of formula (11)



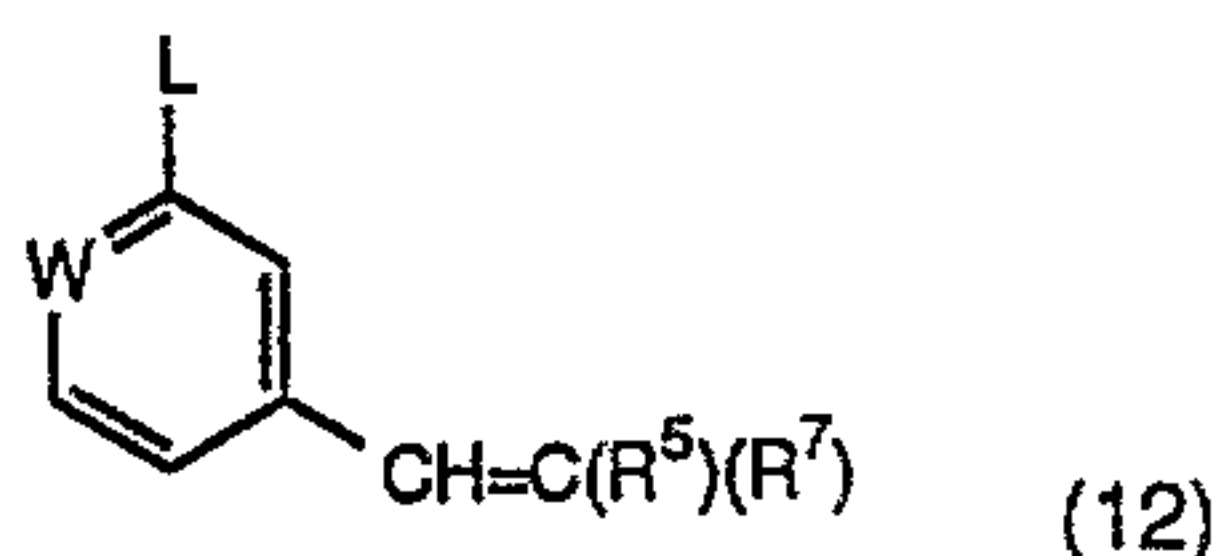
- 10 where L^2 is a halogen atom or a sulfuric or sulfonic ester with a thiol reagent $R^{12}L^1SH$, or $R^{12a}SH$ if necessary in the presence of a base, such as 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) or an alkali metal carbonate, e.g. potassium carbonate, in a solvent, such as an aromatic solvent, e.g. benzene.

15

- Intermediates of formula (11) where L^2 is Hal, e.g. a chlorine atom, may be prepared by halogenation of an alcohol of formula (5) using a halogenating agent, such as a chlorinating agent, e.g. thionyl chloride ($SOCl_2$) or phosphorous oxychloride ($POCl_3$) in an aromatic solvent, such as an aromatic amine, e.g. pyridine. Intermediates of formula (11) where L is a chlorine atom may also be prepared by bubbling hydrogen chloride gas in a solution of an alcohol of formula (5) in a solvent such as diethyl ether, whilst keeping the reaction temperature between $0^\circ C$ to room temperature.

25

- Compounds of formula (1) where Z is a group $-C(R^3)(R^4)C(R^5)(R^6)(R^7)$ in which R^3 and R^6 is a hydrogen atom and R^4 is a $-SL^1R^{12}$ group, may also be prepared by reacting a compound of formula (12)



with a thiol reagent $R^{12}L^1SH$ or $R^{12a}SH$, in the presence of a base, such as an organometallic base, for example n-butyllithium, in a solvent, such as a cyclic ether, e.g. tetrahydrofuran.

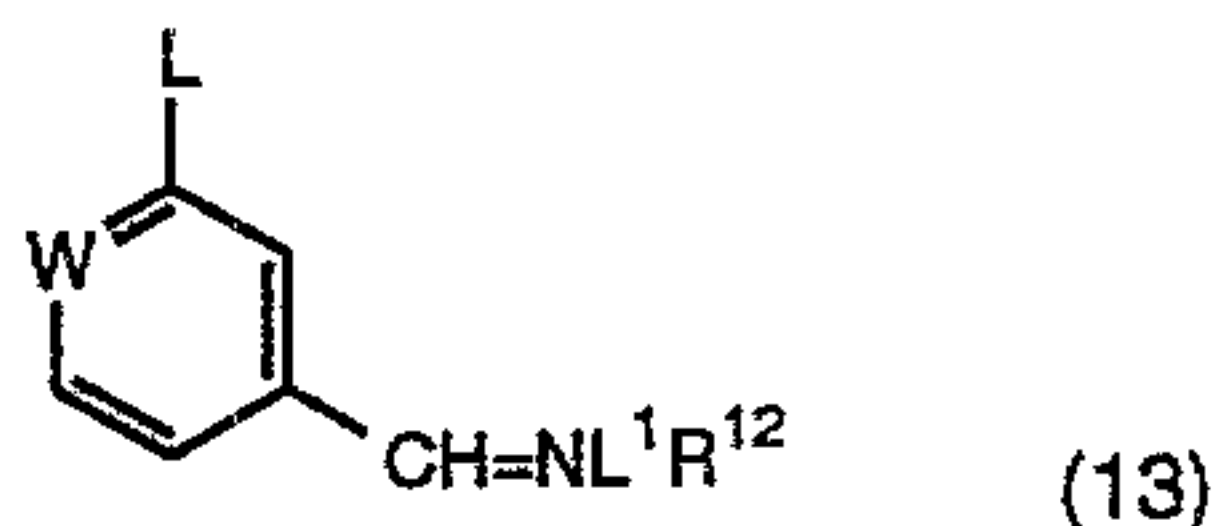
Intermediates of formula (12) may be prepared by reacting a compound $HalCH(R^5)(R^7)$ (where Hal is a halogen atom, e.g. a chlorine atom) with an aldehyde of formula (6) using a base, such as an organometallic base, for example, n-butyllithium, followed by dehydration of the resulting alcohol, using an acid, such as trifluoacetic acid, in the presence of a solvent, such as pyridine.

In another example according to the invention, a compound of formula (1) where R^4 is a $-OC(O)L^1R^{12}$ group, may be prepared by esterification of an alcohol of formula (5) with a carboxylic acid $R^{12}L^1CO_2H$ or an active derivative thereof, such as an acyl halide, e.g. acyl chloride if necessary in the presence of a catalyst, such as an acid catalyst, e.g. sulphuric acid.

In yet another example according to the invention, a compound of formula (1) where R^4 is $-OC(O)NH(L^1R^{12})$ or $-OC(S)NH(L^1R^{12})$ may be prepared by reaction of an alcohol of formula (5) with an isocyanate $R^{12}L^1N=C=O$ or an isothiocyanate $R^{12}L^1N=C=S$, in the presence of a base, such as sodium hydride, in a solvent, such as tetrahydrofuran. Compounds $R^{12}L^1N=C=O$ and $R^{12}L^1N=C=S$ are known compounds or may be prepared using the reagents and conditions used for the preparation of the known compounds. When $R^{12}L^1N=C=S$ is not available, a compound of formula (1) where R^4 is $-OC(S)NH(L^1R^{12})$ may be prepared by interconverting a compound of formula (1) where R^4 is $-OC(O)NH(L^1R^{12})$ using a thiation reagent, such as a Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane -2,4-disulphide], in an aromatic solvent, such as xylene or toluene.

Compounds of formula (1) where Z is $-C(R^3)(R^4)C(R^5)(R^6)(R^7)$ where R^3 is a hydrogen atom and R^4 is $NH(L^1R^{12})$ may be prepared by reacting an imine of formula (13)

5



with a reagent $CH(R^5)(R^6)(R^7)$, in the presence of a base, such as an organometallic, for example n-butyllithium, in a solvent, such as an ether, for example diethylether or tetrahydrofuran.

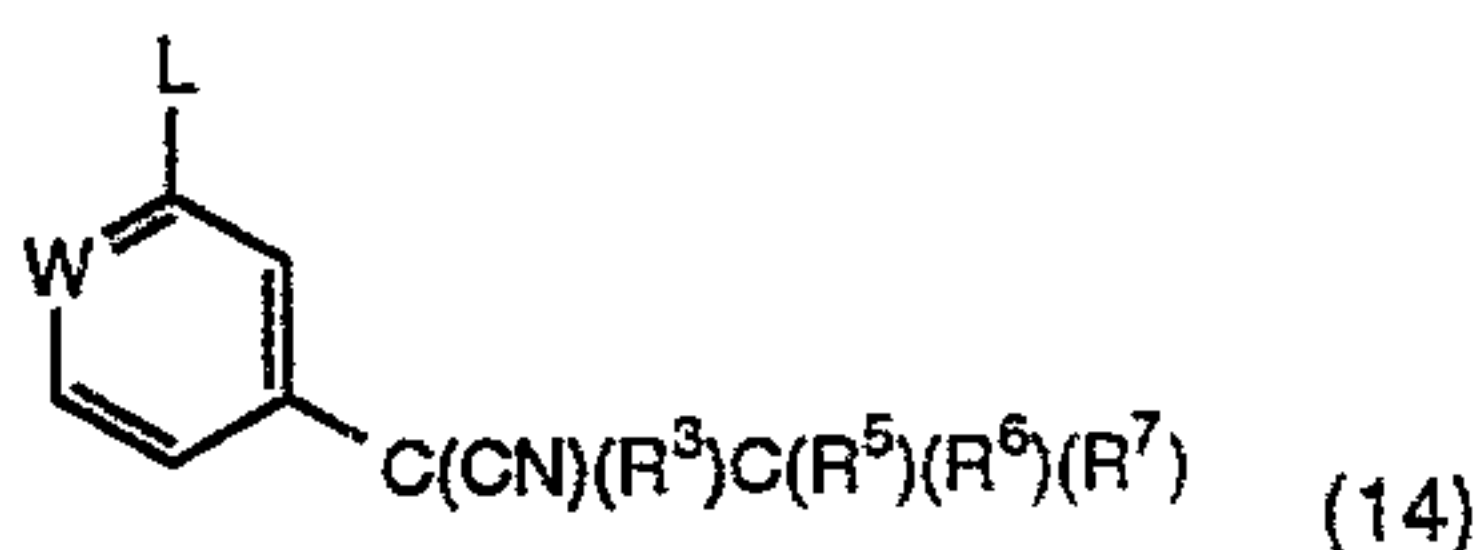
10

Intermediates of formula (13) may be prepared by condensation of an aldehyde of formula (6) with an amine $R^{12}L^1NH_2$, in a solvent such as dichloromethane, at a temperature from room temperature to reflux, if necessary in the presence of a drying agent, such as 3Å molecular sieve.

15

According to a further aspect of the invention, compounds of formula (1) where R^4 is a group $-C(O)L^1R^{12}$ may be prepared by reacting a nitrile of formula (14)

20

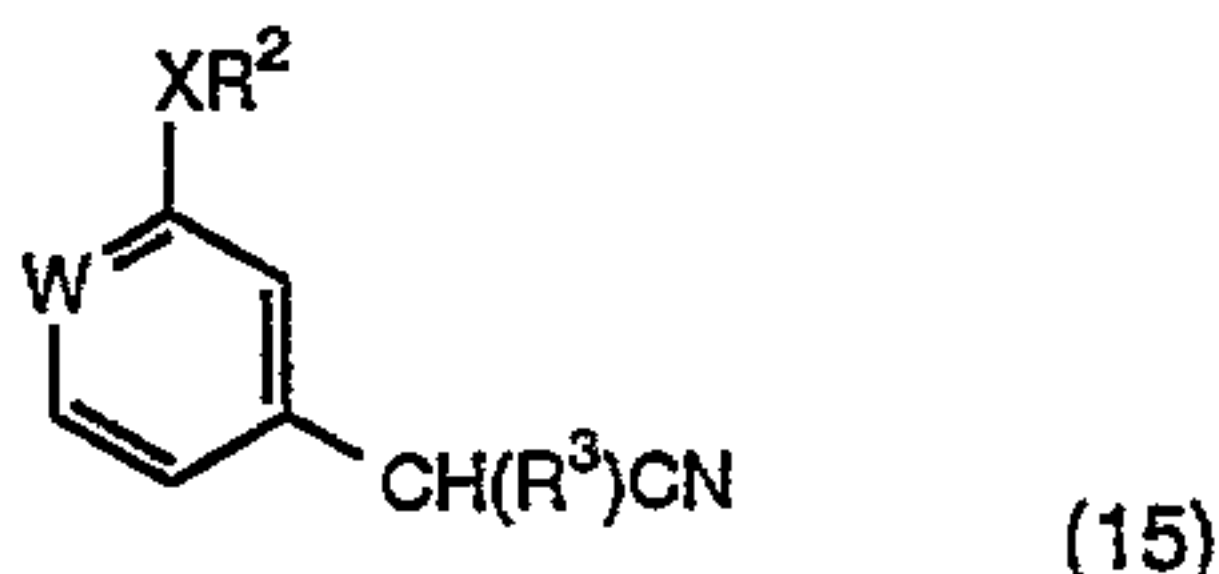


with an organomagnesium reagent followed by hydrolysis.

Examples of organomagnesium reagents include compounds $R^{12}L^1MgHal$, where Hal is a halogen atom, for example a chlorine atom. The reaction may take place in a solvent, such as an ether, for example tetrahydrofuran.

25

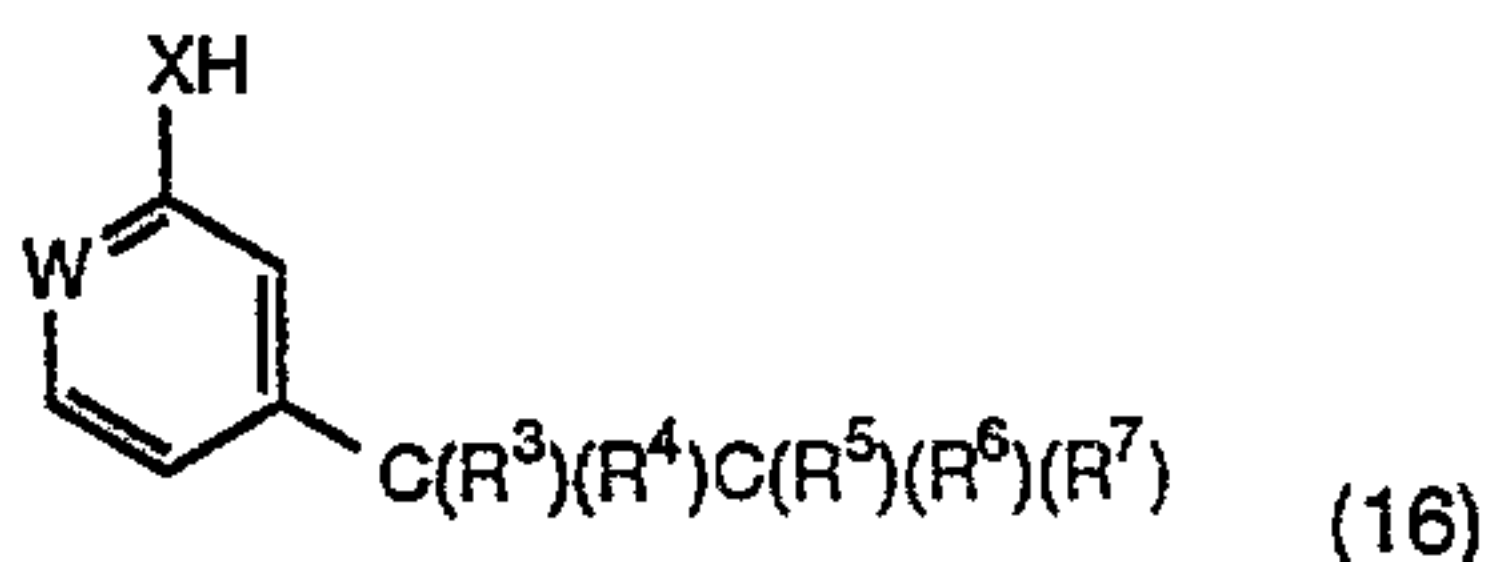
Intermediates of formula (14) may be prepared by reacting a nitrile of formula (15)



5

with a compound $\text{HalCH}(\text{R}^5)(\text{R}^6)(\text{R}^7)$, in the presence of a base, such as an organometallic base, for example n-butyllithium.

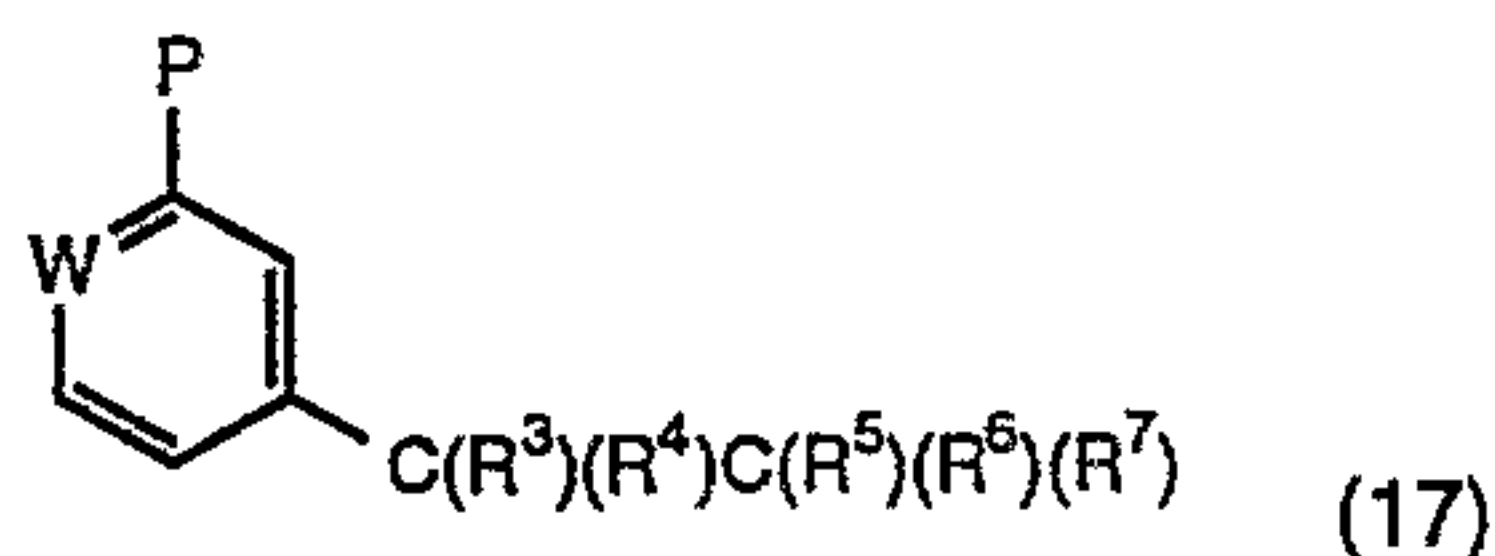
According to a still further aspect of the invention, a compound of formula (1) where L is -XR may be prepared by alkylation of a compound of formula (16)



15 The reaction may be performed as described above for the alkylation of an intermediate of formula (7) to give an intermediate of formula (6).

Intermediates of formula (16) may be obtained from the corresponding protected compound of formula (17):

20



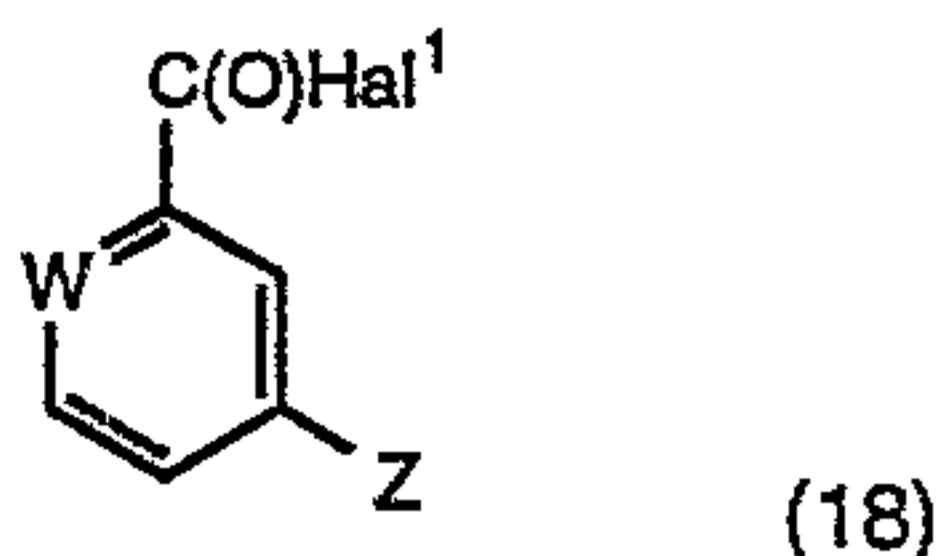
wherein P is a protected hydroxy, thio or amino group using conventional procedures [see Green, T. W. *ibid*]. Thus, for example, where P is a t-butylidimethylsilyloxy group, the required hydroxyl group may be obtained by treatment of the protected intermediate with tetrabutylammonium

25

fluoride. The protected intermediate of formula (17) may be prepared in an analogous manner to the compounds of formula (1) using the reactions described herein and appropriately protected intermediates.

- 5 In yet another aspect of the invention, a compound of formula (1) where Z is a group $-C(R^4)=C(R^5)(R^6)$ may be prepared by coupling an aldehyde of formula (7a) with an olefination agent $(R^5)(R^6)CHP(D)_3Hal$, $(R^5)(R^6)C=P(D)_3$, $(DO)_2P(O)CH(R^5)(R^6)$ or $(D)_3SiC(R^5)(R^6)$ as described herein above for the production of a compound of formula (1) from an
10 intermediate of formula (3).

- Compounds of formula (1) where L is a group $[-CH(R^{11})]_nCH(R^1)(R^2)$ where n is zero, R^1 is as described for compounds of formula (1) but is not a $-CO_2R^8$, $CONR^9R^{10}$ or $CSNR^9R^{10}$ group and R^2 is a CO_2R^8 or a
15 $CONR^9R^{10}$ group may be prepared by reacting a compound of formula (18)



- 20 where Hal^1 is a halogen atom, such as a chlorine or a bromine atom, with a diazoalkane R^1CHN_2 to give the corresponding diazoketone derivative which is then treated with water, an alcohol R^8OH , ammonia or a primary or secondary amine and silver oxide or with silver benzoate and triethylamine.

- 25 Intermediates of formula (18) may be prepared by oxidation of an intermediate of formula (3), using an oxidising agent, such as permanganate or chromic acid, to give the corresponding carboxylic acid which is then reacted with a halide reagent, such as thionylchloride,
30 phosphorous pentachloride or phosphorous pentabromide.

Compounds of formula (1) where L is a group $-\text{CH}(\text{R}^{11})_n\text{CH}(\text{R}^1)(\text{R}^2)$ may be prepared by interconversion of another compound of formula (1) where L is a group $-\text{C}(\text{R}^{11})=\text{C}(\text{R}^1)(\text{R}^2)$ for example. By hydrogenation using for example hydrogen in the presence of a catalyst. Suitable catalysts include
5 metals such as platinum or palladium optionally supported on an inert carrier such as carbon or calcium carbonate; nickel, e.g. Raney nickel, or rhodium. The reaction may be performed in a suitable solvent, for example an alcohol such as methanol or ethanol, an ether such as tetrahydrofuran or dioxane, or an ester such as ethyl acetate, optionally in
10 the presence of a base, for example a tertiary organic base such as triethylamine, at for example ambient temperature.

Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent. Suitable hydrogen
15 donors include for example acids, such as formic acid, formates, e.g. ammonium formate, alcohols, such as benzyl alcohol or ethylene glycol, hydrazine, and cycloalkenes such as cyclohexene or cyclohexadiene. The transfer agent may be for example a transition metal, for example palladium or platinum, optionally supported on an inert carrier as
20 discussed above, nickel, e.g. Raney nickel, ruthenium, e.g. tris (triphenylphosphine) ruthenium chloride or copper. The reaction may generally be performed at an ambient or elevated temperature, optionally in the presence of a solvent, for example an alcohol such as ethanol or an acid such as acetic acid.

25 In another example substituted monocyclic or bicyclic aryl groups R^5 , R^{12} and R^{12a} in compounds of formula (1) may be generally obtained by an appropriate substitution reaction using the corresponding unsubstituted compound of formula (1) and a R^{13} containing nucleophile or electrophile.
30 In another general process, a group R^3 and/or R^4 in formula (1) may be manipulated using conventional chemical procedures to yield other groups R^3 and/or R^4 .

For example, a compound of formula (1) where R^4 is a $-\text{OC}(\text{S})\text{L}^1\text{R}^{12}$
35 group may be prepared by interconverting a corresponding compound of formula (1) where R^4 is a $-\text{OC}(\text{O})\text{L}^1\text{R}^{12}$ group using a thiation reagent, as

described above for the interconversion of a compound of formula (1) where R^4 is a $-\text{OC}(\text{O})\text{NHL}^1(\text{R}^{12})$ group to a compound of formula (1) where R^4 is a $-\text{OC}(\text{S})\text{NHL}^1(\text{R}^{12})$ group.

- 5 In another example of an interconversion process a compound of formula (1) wherein R^5 , R^{12} and R^{12a} contains a $-\text{CH}_2\text{NH}_2$ substituent may be prepared by reduction of a corresponding compound wherein R^5 , R^{12} and R^{12a} contains a nitrile group, using for example a complex metal hydride such as lithium aluminium hydride in a solvent such as an ether e.g. diethylether.

- In a further example, a compound of formula (1) wherein R^5 , R^{12} and R^{12a} contains a $-\text{NHCOR}^{8a}$, $-\text{NHCONHR}^{8a}$, $-\text{NHCON}(\text{R}^{8a})_2$, $-\text{NHCSR}^{8a}$ or alkanoylaminoalkyl substituent may be prepared by acylation or thiolation of a corresponding compound wherein R^5 and/or R^{12} contains a $-\text{NH}_2$ or alkylamino group by reaction with an acyl halide e.g. an acyl chloride, an alkyl or aryl isocyanate, or a thiol halide in the presence of a base, such as a tertiary amine e.g. triethylamine or pyridine, optionally in a solvent such as dichloromethane.

- 20 In a still further example, a compound of formula (1) wherein R^5 , R^{12} and R^{12a} contains an alkoxy substituent may be prepared by alkylation of a corresponding compound wherein R^5 , R^{12} and R^{12a} contains a hydroxyl group by reaction with a compound AlkHal [where Alk is a C_{1-6} alkyl group such as a methyl or ethyl group and Hal is a halogen atom such as an iodine atom] in the presence of a base such as caesium or potassium carbonate in a dipolar aprotic solvent such as an amide, e.g. dimethylformamide at ambient temperature or above.

- 30 Compounds of formula (1) where Z is a group $-\text{C}(\text{R}^4)=\text{C}(\text{R}^5)(\text{R}^6)$ may be prepared by dehydration of another compound of formula (1) where Z is a group $-\text{C}(\text{R}^3)(\text{R}^4)\text{C}(\text{R}^5)(\text{R}^6)(\text{R}^7)$ where R^3 is a hydroxyl group and R^7 is a hydrogen atom using an acid at an elevated temperature.

- 35 Suitable acids include for example phosphoric or sulphonic acids, e.g. 4-toluenesulphonic acid. The reaction may be performed in an inert organic

solvent, for example a hydrocarbon such as toluene, at an elevated temperature, for example the reflux temperature.

5 Compounds of formula (1) where R^3 is a fluorine atom may be prepared by reacting a corresponding compound of formula (1) where R^3 is a hydroxyl group with a fluorinating reagent, such as diethylaminosulphur trifluoride (DAST), in a solvent, for example a chlorinated solvent, e.g. dichloromethane, at a low temperature, e.g. around 0°C.

10 N-oxides of compounds of formula (1) may be prepared 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.

15 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent using conventional procedures.

20 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 the mixture of enantiomers of formula (1) and an appropriate chiral compound e.g. a chiral acid or base. The
25 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 or base 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.

30

The following examples illustrate the invention.

The following abbreviations are used:

DMF - dimethylformamide; THF - tetrahydrofuran; DME - dimethoxy-
35 ethane; EtOAc - ethyl acetate; Et₂O - diethylether; RT - room

temperature; LDA - lithium diisopropylamide; CH₂Cl₂ - dichloromethane; tlc - thin layer chromatography; BuLi - butyllithium

Intermediates 1, 2 and 10 were prepared as described in International Patent Specification No. WO 94/20446.

INTERMEDIATE 1

3-Cyclopentyloxy-4-methoxybenzaldehyde

10 INTERMEDIATE 2

a) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridine

The following intermediate was prepared in a manner similar to Intermediate 2a):

b) (±) 3,5-Dichloro-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridine

20 INTERMEDIATE 3

3-Cyclopentyloxy-4-methoxybenzylalcohol

From 3-hydroxy-4-methoxybenzyl alcohol (50g, 0.324mol), cyclopentyloxybromide (70ml, 0.648mol), caesium carbonate (72.83g, 0.222mol) and sodium iodide (5.63g, 0.037mol). Chromatography (SiO₂; EtOAc-C₆H₁₄ 1:3) to yield the title compound (25.782g). (Found C, 69.92; H, 8.18. C₁₃H₁₈O₃ requires C, 70.25; H, 8.16).

INTERMEDIATE 4

3-Cyclopentyloxy-4-methoxybenzylchloride

30 Anhydrous HCl gas was bubbled through a solution of Intermediate 3 (10.0g, 45mmol) in dry Et₂O (300ml) and the stirred reaction mixture cooled by means of an ice bath. The reaction was followed by tlc until complete disappearance of the starting material. Nitrogen was bubbled through the solution to remove excess HCl and the solvent evaporated in
35 vacuo. A further portion of Et₂O was added and the solution dried

(MgSO₄). The solvent was evaporated to afford the title compound as a clear oil.

INTERMEDIATE 5

5 (3-Cyclopentyloxy-4-methoxyphenyl)acetonitrile

To a stirred solution of Intermediate 4 (9.0g, 37.4mmol) in dry DMF (200ml) under N₂ at RT, was added a solution of LiCN in DMF (0.5M; 75ml, 37.5mmol). The mixture was stirred at RT for 16h before adding a further portion of LiCN solution (8ml) and stirring maintained for another
10 4h. The DMF was evaporated, the residue treated with 2M K₂CO₃ solution (150ml) and extracted with Et₂O(3x100ml). The combined organic extract was washed with brine (60ml), dried (MgSO₄) and concentrated to dryness. The crude product was subjected to chromatography (SiO₂; hexane - Et₂O, 3:1 (1000ml) then 7:3 (200ml)) to
15 give the title compound (6.66g) as a clear oil.

INTERMEDIATE 6

(±)-2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-pyridyl)propane nitrile.

20 Intermediate 5 (0.4g, 1.73mmol) in dry DMF (2ml) was added to a solution of LDA in THF (10ml) [made *in situ* from diisopropylamine (0.19g, 0.27ml, 1.9mmol) in THF (10ml) and *n*-BuLi (1.6M in hexanes, 1.9mmol, 1.2ml)] at -70°C. After stirring for 30min, a cooled (-70°C) solution of picolyl chloride in THF (1.0ml) [prepared by freeing picolyl chloride hydrochloride (0.3g,
25 2.6mmol) from the salt with K₂CO₃ solution] was added by cannula. The mixture was stirred at -70°C for 2h, warmed to RT overnight then quenched with 10% aqueous NH₄Cl solution and extracted with EtOAc (3 x 50ml). The combined organic extract was washed with NH₄Cl solution (50ml), K₂CO₃ solution (50ml), brine (50ml), dried (MgSO₄) and the
30 solvent evaporated *in vacuo*. The crude product was subjected to chromatography (SiO₂; Et₂O) to give the title compound (0.374g) as a clear viscous oil. δ_H (300MHz; CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.15 (2H, m, CH₂pyridine), 3.84 (3H, s, OCH₃), 3.98 (1H, t, $\downarrow$ 7.1Hz, CHCN), 4.65-4.75 - (1H, br m, OCHCH₂), 6.68 (1H, d, $\downarrow$ 2.1Hz, ArH₂), 6.74 (1H, dd, $\downarrow$ 8.2, 2.1Hz, ArH₆), 6.82 (1H, d, $\downarrow$ 8.3Hz, ArH₅), 7.03 (2H, br d, H₃, H₅ pyridine), 8.52 (2H, br d, H₂, H₆ pyridine).
35

A portion of the free base (0.319g) was dissolved in EtOH (4ml), concentrated sulphuric acid (8 drops) and Et₂O added until the solution became cloudy. The title compound hydrogen sulphate was obtained as a white precipitate m.p. 146-150°C Dec. (Found C, 56.87; H, 5.73; N, 6.50. C₂₀H₂₄N₂O₆S requires C, 57.13; H, 5.75; N, 6.66%). δ_H (300MHz; CD₃OD) 1.55-1.95 (8H, m, (CH₂)₄), 3.56 (2H, d, $\downarrow$ 7.7Hz, CH₂pyridine), 3.80 (3H, s, OCH₃), 4.55 (1H, t, $\downarrow$ 7.5Hz, HCN), 4.75-4.9 (1H, m, OCHCH₂), 6.88-6.96 (3H, m, ArH), 7.94 (2H, unresolved dd, H₃, H₅ pyridine), 8.78 (2H, unresolved dd, H₂, H₆ pyridine).

INTERMEDIATE 7

(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

The title compound was prepared as described in Example 7b in International Patent Specification No. WO 94/20455

INTERMEDIATE 8

(E)-N-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propenoyl]-(1R)-10,2-bornane sultam

The title compound was prepared as described in step [(D) ii] of International Patent Application No. PCT/GB 94/02799.

INTERMEDIATE 9

N-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)-4-pentenoyl]-(1R)-10,2-bornane sultam

Vinylmagnesium bromide (1.0M in TNF) (4.1ml, 4.1mmol) was added dropwise to a stirred solution of Intermediate 8 (1g, 1.86mmol) in Et₂O/THF (30ml, 4:1) at -70°C and under nitrogen. The reaction was followed by tlc (EtOAc/hexane, 1:1) and after 1.25h at -20°C to -30°C the mixture was quenched with 10% aqueous NH₄Cl and the layers separated. The aqueous layer was washed with EtOAc, the combined organic layer washed with brine and dried (MgSO₄). The solution was concentrated *in vacuo* and the residue subjected to chromatography (SiO₂; EtOAc/hexane, 2:8) to give the title compound as a yellow solid. δ_H (CDCl₃) 1.008 (3H, s, CH₃), 1.2445 (3H, s, CH₃), 1.4-2.2 (14H, m, (CH₂)₄ + sultam), 3.45 (1H, d, $\downarrow$ 11.5Hz, SO₂CH₂), 3.59 (1H, d, $\downarrow$ 11.5Hz, SO₂CH₂), 3.73 (3H, s, OCH₃), 3.88-4.98 (1H, d, NCH), 4.62-4.71 (1H, m,

OCH), 4.77 (1H, d, $\downarrow$ 11Hz, ArCH), 5.12 (1H, d, $\downarrow$ 11Hz, pyridine CHCO), 5.28 (1H, br s, CH=CH₂), 5.31 (1H, br s, CH=CH₂), 6.17 (1H, m, CH=CH₂), 6.44 (1H, m, C₆H₃), 6.6 (2H, m, C₆H₃), 7.58 (2H, d, $\downarrow$ 5Hz, pyridine H₃, H₅), and 8.4 (2H, d, $\downarrow$ 5Hz, pyridine H₂, H₆).

5

INTERMEDIATE 10

3,5-Dichloro-4-methylpyridine

The title compound was prepared as described in International Patent Specification No. WO 94/20446.

10

EXAMPLE 1

a) (±)-4-[2-Benzoyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

Concentrated sulphuric acid (0.4g, 4mmol) was added to a solution of Intermediate 2a) (1.0g, 3.2mmol) in benzyl alcohol (15ml) and the mixture stirred at RT for 16h. The reaction mixture was partitioned between EtOAc (20ml) and saturated NaHCO₃ solution (15ml). The organic phase was separated, washed with saturated NaHCO₃ solution (15ml), then dried (MgSO₄) and concentrated *in vacuo* to give a yellow oil. The residue was subjected to chromatography (SiO₂; EtOAc-hexane, 2:1) to afford the title compound (627mg) as a colourless oil (Found: C, 77.26; H, 7.19; N, 3.44. C₂₆H₂₉NO₃ requires C, 77.38; H, 7.24; N, 3.47%); δ_H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 2.90 (1H, dd, $\downarrow$ 13.6, 5.5Hz, CHH pyridine), 3.11 (1H, dd, $\downarrow$ 13.6, 6.8Hz, CHH pyridine), 3.85 (3H, s, OMe), 4.22 (1H, d, $\downarrow$ 11.8Hz, OCHHPh), 4.43-4.47 (2H, m, OCHHPh and CHCH₂ pyridine), 3.71 (1H, m, OCH), 6.71-6.84 (3H, m's, ArH's), 7.02 (2H, d, $\downarrow$ 6Hz, pyridine H₃, H₅), 7.13-7.31 (5H, m's, Ph-H's), and 8.44 (2H, d, $\downarrow$ 6Hz, pyridine H₂, H₆).

The following compounds were prepared in a manner similar to the compound of Example 1a).

b) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propyloxyethyl]pyridine

From Intermediate 2a) (1.00g, 3.2mmol) and 1-propanol (15ml). The crude product was subjected to chromatography (SiO₂; Et₂O) to afford the

title compound (1.03g) as a colourless oil (Found: C, 74.41; H, 8.13; N, 3.97. $C_{22}H_{28}NO_3$ requires C, 74.55; H, 7.96; N, 3.95%); δ_H ($CDCl_3$) 0.83 (3H, t, $\downarrow$ 7.3Hz, $MeCH_2$), 1.47-1.61 (2H, m, $MeCH_2$), 1.5-2.0 (8H, br m, $(CH_2)_4$), 2.85 (1H, dd, $\downarrow$ 13.6, 5.7Hz, CHH pyridine), 3.05 (1H, dd, $\downarrow$ 13.6, 7.5Hz, CHH pyridine), 3.09-3.17 (1H, m, $OCHHEt$), 3.23-3.31 (1H, m, $OCHHEt$), 3.82 (3H, s, OMe), 4.32 (1H, dd, $\downarrow$ 7.5, 5.7Hz, $CHCH_2$ pyridine), 4.70 (1H, br m, OCH), 6.67-6.79 (3H, m's ArH 's), 7.03 (2H, d, $\downarrow$ 6Hz, pyridine H_3 , H_5), and 8.43 (2H, d, $\downarrow$ 6Hz, pyridine H_2 , H_6).

10 c) (±)-4-[2-Cyclopentyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

From Intermediate 2a) (1.00g, 3.2mmol) and cyclopentanol (15ml). The crude product was subjected to chromatography (SiO_2 ; EtOAc-hexane, 2:1) to afford the title compound (719mg) as a colourless oil (Found: C, 75.32; H, 8.08; N, 3.78. $C_{24}H_{31}NO_3$ requires C, 75.56; H, 8.19; N, 3.67%); δ_H ($CDCl_3$) 1.35-2.0 (16H, br m's, 2x $(CH_2)_4$), 2.81 (1H, dd, $\downarrow$ 13.4, 5.2Hz, $CHCH$ pyridine), 2.96 (1H, dd, $\downarrow$ 13.4, 8.1Hz, CHH pyridine), 3.74 (1H, br m, OCH), 3.83 (3H, s, OMe), 4.37 (1H, dd, $\downarrow$ 8.1, 5.2Hz, $CHCH_2$ pyridine), 4.73 (1H, br m, $ArOCH$), 6.70-6.81 (3H, m's, ArH 's), 7.05 (2H, d, $\downarrow$ 6Hz, pyridine H_3 , H_5), and 8.44 (2H, d, $\downarrow$ 6Hz, pyridine H_2 , H_6).

d) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-butyloxy)ethyl]pyridine

25 From Intermediate 2a) (1.0g, 3.2mmol) and 2-butanol (15ml). The crude product was subjected to chromatography (SiO_2 ; EtOAc-hexane, 2:1) to afford the title compound (906mg) as a colourless oil (Found: C, 74.79; H, 8.45; N, 3.82. $C_{23}H_{31}NO_3$ requires C, 74.76; H, 8.46; N, 3.79); δ_H ($CDCl_3$) 0.84 (3H, t, $\downarrow$ 7Hz, $MeCH_2$), 1.22-1.38 (2H, m, CH_2Me), 1.45-1.57 (2H, m, CH_2Et), 1.52-2.0 (8H, br m, $(CH_2)_4$), 2.85 (1H, dd, $\downarrow$ 13.5, 5.7Hz, CHH pyridine), 3.05 (1H, dd, $\downarrow$ 13.5, 7.5Hz, CHH pyridine), 3.12-3.22 (1H, m, $OCHHPr$), 3.38-3.47 (1H, m, $OCHHPr$), 3.81 (3H, s, OMe), 4.34 (1H, dd, $\downarrow$ 7.5, 5.7Hz, $CHCH_2$ pyridine), 4.71 (1H, br m, OCH), 6.68-6.80 (3H, m's, ArH 's), 7.05 (2H, d, $\downarrow$ 6Hz, pyridine H_3 , H_5), and 8.45 (2H, d, $\downarrow$ 6Hz, pyridine H_2 , H_6).

e) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methyl-propyloxy)ethyl]pyridine

From Intermediate 2a) (1.0g, 3.2mmol) and 2-methylpropanol (15ml). The crude product was subjected to chromatography (SiO₂; EtOAc-hexane, 3:1) to afford the title compound (845mg) as a colourless oil (Found: C, 74.76; H, 8.49; N, 3.41. C₂₃H₃₁NO₃ requires C, 74.76; H, 8.46; N, 3.79%); δ_H (CDCl₃) 0.82 (6H, d, J 6.6Hz, CHMe₂), 1.2-1.9 (9H, br m, (CH₂)₄), 2.8-3.15 (4H, complex m (16 lines), CH₂CHOCH₂), 3.83 (3H, s, OMe), 4.31 (1H, dd, J 7.6, 5.4Hz, CH₂OCH), 4.7 (1H, br m, ArOCH), 6.69 (1H, dd, J 8.1, 1.9Hz, ArH para to cyclopentyloxy), 6.76 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy), 6.79 (1H, d, J 8.1Hz, ArH ortho to OMe), 7.05 (2H, dd, J ca 6.0, 0.5Hz, pyridine H₃, H₅), and 8.44 (2H, dd J ca 6.0, 0.5Hz, pyridine H₂, H₆).

f) (±)-4-[2-Cyclohexylmethoxy-2-(3-cyclopentyloxy-4-methoxy-phenyl)ethyl]pyridine

From Intermediate 2a) (1.0g, 3.2mmol) and cyclohexylmethanol (15ml). The crude product was subjected to chromatography (SiO₂; EtOAc-hexane, 1:1) to afford the title compound (498mg) as a clear oil (Found: C, 76.10; H, 8.65; N, 3.43. C₂₆H₃₅NO₃ requires C, 76.24; H, 8.61; N, 3.41%) δ_H (CDCl₃) 0.7-1.97 (19H, br m's, alkyl CH₂ and CH), 2.8-3.15 (4H, m, OCH₂ cyclohexyl and CH₂ pyridine), 3.83 (3H, s, OMe), 4.30 (1H, dd, J 7.6, 5.4Hz CH-CH₂-pyridine), 4.70 (1H, br m, OCH cyclopentyl), 6.67-6.80 (3H, m, 3x ArH), 7.04 (2H, d, J 6Hz pyridine H₃, H₅), and 8.44 (2H, d, J 6Hz, pyridine H₂, H₆).

g) (±)-3,5-Dichloro-4-[2-cyclopentyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

From Intermediate 2b) (0.6g, 1.6mmol) and cyclopentanol (15ml). The title compound (478mg) was obtained as a golden oil. (Found: C, 64.2; H, 6.62; N, 3.07. C₂₄H₂₉Cl₂NO₃ requires C, 64; H, 6.49; N, 3.11%). δ_H (CDCl₃) 1.35-2.0 (16H, br m, 2x (CH₂)₄), 3.12 (1H, dd, J 13, 5.5Hz, CHH pyridine), 3.36 (1H, dd, J 13, 8.6Hz, CHH pyridine), 3.7 (1H, br m, OCH), 3.84 (3H, s, OMe), 4.58 (1H, dd, J 8.6, 5.5Hz, CHCH₂ pyridine), 4.78 (1H, br m, ArOCH), 6.79 (2H, app. s, ArH), 6.91 (1H, app. s, ArH), and 8.42 (2H, s, pyridine H's)

h) (±)-3,5-Dichloro-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1-butyloxy)ethyl] pyridine

From Intermediate 2b) (1.0g, 2.6mmol) and n.butanol (15ml). The crude product was subjected to chromatography (SiO₂; EtOAc-hexane, 1:1) to afford the title compound (600mg) as a clear oil. (Found: C, 62.41; H, 6.64; N, 3.13. C₂₃H₂₉NO₃Cl₂ requires C, 63.02; H, 6.67; N, 3.20%) δ_H (CDCl₃) 0.81 (3H, t, $\downarrow$ 7.3Hz, MeCH₂), 1.2-1.34 (2H, m, MeCH₂), 1.35-1.51 (2H, m, MeCH₂CH₂), 1.55-2.0 (8H, br m, (CH₂)₄), 3.1-3.5 (4H, m's, CH₂O and CH₂CH pyridine), 3.84 (3H, s, OMe), 4.53 (1H, app. t, $\downarrow$ 7Hz, CHCH₂ pyridine), 4.76 (1H, br m, OCH), 6.73-6.87 (3H, m's, ArH's), and 8.41 (2H, s, pyridine H's).

i) (±)-3,5-Dichloro-4-[2-cyclopentyloxy-4-methoxyphenyl)-2-methoxyethoxyethyl] pyridine

From Intermediate 2b) (1.0g, 2.6mmol) and 2-methoxyethanol (10ml). The crude product was subjected to chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound (6.96mg) as a clear oil. (Found: C, 60.03; H, 6.17; N, 3.12. C₂₂H₂₉NO₄Cl₂ requires C, 59.73; H, 6.60; N, 3.16%) δ_H (CDCl₃) 1.5-2.0 (8H, br m (CH₂)₄), 3.2-3.55 (6H, m's, 2x CH₂O and CH₂-pyridine), 3.27 (3H, s, MeOCH₂), 3.82 (3H, s, MeOAr), 4.63 (1H, app. t, $\downarrow$ 7.1Hz, CHCH₂ pyridine), 4.74 (1H, br m, OCH), 6.7-6.85 (3H, m's, ArH's), 6.7-6.85 (3H, m's ArH's), and 8.39 (2H, s, pyridine H's).

j) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-ethoxyethyl] pyridine

From Intermediate 2b) (1.0g, 3.2mmol) and ethanol (15ml). The crude product was subjected to chromatography (SiO₂; Et₂O) to afford the title compound (854mg) as a clear oil. (Found: C, 73.77; H, 8.06; N, 3.95. C₂₁H₂₇NO₃ requires C, 73.87; H, 7.97; N, 4.1%) δ_H (CDCl₃) 1.13 (3H, t, $\downarrow$ 7Hz, CH₃CH₂), 1.5-2.0 (8H, br m, (CH₂)₄), 2.85 (1H, dd, $\downarrow$ 13.5, 6Hz, CHH pyridine), 3.07 (1H, dd, $\downarrow$ 13.5, 7.3Hz, CHH pyridine), 3.20-3.32 (1H, m, OCHHMe), 3.32-3.42 (1H, m, OCHHMe), 3.83 (3H, s, OMe), 4.34 (1H, dd, $\downarrow$ 7.3, 6Hz, CHCH₂ pyridine), 4.71 (1H, br m, OCH), 6.68-6.82 (3H, m, 3x ArH), 7.01 (2H, d, $\downarrow$ 6Hz, pyridine H₃, H₅), and 8.43 (2H, d, $\downarrow$ 6Hz, pyridine H₂, H₆).

EXAMPLE 2**(±)-2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-pyridyl)-1-propyl-amine bis-hydrochloride**

- 5 A solution of Intermediate 6 (1.90g, 5.9mmol) in THF was added to a cold (0°C) solution of LiAlH₄ (1.0M in Et₂O, in excess) in THF. The solution was heated to reflux for 2h before adding another portion of LiAlH₄. The mixture was quenched with water (0.8ml), 20% aqueous NaOH solution (0.6ml), then water (2.5ml) and the fine precipitate of aluminium salts
- 10 separated by suction filtration. The filtrate was evaporated *in vacuo*, dissolved in EtOAc, dried (MgSO₄), filtered and concentrated to dryness. The crude product was subjected to chromatography to afford the title compound free base (0.88g) as a pale brown clear oil.
- 15 A portion of the title compound free base in Et₂O was treated with ethereal HCl, heated to reflux and EtOH added to complete dissolution. Upon cooling the title compound was obtained as a white powder (mp 208-210°C. dec). [Found C, 57.97; H, 6.65; N, 6.74. C₂₀H₂₈Cl₂N₂O₂. H₂O requires C, 57.55; H, 6.71; N, 6.71%]. δ_H (300 MHz, CD₃OD) 1.5-
- 20 2.0 (8H, br m, (CH₂)₄), 3.20-3.50 (5H, m, (methanol signal overlaps) H₂NCH₂CHCH), 3.76 (3H, s, OCH₃), 4.75-4.85 (1H, m, OCHCH₂), 6.79-6.91 (3H, m, ArH), 7.80 (2H, d, (unresolved dd), H₃, H₅ pyridine), and 8.65 (2H, dd, J 5.7, 1.1Hz, H₂, H₆ pyridine).

25 EXAMPLE 3**N-[2-(RS)-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-pyridyl)propyl]acetonitrile**

- To a cold (0°C) stirred solution of the compound of Example 2 (0.366g,; 1.12mmol) and triethylamine (0.310g, 3.02mmol, 0.42ml) in dry CH₂Cl₂
- 30 (5ml) under a nitrogen atmosphere was added acetyl chloride (0.097g, 1.23mmol, 0.095ml). After stirring for 45min the mixture was quenched with 1M potassium carbonate solution (25ml), extracted with CH₂Cl₂ (3x20ml), the combined organic extract dried (Na₂SO₂) and concentrated *in vacuo*. The crude product was subjected to chromatography (SiO₂;
- 35 EtOAc-MeOH, 9:1), dissolved in CH₂Cl₂ then filtered through cotton wool and activated charcoal to give the title compound (0.304g) as a pale

yellow oil. δ_H (300 MHz, C_6D_6), 1.46 (3H, s, OCH_3), 1.30 -1.95 (8H, m, $(CH_2)_4$), 2.48 (1H, dd, J 13.6, 9.4Hz, CH_AH_B pyridine), 2.65 (1H, dd, J 13.6, 5.4Hz, CH_AH_B pyridine), 2.8-2.95 (1H, m, $CHCH_2$), 3.11 (1H, ddd, J 13.5, 8.7, 5.0Hz, $HNCH_AH_B$), 3.38 (3H, s, OCH_3), 3.6-3.7 (1H, m, $HNCH_AH_B$), 4.55-4.65 (1H, m, $OCHCH_2$), 4.74 (1H, br s, NH), 6.45 (1H, dd, J 8.1, 2.1Hz, ArH_6), 6.5-6.6 (2H, m, ArH), 6.63 (2H, dd, J 4.4, 1.6Hz, H_3 , H_5 pyridine), and 8.42 (2H, dd, J 4.4, 1.6Hz, H_2 , H_6 pyridine).

EXAMPLE 4

10 (±) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-propylthioethyl]pyridine

n -BuLi (1.6M in hexanes; 5.4ml) was added dropwise to a stirred, ice bath cooled solution of 1-propanethiol (0.87g, 1.04ml) in dry THF (20ml). After stirring for 30min, Intermediate 7 (1.0g) in DMF (2ml) was added and the
15 reaction mixture heated to reflux for a couple of days. Upon cooling the reaction mixture was partitioned between EtOAc (100ml) and aqueous NH_4Cl (100ml). The aqueous phase was extracted with EtOAc (2x50ml) and the combined organic extract washed with brine (25ml), dried (Na_2SO_3) and evaporated *in vacuo*. The crude product was subject to
20 chromatography (SiO_2 ; EtOAc-hexane, 1:1) to afford the title compound (505mg) as a clear, slightly yellow oil. (Found, C, 71.08; H, 7.90; N, 3.92. $C_{22}H_{29}NO_2S$ requires C, 71.12; H, 7.87; N, 3.77%). δ_H ($CDCl_3$) 0.87 (3H, t, J 7.3Hz, CH_3-CH_2), 1.42-1.52 (2H, m, CH_2CH_3), 1.5-2.0 (8H, br m, $(CH_2)_4$), 2.19-2.35 (2H, m, CH_2S), 2.97-3.19 (2H, m, CH_2 pyridine),
25 3.80 (3H, s, OMe), 3.91 (1H, dd, J 8.9, 6.0Hz, $CHCH_2$ pyridine), 4.70 (1H, br m, OCH), 6.63-6.83 (3H, m, 3x ArH), 6.91 (2H, d, J 6Hz, pyridine H_3 , H_5), and 8.39 (2H, d, J 6Hz, pyridine H_2 , H_6).

EXAMPLE 5

30 N-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl]-1-propylamine

n -BuLi (1.6M in hexanes) (5.7ml) was added dropwise to a solution of 4-methylpyridine (0.89g) in dry Et_2O (40ml) at $-70^\circ C$. A solution of N-propyl-(3-cyclopentyloxy-4-methoxyphenyl)methylimine (2.51g) [made by reacting
35 Intermediate 1 (5g) in CH_2Cl_2 (20ml) and propylamine (5ml) in the presence of 3Å molecular sieves and stirring overnight at RT. Upon

filtration and concentration to dryness, the imine was obtained as a near colourless oil.] in dry Et₂O (10ml) was added and stirred at -70°C for 30min then warmed to -10 to 0°C for 2h. The reaction was quenched with aqueous saturated NH₄Cl (10ml) then partitioned between EtOAc (100ml) and saturated aqueous NaHCO₃ (100ml). The organic phase was washed with brine (20ml), dried (K₂CO₃) and evaporated *in vacuo*. The crude product was purified by chromatography (SiO₂; EtOAc then MeOH-EtOAc, 1:9) to afford the title compound as a clear, brown tainted oil (330mg). δ_H (CDCl₃) 0.82 (3H, t, $\downarrow$ 7.3Hz, CH₂Me), 1.3-1.45 (2H, m, CH₂Me), 1.5-2.0 (8H, br m (CH₂)₄), 2.40 (2H, t, $\downarrow$ 7.2Hz, NHCH₂), 2.8-3.0 (2H, m, CH₂ pyridine), 3.77 (1H, t, $\downarrow$ 7.0Hz, NCHCH₂), 3.82 (3H, s, OMe), 4.73 (1H, br m, OCH), 6.68 (1H, dd, $\downarrow$ 8.1, 2.0Hz, ArH para to cyclopentyloxy), 6.76 (1H, d, $\downarrow$ 8.1Hz, ArH ortho to OMe), 6.77 (1H, d, $\downarrow$ 2.0Hz, ArH ortho to cyclopentyloxy), 6.96 (2H, ca d, ca 4.5Hz, pyridine H₃, H₅), and 8.42 (2H, ca d, ca 4.5Hz, pyridine H₂, H₆).

EXAMPLE 6

4-[2(R)-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylbut-3-enyl]-pyridine hydrochloride

n-BuLi (1.6M in hexanes) (324 μ l, 0.52mmol) was added to a stirred solution of ethanethiol (68.5 μ l, 0.92mmol) in anhydrous THF at -10°C and under nitrogen. The solution was stirred at -10°C for 30min before being added to a solution of Intermediate 9 (208.9mg, 0.37mmol) in anhydrous THF. The reaction was stirred overnight at RT before adding a further portion of ethanethiol (68.5 μ l) (the reaction was followed by tlc EtOAc/hexane, 1:1) and stirring maintained overnight. The reaction was quenched with a little water and the solvent removed *in vacuo*. The residue was taken in EtOH, aqueous NaOH (2M) added and the reaction heated to reflux for 3h, cooled, the pH adjusted to 5 with concentrated HCl and heated to reflux for another 3h. The reaction was cooled and the pH adjusted to 14. The reaction mixture was partitioned between water and Et₂O and the combined organic layer washed with NaOH (1M), brine and dried (MgSO₄). The solvent was removed *in vacuo* to give the title compound free base as a yellow oil.

The title compound free base was dissolved in EtOH and treated with ethanolic HCl to give the title compound as a pale yellow solid.

5 FORMULATION EXAMPLES

The compounds of the invention may be formulated for pharmaceutical use in a number of forms using any suitable excipients. Thus, for example, for oral use the compounds of the invention such as the compounds of the Examples may be formulated as a solid dosage form, by mixing an appropriate weight of compound (for example 50mg) with maize starch (50-99%w/w), anhydrous colloidal silica (0-10%w/w) and organic or inorganic acid (up to 1%w/w), to fill capsules of an appropriate size, e.g. white opaque hard gelatine capsules size 3. If desired the same mixture may be compressed into tablets.

15

The activity and selectivity of compounds according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

20 Isolated Enzyme

The potency and selectivity of the compounds of the invention was determined using distinct PDE isoenzymes as follows:

- i. PDE I, rabbit heart
- 25 ii. PDE II, rabbit heart
- iii. PDE III, rabbit heart, Jurkat cells
- iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV
- v. PDE V, rabbit lung, guinea pig lung

30

A gene encoding human PDE IV has been cloned from human monocytes (*Livi, et al., 1990, Molecular and Cellular Biology, 10, 2678*). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been

35

expressed which have the biochemical characteristics of PDE IV (*Beavo and Reifsnyder, 1990, TIPS, 11, 150*). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.

5

The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

Phosphodiesterase activity was assayed as follows. The reaction was
10 conducted in 150µl of standard mixture containing (final concentrations):
50mM 2-[[tris(hydroxymethyl)methyl]amino]-1-ethane-sulphonic acid (TES)
-NaOH buffer (pH 7.5), 10mM MgCl₂, 0.1µM [³H]-cAMP and vehicle or
various concentrations of the test compounds. The reaction was initiated
by addition of enzyme and conducted at 30°C for between 5 to 30 min.
15 The reaction was terminated by addition of 50µl 2% trifluoroacetic acid
containing [¹⁴C]-5'AMP for determining recovery of the product. An aliquot
of the sample was then applied to a column of neutral alumina and the
[³H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [³H]-5'-AMP
product was eluted with 2ml 2M NaOH into a scintillation vial containing
20 10ml of scintillation cocktail. Recovery of [³H]-5'AMP was determined
using the [¹⁴C]-5'AMP and all assays were conducted in the linear range of
the reaction.

Compounds according to the invention such as compounds of the
25 Examples herein cause a concentration-dependent inhibition of
recombinant PDE IV at 0.1 - 1000nM with little or no activity against PDE I,
II, III or V at concentrations up to 100µM.

2. The Elevation of cAMP in Leukocytes

30 The effect of compounds of the invention on intracellular cAMP was
investigated using human neutrophils or guinea pig eosinophils.
Human neutrophils were separated from peripheral blood, incubated
with dihydrocytochalasin B and the test compound for 10 min and
then stimulated with FMLP. Guinea pig eosinophils were harvested
35 by peritoneal lavage of animals previously treated with intra-
peritoneal injections of human serum. Eosinophils were separated

5 from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

10 The most potent compounds according to the Examples induced a concentration -dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1µM.

3. **Suppression of Leukocyte Function**

15 Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocytochalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The most potent compounds of the Examples caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at concentrations of 0.1nM to 1µM.

20 Lipopolysaccharide (LPS)-induced synthesis of tumour necrosis factor (TNF) by human peripheral blood monocytes (PBM) is inhibited by compounds of the Examples at concentrations of 0.01nM to 10µM.

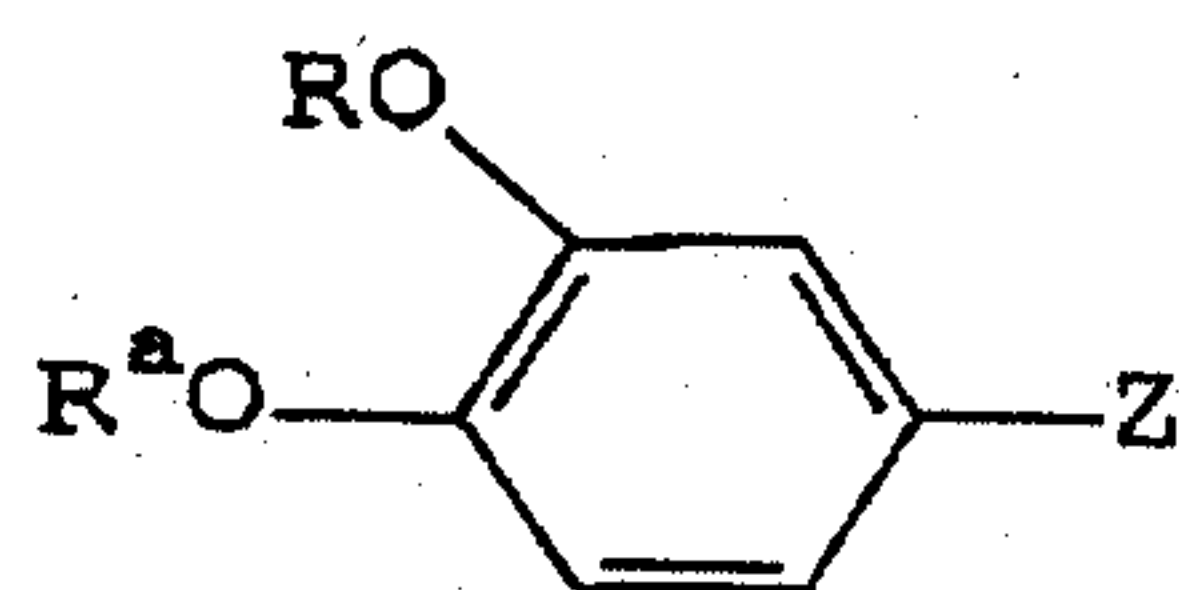
25 4. **Adverse Effects**

In general, in our tests above, compounds of the invention have had no observed toxic effects when administered to animals at pharmacologically effective doses.

CLAIMS

1. A compound of formula (1):

5



(1)

wherein:

10

R^a is a C_{1-6} alkyl group that is unsubstituted or substituted by up to three halogen atoms;

15

R is a C_{1-6} alkyl or C_{2-6} alkenyl group that is unsubstituted or substituted by up to three substituents selected from halogen atoms and hydroxyl, C_{1-6} alkoxy, $-CN$, $-CO_2R^8$, $-CONR^9R^{10}$ and $-CSNR^9R^{10}$ groups (where R^8 , R^9 and R^{10} are the same or different and are each selected from hydrogen atoms and C_{1-3} alkyl, C_{6-12} aryl and C_{6-12} aryl- C_{1-3} alkyl groups) or a C_{3-8} cycloalkyl or cycloalkenyl group that is unsubstituted or substituted by up to three substituents selected from halogen atoms and hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy groups; and

20

Z is a group $-CH(R^4)-CH_2(R^5)$ or $-C(R^4)=CH(R^5)$ in which

25

R^4 is an $-X^aAlk^2R^{12}$ or $-X^aR^{12a}$ group where

30

X^a is $-O-$, $-S(O)_m-$ (where m is zero or an integer of value 1 or 2) or $-N(R^b)-$ (where R^b is a hydrogen atom or an alkyl group that is unsubstituted or substituted by up to three substituents selected from halogen atoms and hydroxyl, C_{1-6} alkoxy, $-CN$, $-COOR^8$, $-CONR^9R^{10}$ and $-CSNR^9R^{10}$ groups where R^8 , R^9 and R^{10} are as defined above);

Alk² is a C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain that is unsubstituted or substituted by up to three substituents selected from halogen atoms and hydroxyl, C₁₋₆ alkoxy, -CN, -COOR⁸, -CONR⁹R¹⁰ and -CSNR⁹R¹⁰ groups (where R⁸, R⁹ and R¹⁰ are as defined above) and containing zero, one, two or three -O- or -S- atoms or cyclopentyl, cyclopentenyl, cyclohexenyl, -S(O)-, -S(O)₂-, -N(R^b)-, -C(O)-, -C(S)-, -C(NR^b)-, -CON(R^b)-, -CSN(R^b), -N(R^b)CO-, -N(R^b)CS-, -SON(R^b)-, -SO₂N(R^b)-, -N(R^b)SO-, -N(R^b)SO₂-, -N(R^b)SO₂N(R^b)-, -N(R^b)SON(R^b)-, -N(R^b)CON(R^b- or -N(R^b)CSN(R^b) groups (where R^b is as defined above);

R¹² is a hydrogen atom; a C₃₋₈ cycloaliphatic or C₃₋₈ heterocycloaliphatic group that is unsubstituted or substituted by up to three substituents selected from halogen atoms and C₁₋₆ alkyl, hydroxyl and C₁₋₃ alkoxy groups; or a phenyl, naphthyl, indenyl or isoindenyl group that is unsubstituted or substituted by up to four R¹³ substituents selected from fluorine, chlorine, bromine and iodine atoms and C₁₋₆ alkyl, C₁₋₆ alkylamino, C₁₋₆ hydroxyalkyl, C₁₋₆ alkylthiol, C₁₋₆ alkoxy, C₅₋₇ cycloalkyl, C₅₋₇ cycloalkoxy, C₁₋₆ haloalkyl, amino, C₁₋₆ aminoalkyl, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, nitro, cyano, hydroxyl, formyl, carboxyl, -CO₂Alk⁵ (where Alk⁵ is a C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ aryl-C₁₋₈ alkyl, C₆₋₁₂ aryloxy-C₁₋₈ alkyl, C₁₋₈ alkanoyloxy-C₁₋₈ alkyl or C₆₋₁₂ aroyloxy-C₁₋₈ alkyl group), C₁₋₆ alkanoyl, thiol, C₁₋₆ thioalkyl, sulphonyl, C₁₋₆ alkylsulphonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl, C₁₋₆ dialkylaminosulphonyl, phenylaminosulphonyl, benzylaminosulphonyl, carboxamido), C₁₋₆ alkylaminocarbonyl, C₁₋₆ dialkylaminocarbonyl, phenylaminocarbonyl, sulphonylamino, C₁₋₆ alkylsulphonylamino, C₁₋₆ dialkylsulphonylamino, aminosulphonylamino, C₁₋₆ alkylaminosulphonylamino, C₁₋₆ dialkylaminosulphonylamino, phenylaminosulphonylamino, C₁₋₆ alkanoylamino, C₁₋₆ alkanoylamino-C₁₋₆ alkyl, C₁₋₆ alkoxycarbonylamino, thiocarboxamido, C₁₋₆ alkylaminothiocarbonyl, C₁₋₆ dialkylaminothiocarbonyl, phenylaminothiocarbonyl, aminocarbonylamino,

C₁₋₆ alkylaminocarbonylamino, C₁₋₆ dialkylaminocarbonylamino,
 aminothiocarbonylamino, C₁₋₆ alkylaminothiocarbonylamino,
 C₁₋₆ dialkylaminothiocarbonylamino, aminocarbonyl-C₁₋₆ alkylamino,
 aminothiocarbonyl-C₁₋₆ alkylamino, formylamino-C₁₋₆
 5 alkylsulphonylamino, thioformylamino-C₁₋₆ alkylsulphonylamino,
 C₁₋₆ acylaminosulphonylamino and C₁₋₆ thioacylaminosulphonylamino
 groups, or wherein two R¹³ substituents together form a
 C₂₋₆ alkylenedioxy group; and

10 R^{12a} is as defined for R¹² but is not a hydrogen atom; and

R⁵ is a -(CH₂)_pAr group where p is zero or an integer 1, 2 or 3 and
 Ar is a phenyl, pyridyl, thienyl or pyrimidinyl group that is
 unsubstituted or substituted by up to four R¹³ substituents as defined
 15 above;

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

2. A compound according to claim 1 wherein R^a is a C₁₋₃ alkyl group
 20 and R is a cyclopentyl group that is unsubstituted or substituted by up to
 three substituents selected from halogen atoms and hydroxyl, C₁₋₆ alkyl
 and C₁₋₆ alkoxy groups.

3. A compound according to claim 1 or claim 2 wherein Z is a group
 25 -CH(R⁴)-CH₂(R⁵).

4. A compound according to any one of claims 1 to 3 wherein R⁴ is a
 C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl-C₁₋₆ alkoxy group that is
 unsubstituted or substituted by up to three substituents selected from
 30 halogen atoms and C₁₋₆ alkyl, hydroxyl and C₁₋₃ alkoxy groups, or a
 phenoxy or phenyl-C₁₋₆ alkoxy group in which the phenyl ring that is
 unsubstituted or substituted by up to four R¹³ substituents as defined in
 claim 1.

5. A compound according to any one of claims 1 to 4 wherein R⁵ is a pyridyl group that is unsubstituted or substituted by up to four R¹³ substituents as defined in claim 1.

5 6. A compound which is:

(±)-4-[2-benzyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;

(±)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-propyloxyethyl]pyridine;

(±)-4-[2-cyclopentyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;

10 (±)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2-butyloxy)ethyl]pyridine;

(±)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2-methylpropyloxy)ethyl]pyridine;

(±)-4-[2-cyclohexylmethoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;

15 (±)-3,5-dichloro-4-[2-cyclopentyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;

(±)-3,5-dichloro-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1-butyloxy)ethyl]pyridine;

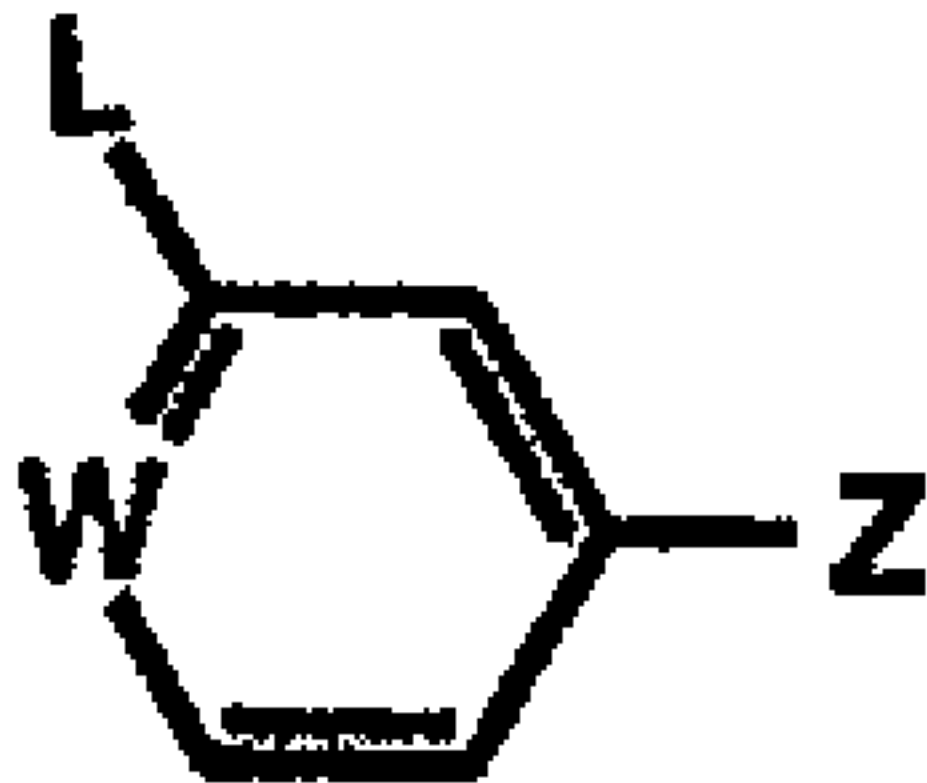
(±)-3,5-dichloro-4-[2-cyclopentyloxy-4-methoxyphenyl)-2-

20 methoxyethoxyethyl]pyridine; or

(±)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-ethoxyethyl]pyridine;

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

25 7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 together with one or more pharmaceutically acceptable carriers, excipients or diluents.



(1)