AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Celltech Therapeutics Limited,** the applicant/Nominated Person in respect of Application No. 61488/94 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY NINTH day of NOVEMBER 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1702770)

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STYRYL DERIVATIVES, THEIR PREPARATION AND USE AS PDE-IV INHIBITORS

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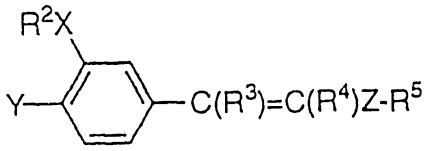
(57) Claim

1. A compound of formula (1)



(1)

wherein

Y is a halogen atom or a group $-OR^1$, wherein R^1 is an optionally substituted alkyl group;

X is -O-, -S-, or $-N(R^6)-$, wherein R^6 is a hydrogen atom or an optionally substituted alkyl group;

R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4 which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (wherein R^7 is a hydrogen atom, an optionally substituted alkyl, aralkyl or aryl group), $-CONR^8R^9$ (wherein R^8 and R^9, which may be the same or different, is as defined for R^7), $-CSNR^8R^9$, -CN or $-CH_2CN$ group;

. . ./2

Z is -$(CH_2)_n$- where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

(but excluding:

methyl 3-[2-[3-cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate and 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic acid)

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

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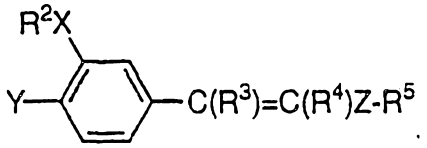
(54) Title: STYRYL DERIVATIVES, THEIR PREPARATION AND USE AS PDE-IV INHIBITORS

(57) Abstract



(1)

Compounds of general formula (1) are described wherein Y is a halogen atom or a group $-OR^1$, wherein R^1 is an optionally substituted alkyl group; X is -O-, -S-, or $-N(R^6)$, wherein R^6 is a hydrogen atom or an optionally substituted alkyl group; R^2 is an optionally substituted cycloalkyl or cycloalkenyl group; R^3 and R^4, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (wherein R^7 is a hydrogen atom, an optionally substituted alkyl, aralkyl, aryl, aryloxyalkyl, alkanoyloxyalkyl or aroyloxyalkyl group), $-CONR^8R^9$ (where R^8 and R^9, which may be the same or different, is as defined for R^7), $-CSNR^8R^9$, -CN or $-CH_2CN$ group; Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3; R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; and the salts, solvates, hydrates, prodrugs an N-oxides thereof. Compounds according to the invention are potent and selective phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of diseases such as asthma where an unwanted inflammatory response or muscular spasm is present.

STYRYL DERIVATIVES, THEIR PREPARATION AND USE AS PDE-IV INHIBITORS

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

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 mecnanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenyiyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell 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 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].

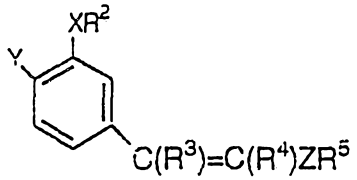
There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV plays a major role in the hydrolysis of cAMP. It can be expected, therefore, that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

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 styryl derivatives, members of which, compared to known structurally similar compounds, are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit human recombinant PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs. Advantageously, compounds according to the invention have good oral activity and at orally effective doses exhibit little or none of the side-effects associated with known PDE IV inhibitors, such as rolipram. 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)



(1)

wherein

Y is a halogen atom or a group $-OR^1$, where R^1 is an optionally substituted alkyl group;

X is -O-, -S-, or $-N(R^6)-$, where R^6 is a hydrogen atom or an optionally substituted alkyl group;

R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (where R^7 is a hydrogen atom, or an optionally substituted alkyl, aralkyl or aryl group), $-CONR^8R^9$ (where R^8 and R^9 which may be the same or different is as described for R^7), $-CSNR^8R^9$, -CN or $-CH_2CN$ group;

Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

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

WO 94/12461, which is relevant under Article 54(3), describes a group of compounds including methyl 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate and 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic acid . These two compounds are excluded from the present invention.

The compounds of formula (1) exist as geometrical isomers, and the invention extends to all such individual isomers and mixtures thereof. Formula (1) and the formulae hereinafter should be understood to include all individual isomers and mixtures thereof, unless stated otherwise, and even though only one isomer may be depicted.

In the compounds of formula (1), when Y is a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

When Y in the compounds of formula (1) is a group $-OR^1$, R^1 may be, for example, an optionally substituted straight or branched C_{1-3}alkyl group, such as a methyl, ethyl, n-propyl, or i-propyl groups. Optional substitutents which may be present on R^1 groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms.

When X in compounds of formula (1) is a $-N(R^6)-$ group it may be a -NH- group or a group $-N(R^6)-$ where R^6 is an optionally substitued C_{1-6} alkyl group such as a methyl or ethyl group.

When R^2 in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C_{3-8}cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C_{3-8} cycloalkenyl 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 C_{1-6}alkyl e.g. C_{1-3}alkyl such as methyl or ethyl, hydroxyl or C_{1-6}alkoxy e.g. C_{1-3}alkoxy such as methoxy or ethoxy groups.

Alkyl groups represented by R^3 and R^4 in compounds of formula (1) include optionally substituted straight or branched C_{1-6} alkyl groups for example C_{1-3} alkyl groups, such as methyl, ethyl n-propyl or i-propyl groups. Optional substituents which may be present on R^3 or R^4 include one or more 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 methoxy or ethoxy groups, or thiol or C_{1-6} alkylthio e.g. C_{1-3} alkythio such as methylthio or ethylthio groups. Particular examples of R^3 or R^4 alkyl groups include $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2Cl$, $-CH_2F$, $-CHCl_2$, $-CHF_2$ and $-CH_2OCH_3$ groups.

When R^3 and/or R^4 is a $-CO_2R^7$, $-CONR^8R^9$ or $-CSNR^8R^9$ group it may be for example a $-CO_2H$, $-CONH_2$, or $-CSNH_2$ group, or a group $-CO_2R^7$, $-CONR^8R^9$, $-CSNR^8R^9$, $-CONHR^9$, or $-CSNHR^9$ wherein R^7, R^8 and R^9 where present is a C_{1-3} alkyl group such as a methyl or ethyl group, a C_{6-12} aryl group, for example an optionally substituted phenyl, or a 1- or 2-naphthyl group, or a C_{6-12} arylC_{1-3} alkyl group such as an optionally substituted benzyl or phenethyl group. Optional substituents which may be present on these groups include R^{10} substituents discussed below in relation to the group R^5.

In the compounds of formula (1) Z may represent a bond connecting the group R^5 to the rest of the molecule, or represents a group $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$.

Monocyclic or bicyclic aryl groups represented by the group R^5 in compounds of formula (1) include for example C_{6-12} optionally substituted aryl groups, for example optionally substituted phenyl, 1–or 2-naphthyl, indenyl or isoindenyl groups.

When the monocyclic or bicyclic aryl group contains one or more heteroatoms it may be a C_{1-9} for example a C_{3-9}, 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.

Examples of heteroaryl groups represented by R^5 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.

The heteroaryl group represented by R^5 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. When it is a pyridazinyl group it may be a 3- or 4- pyridazinyl group, and when it is an imidazolyl group it may be a 1-, 2-, 4- or 5- imidazolyl group.

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 extend to such salts. Thus for example when the heteroaryl group 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 in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R^{10}]. The substituent R^{10} may be selected from an atom or group R^{11} or $-Alk^1(R^{11})_m$ wherein R^{11} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-C(O)R^{7a}$ [where R^{7a} is as defined above for R^7], $-SO_3H$, $-SO_2R^{7a}$, $-SO_2N[R^{7a}R^{8a}]$, (where R^{8a} is as defined for R^{7a} and may be the same as or different to R^{7a}), $-CON[R^{7a}R^{8a}]$, $-NHCONHR^{7a}$, $-NHSO_2R^{7a}$, $-N[SO_2R^{7a}]_2$, $-NHSO_2N[R^{7a}R^{8a}]$, $-NHC(O)R^{7a}$, or $-NHC(O)OR^{7a}$ group; Alk^1 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)p-, [where p is an integer 1 or 2] or $-N(R^6)$- groups; and m is zero or an integer 1, 2 or 3.

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

When R^{11} is a substituted amino group it may be a group $-NH[Alk^1(R^{12})_m]$ [where Alk^1 and m are as defined above and R^{12} is as defined above for R^{11} but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group $-N[Alk^1(R^{12})_m]_2$ wherein each $-Alk^1(R^{12})_m$ group is the same or different.

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

When R^{11} is a cycloalkoxy group it may be for example a C_{5-7}cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R^{11} is a substituted hydroxyl or substituted thiol group it may be a group $-OAlk^1(R^{12})_m$ or $-SAlk^1(R^{12})_m$ respectively, where Alk^1, R^{12} and m are as just defined.

Esterified carboxyl groups represented by the group R^{11} include groups of formula $-CO_2Alk^2$ wherein Alk^2 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^2 group include R^{10} substituents described above.

When Alk^1 is present in or as a substituent R^{10} it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^6)-$ groups.

Particularly useful atoms or groups represented by R^{10} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC$_{1-6}$alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC$_{1-6}$alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], $-CO_2H$, $-CO_2Alk^2$[where Alk^2 is as defined

above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, arylaminosulphonyl, e.g. optionally substituted phenylaminosulphonyl, aralkylaminosulphonyl, e.g. optionally substituted benzylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethyl-aminocarbonyl or diethylaminocarbonyl, sulphonylamino (-$NHSO_2H$), C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonyl-amino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethyl-sulphonylamino, aminosulphonyl-amino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonyl-amino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, C_{1-6}alkanoylamino C_{1-6}alkyl, e.g. acetylaminomethyl or C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonyl-amino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6}alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. The R^{10} substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by R^5 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 -CO_2Alk^2 this may advantageously be a metabolically labile ester.

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

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

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

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

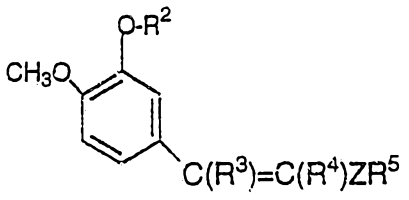
Prodrugs of compounds of formula (1) include those compounds for example esters, alcohols or amines, which are convertible, *in vivo*, by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

In general in compounds of formula (1), the group R^5 and the phenyl ring to which the group $C(R^3)=C(R^4)ZR^5$ is attached are in a "trans" position relative to one another.

In the compounds of formula (1), the group Y is preferably an $-OR^1$ group, especially where R^1 is an optionally substituted C_{1-3}alkyl group, particularly an ethyl group or, especially, a 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-.

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



(2)

where R^2 is an optionally substituted cycloalkyl group; R^3 ,R^4, R^5 and Z are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formulae (1) and (2) R^2 is preferably an optionally substituted cyclopentyl group. In particular, R^2 is a cyclopentyl group.

The group R^3 in compounds of formulae (1) or (2) is preferably a $-CH_3$ group, or especially a hydrogen atom.

In compounds of formulae (1) or (2) the group R^4 is preferably a hydrogen atom, a -CN or a $-CH_3$ group.

Z in the compounds of formulae (1) or (2) is preferably $-(CH_2)_n-$ where n is zero, 1 or 2. In particular, however, Z is especially $-(CH_2)_n-$ where n is zero.

R^5 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 R^{10} groups, and is especially a 2-, 3- or 4-monosubstituted or 2,6-disubstituted phenyl group. Particular substituents include halogen atoms, especially fluorine or chlorine atoms and nitro, amino, alkoxy, haloalkyl, hydroxy, $-NHCOR^{7a}$, $-NHCONHR^{7a}$ and $-NHSO_2R^{7a}$ groups.

Particular R^5 groups include 2-nitrophenyl, 2-haloalkylphenyl, e.g. 2-trifluoroalkylphenyl, 2-halophenyl, e.g. 2-fluorophenyl, 2-chlorophenyl, or 2-bromophenyl, 3-halophenyl, e.g. 3-fluorophenyl, 4-hydroxyphenyl, 2,6-di-halophenyl, e.g. 2,6-difluorophenyl, or 2,6-dichlorophenyl and 2,6-dialkoxyphenyl, e.g. 2, 6-dimethoxyphenyl.

Other particularly useful R^5 groups in compounds of formulae (1) and (2) include 2-,3- and 4-pyridinyl, thienyl e.g. 2-thienyl, pyridazinyl, e.g. 3- or 4-pyridazinyl, and imidazolyl e.g. 1-, 2-, 4- or 5- imidazolyl groups, optionally substituted by one, two or more R^{10} groups, especially halogen atoms, e.g. fluorine or chlorine atoms, e.g. 3,5-dichloro-4-pyridinyl, nitro, amino, alkoxy, haloalkyl, hydroxy, $-NHCOR^{7a}$, $-NHCONHR^{7a}$ or $-NHSO_2R^{7a}$ groups.

Particularly useful groups of compounds of formulae (1) or (2) are those wherein R^3 is a hydrogen atom, R^4 is a hydrogen atom, or a $-CH_3$ or -CN group and Z is a group $(CH_2)_n$ where n is zero, and the salts, solvents, hydrates and N-oxides thereof. Especially useful compounds in groups of these types are those wherein R^5 is an optionally substituted phenyl or pyridinyl group.

Particularly useful compounds according to the invention are

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl) propenenitrile;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl)propenenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4,5-dichloro-1-imidazolyl) propenenitrile
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propenenitrile;
(E)-4-{2-[1-(3-Cyclopentyloxy-4-methoxy)phenyl]-1-propenyl}pyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl) propenenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl) propenenitrile;

(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)-propenenitrile;
N-{4-[2-(3--Cyclopentyioxy-4-methoxyphenyl)ethenyl]-3-pyridyl} phenylsulphonamide;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine;
(E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine; or
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine;
and the salts, solvates, hydrates 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.

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 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 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, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and artherosclerosis.

Compounds of the invention also suppress neurogenic inflammation 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 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 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 osteo-arthritis.

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 or nasal 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 pediatric 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 continuous infusion. Formulations for injection may be presented in unit dosage form. 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 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 transdermal administration, the compounds according to the invention may be formulated in delivery vehicles such as patches,

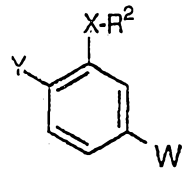
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane,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

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispense 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 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 for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. The symbols Y, R^2, R^3, R^4, R^5, X and Z, when used in the formulae below are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reacting a compound of formula (3):



(3)

where

(a) W is a $-C(O)R^3$ group wherein R^3 is as defined for formula (1) but is not a -CN or $-CH_2CN$ group, with a compound $R^5ZCH_2R^4$; or where

(b) W is a $-CH_2R^3$ group with an aldehyde or ketone R^5ZCOR^4, where R^4 is as just defined for R^3; or where

(c) W is a $-CO(R)^3$ group with a silane derivative $Alk_3SiCH(R^4)(R^5)$, where Alk is an alkyl group; in the presence of a base or an acid in a suitable solvent.

Bases for use in these reactions include inorganic bases, for example alkali and alkaline earth metal bases, e.g. hydroxides, such as sodium or potassium hydroxide; alkoxides, for example sodium ethoxide, and organic bases, for example amines such as piperidine; or an organolithium, such as an alkyllithium, e.g. n-butyllithium. Suitable solvents include alcohols such as ethanol, or ethers such as tetrahydrofuran. Acids for use in the reaction include organic acids, e.g. carboxylic acids such as acetic acid.

The reaction may be performed at any suitable temperature, for example from around -78°C to ambient temperature to the reflux temperature depending on the nature of the starting materials.

In general, the base, acid, solvent and reaction conditions may be selected depending on the nature or the starting materials, from a range of known alternatives for reactions of this type.

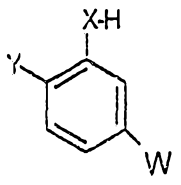
In silane derivatives of formula $AlkSiCH(R^4)(R^5)$, Alk may be for example a C_{1-6}alkyl group such as a methyl group. Derivatives of this type may be prepared for example by reacting a compound $R^5-CH_2-R^4$ with a silane

derivative, such as chlorotrimethylsilane, in the presence of a base, e.g. lithium diisopropylamide, in a solvent, e.g. tetrahydrofuran, at a low temperature e.g. around -10°C.

The starting materials $R^5ZCH_2R^4$, R^5ZCOR^4, and $R^5CH_2R^4$ 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.

Intermediates of formula (3) where W is a $-C(O)R^3$ group where R^3 is an alkyl group, such as a methyl group, may be prepared by reacting an aldehyde of formula (3) where W is a -CHO group with an organometallic reagent, such as methylmagnesiumbromide, in a solvent, e.g. tetrahydrofuran, at low temperature, e.g. around 10°C, followed by oxidation with an oxidising agent, such as manganese dioxide, in a solvent, e.g. dichloromethane.

Alternatively, intermediates of formula (3) may be prepared by alkylation of a corresponding compound of formula (4)

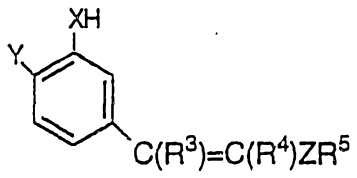


(4)

using a compound R^2Hal [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.

Intermediates of formula (4) 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.

In another aspect of the invention, a compound of formula (1) may be prepared by alkylation of a compound of formula (5)



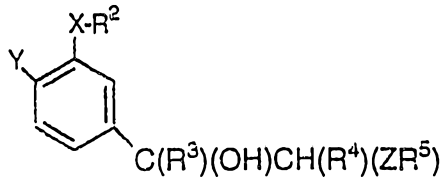
(5)

with a halide R^2Hal, or with an alcohol R^2OH.

The alkylation with the halide R^2Hal may be performed using the reagents and conditions described above for the preparation of compounds of formula (4). Alkylation using an alcohol R^2OH may be performed in the presence of a phosphine, such as triphenylphosphine, and an activator, for example diethyl azodicarboxylate, 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].

Intermediates of formula (5) may be prepared by reaction of an aldehyde or ketone of formula (4) with a compound $R^5ZCH_2R^4$ as described above for the preparation of compounds of formula (1) from compounds of formula (3). In this reaction the group X-H may need to be in a protected state. Conventional hydroxy, amino or thiol 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].

According to a further aspect of the invention a compound of formula (1) may be prepared by dehydration of an alcohol of formula (6)



(6)

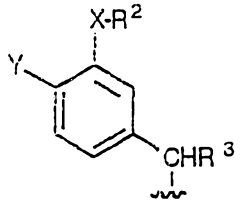
using an acid at an elevated temperature.

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.

Intermediate alcohols of formula (6) may be prepared by reaction of a ketone of formula (3) with an organometallic reagent R^4R^5ZCHM [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 tetranydrofuran, at a low temperature e.g. around -70°C to ambient temperature.

Reagents R^4R^5ZCHM are either known compounds or may be prepared, preferably in situ during the above process, by reaction of a compound $AlkCH_2M$ or $[Alk]_2NM$ [where Alk is an alkyl group such as a n-propyl or i-propyl group] with a compound $R^4R^5ZCH_2$ using the just mentioned reaction conditions.

According to a still further aspect of the invention, a compound of formula (1) may be prepared by reaction of a phosphonium salt $R^{13}P^+Ar_3Hal^-$ where R^{13} is a group of formula

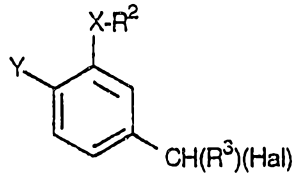


Ar is an aryl group such as a phenyl group and Hal is a halogen atom such as a chlorine, bromine or iodine atom, with a compound R^5ZCOR^4 in the presence of a base in a suitable solvent.

Bases for use in this reaction include alkoxides, for example alkali metal alkoxides such as sodium ethoxide or organometallic bases such as phenyllithium. Suitable solvents include alcohols, such as ethanol, and

ethers, e.g. cyclic ethers such as tetrahydrofuran. The reaction may generally be performed at ambient temperature.

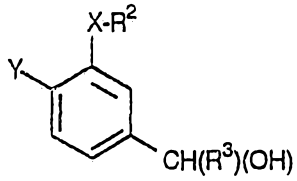
Intermediate phosphonium salts of formula $R^{13}P^+Ar_3Hal^-$ may be prepared by reaction of a halide of formula (7)



(7)

with a phosphine Ar_3P.

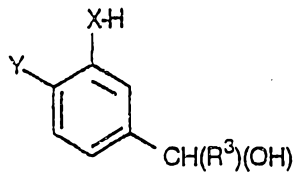
Intermediate halides of formula (7) may be prepared by reaction of an alcohol of formula (8)



(8)

with a hydrogen halide in a solvent such as an ether.

Intermediate alcohols of formula (8) may be prepared by alkylation of a compound of formula (9)

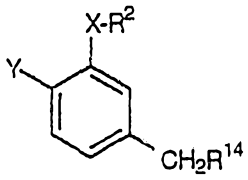


(9)

with a halide R^2Hal as described above for the preparation of compounds of formula (1) from intermediates of formula (5).

Intermediates of formula (9) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

In yet another aspect of the invention, a compound of formula (1) may be prepared by reaction of a phosphonate ester of formula (10)



(10)

[wherein R^{14} is a $-P(O)(OR^{15})(OR^{16})$ group, where R^{15} and R^{16}, which may be the same or different is each an alkyl, e.g. ethyl, aryl, e.g. phenyl or aralkyl e.g. benzyl group] with a compound R^5ZCOR^4 in the presence of a base in a suitable solvent.

Suitable bases include hydrides such as sodium hydride and alkoxides, for example alkali metal alkoxides such as sodium ethoxide. Solvents include ethers, for example cyclic ethers such as tetrahydrofuran.

Phosphonate esters of formula (10) may be prepared by a Michaelis Arbuzov reaction of a halide of formula (8) with a phosphite $P(OR^{15})_2OR^{16}$.

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a substituted monocyclic or bicyclic aryl group R^5 in compounds of formula (1) may generally be obtained by an appropriate substitution reaction using the corresponding unsubstituted compound of formula (1) and a R^{10} containing nucleophile or electrophile. Similarly, where it is desired to obtain a compound of formula (1) where R^3 and/or R^4 is other than a hydrogen atom, an appropriate nucleophile and reagents and/or reaction conditions favouring nucleophilic addition, may be used with the corresponding compound of formula (1) where R^3 and R^4 is a hydrogen atom. Alternatively, 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.

Thus, in one example of an interconversion process a compound of formula (1) wherein R^5 contains a $-CH_2NH_2$ substituent may be prepared by reduction of a corresponding compound wherein R^5 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 contains $-NHCOR^{7a}$, $-NHCONHR^{7a}$, $-NHCON(R^{7a})_2$, $-NHCSR^{7a}$ or alkanoylamino-alkyl substituent may be prepared by acylation or thiolation of a corresponding compound wherein R^5 contains a $-NH_2$ or alkylamino group by reaction with an acyl halide e.g. an acyl chloride, an acyl 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.

In a still further example, a compound of formula (1) wherein R^5 contains an alkoxy substituent may be prepared by alkylation of a corresponding compound wherein R^5 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.

In another example, a compound of formula (1) wherein R^3 and/or R^4 is a $-CN$ or $-CH_2CN$ group may be prepared by dehydration of a corresponding amide where R^3 and/or R^4 is $-CONH_2$ or $-CH_2CONH_2$ using for example trifluoroacetic anhydride in the presence of a base such a pyridine in a solvent such as tetrahydrofuran.

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.

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.

The following examples illustrate the invention.

The following abbreviations are used:

DMF	dimethylformamide
THF	tetrahydrofuran
DME	dimethoxyethane
EtOAc	ethyl acetate
Et_2O	diethylether
RT	room temperature
LDA	lithium diisopropylamide

INTERMEDIATE 1

a) **3-Cyclopentyloxy-4-methoxybenzaldehyde**

Caesium carbonate (214g, 0.66mol) was added to a mixture of 3-hydroxy-4-methoxybenzaldehyde (100g, 0.66mol) and cyclopentyl bromide (98g, 0.66mol) in anhydrous DMF (50ml). The reaction mixture was stirred at RT for 16h then treated with a further portion of cyclopentyl bromide (98g, 0.66mol) and caesium carbonate (214g, 0.66mol). After a further 6h at RT, the mixture was filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (300ml) and washed with sodium hydroxide solution (10%; 2x150ml). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and distilled (150°C, 10^{-2}mbar) to afford the title compound (130g) as a viscous colourless oil. (Found: C, 70.38; H, 7.48. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $CH_2)_4$), 3.87 (3H, s, OMe), 4.80 (1H, br m, $OCHCH_2$), 6.90 (1H, d, J 3.7Hz, ArH ortho to OMe), 7.30-7.45 (2H, m, 2xArH meta to OMe), and 9.77 (1H, s, ArCHO). This is the intermediate referred to below as intermediate 1.

b) 3-Cyclopentyloxy-4-methoxybenzylalcohol

From 3-hydroxy-4-methoxybenzyl alcohol (50g, 0.324mol), cyclopentyloxy-bromide (70ml, 0.648mol), caesium carbonate (72.83g, 0.222mol) and sodium iodide (5.63g, 0.037mol). Chromatography (SiO_2; EtOAc-C_6H_{14}. 1:3) to yield the title compound (25.782g). (Found C, 69.92; H, 8.18. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16).

INTERMEDIATE 2

3,5-Dichloro-4-methylpyridine

3,5-Dichloropyridine (2.04g, 13.5mmol) in THF (5ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.9ml, 13.5mmol) and n-butyllithium (1.6M, 8.4ml, 13.5mmol)] in THF (25ml) at -70°C. After stirring at this temperature for 5 min, iodomethane (0.85ml, 13.5 mmol) was added and the reaction mixture stirred for a further 1.5h at -70°C. Saturated sodium hydrogen carbonate solution (20ml) and dichloromethane (20ml) was added and the organic phase separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to chromatography (SiO_2; Et_2O-hexane, 1:3) to afford the title compound (1.16g) as a pale yellow solid; δ_H ($CDCl_3$) 2.46 (3H, s, Me), and 8.36 (2H, s, pyridine H_2, H_6).

INTERMEDIATE 3

a) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]-3,5-dichloropyridine

Intermediate 2 (2.22g, 13 mmol) in THF (40ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (2.4ml, 17mmol) and n-butyllithium (1.6M, 10.2ml, 16mmol)] in THF (50ml) at -70°C and the mixture stirred at this temperature for 0.25h. A solution of Intermediate 1 (3.32g, 15mmol) in THF (50ml) was then added at -70°C and the reaction mixture allowed to warm to RT overnight. Saturated ammonium chloride solution (50 ml) and dichloromethane (50ml) was added and the organic phase separated, dried ($MgSO_4$), and concentrated in vacuo. The residual yellow solid was triturated with hot Et_2O to afford the title compound (2.65g) as a white solid m.p. 139-140°C (Found: C, 59.49; H, 5.68; N, 3.57. $C_{19}H_{21}Cl_2NO_3$ requires C, 59.69; H, 5.53; N, 3.66%); δ_H ($CDCl_3$) 1.5-2.1 (9H, br m, $CH_2)_4$ + OH), 3.2-3.5 (2H, m, CH_2Ar), 3.81 (3H,

s, OMe), 4.7 (1H, br m, OCHCH$_2$), 5.01 (1H, dd J 5.8, 8.4Hz, CHOH), 6.75-6.9 (3H, m, ArH ortho to OMe + 2xArH meta to OMe), and 8.36 (2H, s, pyridine H$_2$, H$_6$); m/z 383 (10%), 381 (17), 221 (46), 163 (49), 161 (74), 153 (100), 152 (24), 151 (17), 125 (27), 93 (48), 65 (25), and 41 (34).

The following intermediates were prepared in a manner similar to Intermediate 3a:

b) **2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-hydroxyethyl] pyridine**

From 2-methylpyridine (1.02g, 11mmol), LDA (1.0 equiv), and Intermediate 1 (2.45g, 11mmol). The crude product was subjected to chromatography (SiO$_2$; Et$_2$O) to afford the title compound (2.67g) as a yellow solid m.p. 94-96°C (Found: C, 72.89; H, 7.43; N, 4.58. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%); δ_H ($CDCl_3$) 1.5-2.1 (9H, br m, (CH$_2$)$_4$ + OH) ,3.09 (2H, d, J 6.1 Hz, CH$_2$Ar), 3.80 (3H, s, OMe), 4.74 (1H, br, d, OCHCH$_2$), 5.06 (1H, t, J 6.1Hz, CHOH), 6.8-7.2 (5H, m, ArH ortho to OMe + 2xArH meta to OMe + pyridine H$_3$, H$_4$), 7.56 (1H, m, pyridine H$_5$), and 8.47 (1H, dm, J 4.5Hz, pyridine H$_6$); m/z 313 (M$^+$, 5%), 153 (16), 152 (90), 151 (53), 93 (100), 80 (17), and 41 (14).

c) **4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl] pyrimidine**

From 4-methylpyrimidine (2.15g, 23.6mmol), LDA (1.0 equiv), and intermediate 1 (5.12g, 23.0mmol). The crude product was subjected to chromatography (SiO$_2$; Et$_2$O) to afford the title compound (3.83g) as an amber oil. (HCl salt m.p. 211-213°C) (HCl salt Found: C, 62.24; H, 6.68; N, 8.06. $C_{18}H_{23}N_2O_3$ requires C, 61.44; H, 6.87; N, 7.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, (CH$_2$)$_4$), 3.10 (2H, d, J 6.5 Hz, CH$_2$Ar), 3.80 (3H, s, OMe), 4.15 (1H, br, s OH), 4.74 (1H, br, m, OCHCH$_2$), 5.10 (1H, t, J 6.5Hz, CHOH), 6.75-6.9 (3H, m, ArH ortho to OMe + 2xArH meta to OMe), 7.09 (1H, dd, J 4.9Hz, pyrimidine H$_5$), 8.53 (1H, d, J 4.9Hz, pyrimidine H$_6$), and 9.07 (1H, d, J 4.0Hz, pyrimidine H$_2$); m/z 314 (M$^+$, 16%), 296 (19), 228 (23), 227 (75), 166 (18), 153 (22), 152 (20), 151 (16), 94 (100), and 41 (26).

d) **4-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-hydroxy]propyl} pyridine**

From 4-ethylpyridine (2.50g, 2.65ml, 23.33mmol), LDA and Intermediate 1 (5.14g, 23.33mmol). Recrystallisation ($CHCl_3$/hexane) afforded the title compound (0.582g) as colourless fluffy needles. m.p. 131.5-132.3°C. (Found: C, 72.38; H, 7.74; N, 4.22. $C_{20}H_{25}NO_2{}^1/_4H_2O$ requires C, 72.44; H, 7.56; N, 4.10%).

INTERMEDIATE 4

a) **4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl] pyridazine**

n-Butyllithium (1.6M in hexanes) (9.5ml, 6.0mmol) was added dropwise to a solution of methylpyridazine (0.47g, 5.0mmol) in THF (25ml) at -70°C. The reaction mixture was allowed to stir at this temperature for 0.5h then a solution of Intermediate 1 (1.1g, 5.0mmol) in THF (20ml) was added. The mixture was allowed to warm to RT then partitioned between dichloromethane (25ml) and saturated sodium hydrogen carbonate solution (25ml). The organic phase was separated, dried ($MgSO_4$), and concentrated in vacuo to afford the title compound which was used in the next step [Exampie 7a] without any further purification.

The following Intermediates were prepared in a manner similar to Intermediate 4 a.

b) **4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl] pyridine**

From 4-methylpyridine (3.00g, 32.1mmol), n-butyllithium (32.1mmol), and Intermediate 1 (6.82g, 31.0mmol). The crude product was subject to chromatography [SiO_2; EtOAc-hexane, 3:2 (500ml) to 4:1 (1000ml) then EtOAc-methanol 9:1 (1500ml)] to afford the title compound (9.68g) as fine white needles m.p. 97-101°C (from toluene) δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$, 2.45(1H, br, s, CHOH), 2.96 (2H, d, J 6.5 Hz, CH_2 pyridine), 3.80 (3H, s, OMe), 4.70 (1H, br, m, $OCHCH_2$), 4.81 (1H, t, J 6.5Hz, CHOH),

6.76(3H, s, ArH ortho to OMe + 2xArH meta to OMe), 7.00 (2H, dm, J 4.5Hz, pyridine H_3, H_5), and 8.33 (2H, dm, J 4.5Hz, pyridine H_2, H_6).

c) **2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl] pyrazine**

From methylpyrazine (0.94g, 11mmol), n-butyllithium (1.6M; 6.9ml, 11mmol), and intermediate 1 (2.2g, 10mmol) to afford the title compound which was used in the next step [Example 7c)] without any further purification.

INTERMEDIATE 5

(3-Cyclopentyloxy-4-methoxyphenyl)-3-hydroxy-2-(phenylmethyl)propane-1-nitrile

3-Phenylpropionitrile (2.62g, 20mmol) was added dropwise to a solution of LDA [prepared from n-BuLi (1.6M solution in hexanes) (14ml, 22mmol) and N,N-diisopropylamine (3.5ml, 25mmol)] in THF (100ml) at -70°C. A solution of Intermediate 1 (4.4g) in THF (25ml) was then added and the reaction mixture was allowed to warm to RT then poured into $NaHCO_3$ solution (50ml) and extracted with CH_2Cl_2 (2x50ml). The extract was dried (Na_2SO_4), concentrated in vacuo, and the residue subjected to chromatography (SiO_2; Et_2O-hexane, 1:1) to afford the title compound (4.34g) as a pale yellow oil; m/z 351 (M^+, 10%), 221 (22), 153 (100), 152 (19), 151 (15), 125 (15), 93 (25), 92 (25), 65 (14) and 41 (16).

INTERMEDIATE 6

(3-Cyclopentyloxy-4-methoxy)phenyl methyl ketone

To a solution of methylmagnesiumbromide (5.44ml) in THF (150ml) at 10°C was added Intermediate 1. The reaction mixture was left to stir at RT for 5-6hr, then NH_4Cl and Et_2O (100ml) were added and the solution stirred for another 90 min (the solution went from hazy to clear). The layers were separated, the aqueous layer was extracted with Et_2O (50ml) the combined organic layer was extracted with a saturated bicarbonate solution (100ml) then brine (100ml). Evaporation *in vacuo* afforded 1-

methoxy-2-cyclopentyloxy-4-(1-hydroxyethyl)benzene which was disolved in dichloromethane (300ml) before adding MnO_2 (10eq). The reaction mixture was stirred for 120h, then the MnO_2 was filtered off and the solvent evaporation *in vacuo*. Purification by column chromatography (SiO_2; dichloromethane-hexane, 350-150 to dichloromethane) afforded the title compound.

INTERMEDIATE 7

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

To a cold (-78°C) solution of 4-picoline (0.80ml) in THF was added n-BuLi (5.6ml), the solution stirred for 30min then transferred to a cold suspension of cerium chloride anhydrous (2.0g) at -78°C. The reaction mixture was stirred for 1h before adding Intermediate 6 in THF then left to warm to RT overnight. 10% NH_4Cl solution and EtOAc were added, the solution was filtered through Celite, washed with EtOAC (150ml) and the organic layer was separated, washed with brine (100ml) then dried (Na_2SO_4). The solvents were evaporated *in vacuo* to afford the title compound (2.367g) as pale off-white crystals m.p. 99-101°C. Found C, 73.21; H, 7.63; N, 4.20. $C_{20}H_{25}NO_3$ requires C 73.37; H, 7.70; N, 4.28%). m/z (EI) 327 (M^+, 3%), 235 (18), 166 (38), 151 (100), and 93 (54).

INTERMEDIATE 8

3-Cyclopentyloxy-4-methoxybenzyl ~~alcohol~~ chloride

Intermediate 1b (0.6g, 2.7mmol) was dissolved in ethereal HCl, the solution stirred at RT and followed by thin layer chromatography until complete disappearance of the starting material. The solution was washed with saturated sodium bicarbonate solution. The organic layer extracted and dried (Na_2SO_4). Concentration *in vacuo* afforded the title compound (0.395g).

INTERMEDIATE 9

3-Cyclopentyloxy-4-methoxybenzyltriphenylphosphonium chloride

A mixture of Intermediate 8 (10.4g, 43.2mmol) and triphenylphosphine (11.5g, 43.8mmol) in toluene (100ml) was heated to reflux for 18h. The

reaction mixture was concentrated *in vacuo* and the residue triturated with acetone (250ml) to afford the title compound (19.5g) as a white solid.

INTERMEDIATE 10

Diethyl 3-Cyclopentyloxy-4-methoxybenzylphosphonate

A mixture of Intermediate 8 (52.7g, 0.22mol) and sodium iodide (32.9g, 0.22mol) in triethyl phosphite (76.4g, 0.46mol) was heated at 100°C for 24h. The reaction mixture was partitioned between EtOAc (200ml) and water (200ml) and the organic layer was separated. The extract was washed (brine; 50ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow oil (70g). A portion (40g) of the oil was distilled (190-210°C, 10^{-2} mbar) to afford the title compound (20,3g, 27%) as a colourless oil.

EXAMPLE 1

a) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl) propenenitrile**

2-Thiopheneacetonitrile (1.1ml, 10mmol) and Intermediate 1 (2.29g, 10mmol) was dissolved in ethanol (10ml) and added to a solution of sodium hydroxide (0.51g, 12.8mmol) in water (5ml). The reaction mixture was allowed to stir at RT for 2h then partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (15ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give a yellow gum which was recrystallised from ethanol to afford the title compound (3.35g) as yellow crystals m.p. 100-101°C. (Found: C, 69.47; H, 5.80; N, 4.18. $C_{19}H_{19}NO_2S$ requires C, 70.13; H, 5.80; N, 4.18%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.83 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.00 (1H, dd, J 4.5, 3.5Hz, thiophene H_4), 7.15-7.3 (4H, m, ArH para to cyclopentyloxy + CH=CCN+thiophene H_3, H_5), and 7.60 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 326 (M^+ + 1, 23%), 325 (M^+, 87), 259 (34), 258 (85), 257 (100), 224 (24), 214 (27), 197 (21), 196 (93) and 41 (29).

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

b) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenyl-propenenitrile**

From phenylacetonitrile (0.52g, 4.4mmol) and Intermediate 1 (0.95g, 4.3mmol). Chromatography (SiO_2; EtOAc-hexane) gave the title compound (0.81g) as a yellow solid m.p. 84-86% (Found: C, 78.83; H, 6.60; N, 4.38. $C_{21}H_{21}NO_2$ requires C, 78.97; H, 6.63; N, 4.39%); δ_H ($CDCl_3$) 1.5-2.1 (8H, m, $(CH_2)_4$), 3.86 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.8Hz, ArH ortho to OMe), 7.15-7.7 (7H, m, ArH para to cyclopentyloxy + CH=CCN + C_6H_5), and 7.67 (1H, d, J 2.3Hz, ArH ortho to cyclopentyloxy); m/z 319 (M^+, 33%), 252 (49), 251 (100), 218 (15), 208 (32), 190 (48), 180 (15), 152 (15) and 41 (20).

c) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-pyridyl)-propenenitrile**

From 2-pyridylacetonitrile (11mmol) and Intermediate 1 (2.20g, 10mmol). Trituration of the crude product with ethanol gave the title compound (2.40g) as a yellow solid m.p. 82.5-83°C (Found: C, 74.87; H, 6.27; N, 8.46. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.824(3H, s, OMe), 4.80 (1H, br m, $OCHCH_2$), 6.84 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.05-7.25 (1H, m, pyridine H_5), (1H, dd, J 8.6, 1.95Hz, ArH para to OMe), 7.6-7.75 (3H, m ArH ortho to cyclopentyloxy+ pyridine H_3,H_4), 8.29 (1H, s, CH=CCN) and 8.52 (1H, ca.d, J 4.6 Hz, pyridine H_6); m/z 320 (M^+, 15%), 252 (38), 251 (100), 237 (5), 236 (10), 209 (5), 179 (5), and 41 (8).

d) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl)-propenenitrile**

From 3-pyridylacetonitrile (2.35ml, 22mmol) and Intermediate 1 (4.40g, 20mmol). Chromatography (SiO_2; EtOAc) gave the title compound (5.31g) as a pale yellow solid m.p. 86.5-87.5°C (Found: C, 74.80; H, 6.26; N, 8.74. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.2-7.4 (2H, m, ArH para to OMe +

pyridine H_3), 7.42 (1H, s, CH=CCN), 7.70 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy), 7.87 (1H, dm, J 7.6Hz, pyridine H_4), 8.53 (1H, dd, J 4.8, 1.3Hz, pyridine H_6) and 8.84 (1H, d, J 2.4Hz, pyridine H_2); m/z 320 (M^+, 20%), 252 (100), 251 (67), 234 (20), 223 (27), 205 (27), 151 (50), 69 (22), and 41 (31).

e) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl-2-(4-pyridyl)-propenenitrile**

From 4-pyridylacetonitrile (1.7g, 11mmol) and Intermediate 1 (2.20g, 20mmol). Trituration of the crude product with ethanol gave the title compound (2.75g) as an orange solid m.p. 125-127°C. (Found: C, 74.84; H, 6.29; N, 8.33. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.84 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.83 (1H, d, J 8.2Hz, ArH ortho to OMe), 7.26 (1H, dd, J 8.2, 2.2Hz, ArH para to OMe), 7.44 (2H, dd, J 4.7, 1.7Hz pyridine H_3,H_5), 7.53 (1H, s, CH=CCN) 7.69 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy), 8.56 (2H, dd, J 4.7,1.5 Hz, pyridine H_2, H_6); m/z 320 (M^+, 28), 253 (19), 252 (100), 251 (59), 224 (15), 223 (38), 209 (10), and 41 (23).

f) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl-2-(1-naphthyl) propenenitrile**

From 1-naphthylacetonitrile (1.67g, 10mmol) and Intermediate 1 (2.2g, 10mmol). The reaction mixture was extracted with dichloromethane then the extract dried ($MgSO_4$) and concentrated in vacuo to afford the title compound (2.56g) as a yellow solid.p. 161-163°C (Found: C, 81.22; H, 6.29; N, 3.77. $C_{25}H_{23}NO_2$ requires C, 81.27; H, 6.27; N, 3.79%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.89 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.87 (1H, d, J 8.1Hz, ArH ortho to OMe), and 7.15-8.1 (10H, m, 2xArH ortho to OMe + CH=CCN + $C_{10}H_7$); m/z 320 ($M^+ + 1$, 9%), 369 (M^+, 30), 302 (28), 301 (100), 268 (10), 240 (17), 202 (5), and 41 (5).

g) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-naphthyl) propenenitrile**

From 2-naphthylacetonitrile (1.67g, 10mmol) and Intermediate 1 (2.2g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.14g) as a pale yellow solid. m.p. 147-148°C (Found: C, 81.15; H, 6.24; N, 3.56. $C_{25}H_{23}NO_2$ requires C, 81.27; H, 6.27; N, 3.79%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.87 (1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.3Hz, ArH meta to OMe), and 7.2-8.1 (10H, m, 2xArH meta to OMe + CH=CCN + $C_{10}H_7$); m/z 370 (M^+ + 1, 10%), 369 (M^+, 40), 302 (23), 301 (100), 240 (20), 167 (12), 124 (38), and 41 (10).

h) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-thienyl) propenenitrile**

From 3-thienylacetonitrile (1.2ml, 10.5mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.50g) as a yellow solid m.p. 83-84°C (Found: C, 69.86; H, 5.85; N, 4.18. $C_{19}H_{19}NO_2S$ requires C, 70.13; H, 5.89; N, 4.30%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, $(CH_2)_4$), 3.86 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.84 (1H, d, J 8.0Hz, ArH ortho to OMe) 7.15-7.5 (5H, m, para to cyclopentyloxy + CH=CCN) + thiophene H_2, H_4, H_5) and 7.62 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 325 (M^+, 34%), 258 (23), 257 (100), 256 (10), 226 (11), 214 (19), 197 (12), and 196 (30).

i) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-fluorophenyl) propenenitrile**

From 2-fluorophenylacetonitrile (1.35g, 10mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO_2; Et_2O-hexane) gave the title compound (0.51g) as a yellow solid m.p. 70-73°C (Found: C, 74.58; H, 6.08; N, 4.03. $C_{21}H_{20}NO_2$ requires C, 74.76; H, 5.97; N, 4.15%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br. m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.6Hz, ArH ortho to OMe), 6.9-7.6 (5H, m, ArH para to cyclopentyloxy + C_6H_4F),7.40 (1H, s, CH=CCN), and 7.69 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 337 (M^+, 5%), 269 (55), 220 (13), 153 (25), 152 (100), 151 (96), 69 (17), 67 (13), and 41 (51).

j) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-fluorophenyl) propenenitrile**

From 3-fluorophenylacetonitrile (1.2g, 10mmol) and Intermediate 1 (2.20g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.77g) as yellow crystals m.p. 114-116°C (Found: C, 74.79; H, 5.96; N, 4.07. $C_{21}H_{20}FNO_2$ requires C, 74.76; H, 5.97; N, 4.15%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.4Hz, ArH ortho to OMe), 7.0-7.45 (6H, m, ArH para to OMe + CH=CCN + C_6H_4F), and 7.68 (1H, d, J 1.8Hz, ArH ortho to cyclopentyloxy); m/z 337 (M^+, 10%), 270 (23), 269 (100), 208 (30), 149 (13), 55 (14) and 41 (17).

k) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-fluorophenyl) propenenitrile**

From 4-fluorophenylacetonitrile (1.3g, 10mmol) and Intermediate 1 (2.41g, 11mmol). The reaction mixture was filtered to afford the title compound (3.34g) as colourless crystals m.p. 139-141°C (Found: C, 74.80; H, 5.95; N, 4.05. $C_{21}H_{20}FNO_2$ requires C, 74.76; H, 5.97; N, 4.15%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.6Hz, ArH ortho to OMe), 6.95-7.2 (3H, m, ArH para to cyclopentyloxy + 2xArH ortho to F), 7.30 (1H, s, CH=CCN), 7.45-7.7 (3H, m, ArH ortho to OCp + 2xArH meta to F); m/z 337 (M^+, 11%), 271 (21), 269 (100), 226 (13), 208 (25), and 41 (19).

l) **(Z)-2-(3-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 3-chlorophenylacetonitrile (1.53g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.01g) as yellow crystals m.p. 98-100.5°C (Found: C, 71.40; H, 5.70; N, 4.03. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), and 7.2-7.7 (7H, m, 2xArH meta to OMe + C_6H_4Cl + CH=CCN); m/z 353 (M^+, 26%), 288 (18), 287 (85), 286 (56), 285 (100),224 (37), 207 (22) and 41 (45).

m) **(Z)-2-(3-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 3-bromophenylacetonitrile (1.97g, 10mmol) and Intermediate 1 (2.24g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.94g) as yellow crystals m.p. 90-91.5°C (Found: C, 63.38; H, 5.01; N, 3.48. $C_{21}H_{20}BrNO_2$ requires C, 63.33 H, 5.06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.5Hz, ArH ortho to OMe), and 7.15-7.75 (7H, m, 2xArH meta to OMe + C_6H_4Br + CH=CCN) ; m/z 399 (8%), 397 (8), 332 (21), 331 (100), 330 (23), 329 (100), 235 (15), 217 (16), 207 (26), 190 (14), 178 (12), and 41 (38).

n) **(E)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl) propenenitrile**

From 2,6-difluorophenylacetonitrile (1.86g, 10mmol) and Intermediate 1 (2.19g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:4) followed by recrystallisation from ethanol gave the title compound (0.3g) as yellow crystals m.p. 111-113°C. (Found: C, 70.78; H, 5.37; N, 3.85. $C_{21}H_{19}F_2NO_2$ requires C, 70.97 H, 5.39; N, 3.94%); δ_H ($CDCl_3$) 1.4-1.8 (8H, br s, $(CH_2)_4$), 3.80 (3H, s, OMe), 4.22 (1H, br s, $OCHCH_2$), 6.52 (1H, br s, ArH ortho to OMe), and 6.7-7.5 (6H, m, 2xArH meta to OMe + $C_6H_4F_2$) ; m/z 355 (M^+, 21%), 288 (19), 287 (100), 244 (11), 152 (48), 151 (31), and 41 (22).

o) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl) propenenitrile**

From 2,6-dichlorophenylacetonitrile (1.88g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.95g) as a white solid m.p. 164-166°C. (Found: C, 64.88; H, 4.93; N, 3.60. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.94 (1H, d, J 8.4Hz, ArH ortho to OMe), 6.86 (1H, s, CH=CCN), 7.1-7.45 (4H, m, ArH para to cyclopentyloxy + $C_6H_3Cl_2$), and 7.75(1H, d, J 1.8Hz, ArH ortho to cyclopentyloxy); m/z 389 (18%), 388 (7), 387 (29), 323 (19), 322 (19), 321 (87), 320 (29), 319 (100), 284 (18), 252 (19), 249 (24), 241 (25), 177 (14), and 41 (33).

p) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3,4-dichlorophenyl) propenenitrile**

Fromng 3,4-dichlorophenylacetonitrile (1.88g, 10mmol) and Intermediate 1 (2.23g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.56g, 90%) as a yellow solid m.p. 151.5-154°C (Found: C, 64.89; H, 4.93; N, 3.61. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.82(1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.4Hz, ArH ortho to OMe), and 7.2-7.7 (6H, m, 2xArH meta to OMe + CH=CCN+ $C_6H_3Cl_2$); m/z 389 (13%), 388 (5), 387 (20), 323 (12), 322 (12), 321 (69), 320 (19), 319 (100), and 41 (21).

q) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,4-dichlorophenyl) propenenitrile**

From 2,4-dichlorophenylacetonitrile (1.90g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.25g) as a white solid m.p. 105-107°C (Found: C, 64.93; H, 4.92; N, 3.64. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.86 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.05-7.45 (5H, m, ArH para to cyclopentyloxy + CH=CCN+ $C_6H_3Cl_2$); and 7.70 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy); m/z 389 (12%), 387 (28), 319 (100), 284 (23), 252 (24), 249 (31), and 41 (49)

r) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-trifluoromethyl-phenyl) propenenitrile**

From 2-trifluoromethylphenylacetonitrile (1.8g, 10mmol) and Intermediate 1 (2.27g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:2) followed by recrystallisation from ethanol gave the title compound (0.82g) as a white solid m.p. 96-98°C (Found: C, 67.93; H, 5.21; N, 3.53. $C_{22}H_{20}F_3NO_2$ requires C, 68.21; H, 5.20; N, 3.62%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 6.98 (1H,s,CH=CCN), 7.18 (1H, dd, J 8.4, 2.2Hz. ArH ortho to cyclopentyloxy), 7.25-7.8 (4H, m, $C_6H_4CF_3$)), and 7.67 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy; m/z 387 (M^+, 17%),

320 (53), 319 (100), 276 (14), 256 (19), 248 (18), 208 (9), 207 (9), and 41 (34).

s) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-trifluoromethylphenyl)propenenitrile**

From 3-trifluoromethylphenylacetonitrile (1.56g, 10mmol) and Intermediate 1 (2.34g, 10.6mmol). Chromatography (SiO_2; Et_2O-hexane, 1:1) gave the title compound (2.62) as a yellow solid m.p. 70-73°C (Found: C, 68.14; H, 5.18; N, 3.55. $C_{22}H_{20}F_3NO_2$ requires C, 68.21; H, 5.20; N, 3.62%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.87 (1H, d, J 8.2Hz, ArH ortho to OMe), 7.29 (1H, dd, J 8.2, 2.1Hz, ArH para to OMe), 7.42 (1H, s, CH=CCN), 7.45-7.85 (4H, m, $C_6H_4CF_3$), and 7.68 (1H, d, J 2.1Hz, ArH ortho to cyclopentyloxy;) m/z 387 (M^+, 11%), 320 (23), 319 (100), 276 (7), 258 (9), 67 (6), and 41 (21).

t) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-trifluoromethylphenyl)propenenitrile**

From 4-trifluoromethylphenylacetonitrile (1.85g, 10mmol) and Intermediate 1 (2.36g, 10.7mmol). Chromatography (SiO_2; Et_2O-hexane, 2:1) gave the title compound (3.77g) as a yellow solid m.p. 96-99°C (Found: C, 68.32; H, 5.26; N, 3.38. $C_{22}H_{20}F_3NO_2$ requires C, 68.21; H, 5.20; N, 3.62%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.89 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.87 (1H, d, J 8.1Hz, ArH ortho to OMe) and 7.2-7.75 (7H, m, 2xArH meta to OMe + $C_6H_4CF_3$ + CH=CCN); m/z 387 (M^+, 14%), 320 (26), 319 (100), 276 (12), 258 (15), and 41 (10).

u) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-methoxyphenyl) propenenitrile**

From 3-methoxyphenylacetonitrile (1.48g, 10mmol) and Intermediate 1 (2.23g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:1) gave the title compound (1.97g) as a yellow solid m.p. 83-85°C (Found: C, 75.80; H, 6.62; N, 4.13. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.00%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 4.84 (1H, br m, $OCHCH_2$), 6.8-6.95 (3H, m + d (δ6.85, J 7.9Hz), 3 x ArH ortho to OMe), 7.1-7.4 (4H, m, ArH para to OMe + ArH para to cyclopentyloxy + ArH meta to OMe and olefin + CH=CCN) and 7.66 (1H,

d, J 1.9Hz, ArH ortho to cyclopentyloxy); m/z 349 (M^+, 27%) 282 (28), 281 (100), 248 (7), 220 (13), and 41 (22).

v) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3,4-dimethoxyphenyl)propenenitrile**

From 3,4-dimethoxyphenylacetonitrile (1.95g, 11mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:1) gave the title compound (2.41g) as a yellow solid m.p. 101-103°C. (Found: C, 72.68; H, 6.46; N, 3.49. $C_{23}H_{25}NO_3$ requires C, 72.80; H, 6.64; N, 3.69%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 4.64 (1H, br m, $OCHCH_2$), 6.85 (2H, d, J 8.1Hz ArH meta to cyclopentyloxy +ArH ortho to OMe), 7.0-7.35 (4H, m, ArH para to cyclopentyloxy + CH=CCN + ArH ortho and ArH para to OMe), and 7.64 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy); m/z 380 (M^+ + 1, 5%), 379 (M^+, 27), 312 (20), 311 (100), 295 (12), 278 (5), 250 (8), and 41 (8).

w) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenyl)propenenitrile**

From 2, 3, 4, 5, 6-pentafluorophenylacetonitrile (2.07g, 10mmol) and Intermediate 1 (2.20g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.1g) as orange crystals m.p.94.5-96°C. (Found: C, 61.64; H, 3.94; N, 3.26. $C_{21}H_{16}F_5NO_3$ requires C, 61.62; H, 3.94; N, 3.42%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.89 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe); 7.15 (1H, slightly broadened s, CH=CCN) and 7.23 (1H, dd, J 8.4, 2.1Hz, ArH para to cyclopentyloxy); m/z 409 (M^+, 12%), 367 (8), 342 (21),341 (100), 298 (20), 27(10), 250 (10), and 41 (21).

EXAMPLE 2

a) **(Z)-2-(4-Aminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

A mixture of Intermediate 1 (2.24g, 10mmol), 4-aminophenylacetonitrile (1.37g, 10mmol), and piperidine (10 drops) in ethanol (8ml) was heated to reflux for 6h. The reaction mixture was partitioned between dichloromethane (20ml) and brine (10ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to chromatography (SiO_2; Et_2O-hexane, 2:1) to afford the title compound (1.15g) as a yellow solid m.p. 82-84°C (Found: C, 75.22; H, 6.68; N, 7.86. $C_{21}H_{22}N_2O_2$ requires C, 75.42; H, 6.63; N, 8.38%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.72 (2H, s, $ArNH_2$) 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.87 (1H, d, J 8.3Hz, ArH ortho to OMe), 7.05-7.4 (5H, m ArH para to cyclopentyloxy + $C_6H_4NH_2$), 7.52 (1H, d, J 1.8Hz, ArH ortho to cyclopentyloxy) and 8.26 (1H, s, CH=CCN); m/z 314 (M^+, 79%), 268 (13), 267 (98), 266 (100), 265 (100), 250 (19), 143 (14), 116 (34), 89 (21) and 41 (33).

The following compounds were prepared in a manner similar to the compound of Example 2 a.

b) **(Z)-2-(2-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 2-chlorophenylacetonitrile (1.53g, 10mmol) and Intermediate 1 (2.23g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 3:2) gave the title compound (1.85g) as pale yellow crystals m.p. 94-95°C (Found: C, 71.25; H, 5.72; N, 3.84. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.3Hz, ArH ortho to OMe), 7.11 (1H, s, CH=CCN), 7.15-7.5 (5H, m, ArH para to cyclopentyloxy + C_6H_4Cl), and 7.72 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 353 (M^+, 17%), 287 (43), 286 (23), 285 (100), 250 (64), 218 (75), 207 (28), 206 (25), 190 (38), and 41 (52).

c) **(Z)-2-(2-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 2-bromophenylacetonitrile (1.00g, 5.1mmol) and intermediate 1 (1.13g, 5.1mmol). The crude product was recrystallised from ethanol to

afford the title compound (0.48g) as a white solid m.p. 100-103°C (Found: C, 63.36; H, 5.07; N, 3.51. $C_{21}H_{20}BrNO_2$ requires C, 63.33 H, 5..06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.86 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 7.06 (1H, s, CH=CCN), 7.15-7.4 (45H, m, ArH para to cyclopentyloxy + 2xArH meta to Br + ArH para to Br), 7.5-7.65 (1H, m, ArH ortho to Br), and 7.72 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy); m/z 399 (47%), 397 (47), 331 (94), 329 (89), 250 (57), 219 (24), 218 (100), 207 (25), 190 (48), and 41 (36).

d) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-nitrophenyl) propenenitrile**

From 4-nitrophenylacetonitrile (1.66,g 10mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:1) followed by recrystallisation from methanol-ethanol gave the title compound (1.76g) as yellow crystals m.p. 185.5-187°C (Found: C, 69.29; H, 5.40; N, 7.67. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.90 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.88 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.3 (1H, dd, J 8.5, 1.9Hz, ArH para to OMe), 7.52 (1H, s, CH=CCN), 7.73 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy), 7.75 (2H, ca.d, J 8,7Hz, 2xArH ortho to NO_2); m/z 364 (M^+, 7%), 297 (28), 296 (100), 266 (29), 207 (13), 206 (10), 190 (10), and 41 (28).

e) **(Z)-2-(2-Aminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 2-aminophenylacetonitrile (1.3g, 10mmol) and Intermediate 1 (2.20g, 10mmol). Filtration of the reaction mixture gave the title compound (1.75g) as a white solid m.p. 81-82.5°C (Found: C, 74.86; H, 6.63; N, 8.32. $C_{21}H_{22}N_2O_2$ requires C, 75.42; H, 6.63; N, 8.38%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 2.14 (2H. s, NH_2), 3.89 (3H, s, OMe) 4.85 (1H, br m. $OCHCH_2$), 6.88 (1H. d, J 8.4Hz. ArH ortho to OMe), 7.0-7.5 (4H, m, $C_6H_4NH_2$), 7.30 (1H. dd. J 8.4, 1.9Hz, ArH para to cyclopentyloxy), 7.55 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy) and 8.28 (1H, s, CH=CCN);

m/z 334 (M^+, 32%), 266 (41), 265 (97), 252 (12), 251 (65), 250 (26), 249 (100), 69 (11), and 41 (32).

f) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl) propenenitrile**

From 2-nitrophenylacetronitrile (1.62g, 10mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO_2; Et_2O-hexane, 1:1) gave the title compound (2.60g) as a yellow solid m.p. 95.5-97°C (Found: C, 69.14; H, 5.43; N, 7.70. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 46.69%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.86 (1H, br m, $OCHCH_2$), 6.8-7.7 (7H, m, 2xArH meta to OMe + ArH ortho to OMe + CH=CCN + 2xArH meta toNO_2 + ArH para toNO_2), and 7.95-8.1 (1H, m, ArH ortho to NO_2); m/z 364 (M^+, 9%), 332 (19), 296 (33), 265 (20), 264 (100), 250 (12), 249 (35), 225 (10), 221 (17), 152 (60), 151 (26), 69 (16), and 41 (30).

EXAMPLE 3

a) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl)propenenitrile**

Sodium ethoxide [prepared from sodium (0.35g, 15mmol) in ethanol (10ml)] was added dropwise to a mixture of Intermediate 1 (1.09g, 4.95mmol) and 4-hydroxyphenylacetonitrile (0.67g, 5.03mmol) in ethanol (10ml). The reaction mixture was heated to reflux for 3h then partitioned between dichloromethane (25ml) and saturated sodium hydrogen carbonate solution (15ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to chromatography (SiO_2; Et_2O-hexane, 2:3) to afford the title compound (1.57g) as a yellow solid m.p. 138-140°C. (Found: C, 75.16; H, 6.35; N, 4.11. $C_{21}H_{21}NO_3$ requires C, 75.20; H, 6.31; N, 4.18%); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.86 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 5.57 (1H, br s, OH), 6.84 (3H, ca. d, J ca. 8.6Hz, ArH ortho to OMe + 2xArH ortho to OH), 7.22 (1H, dd, J 8.4, 1.9Hz, ArH para to OCp), 7.26 (1H, s, CH=CCN), 7.47 (2H, ca. d, J ca. 8.7Hz, 2x ArH meta to OH) and 7.62

(1H, d, J 8.7Hz, ArH ortho to OCp); m/z 335 (M^+, 58%), 267 (100), 154 (28), 129 (41), 70 (25), 57 (33), and 41 (40).

The following compounds were prepared in a manner similar to the compound of Example 3 a.

b) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methoxyphenyl) propenenitrile**

From 2-methoxyphenylacetonitrile (1.52g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.26g) as white crystals m.p. 85-87.5°C (Found: C, 75.67; H, 6.63; N, 3.95. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.01%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.83 (1H, br m. $OCHCH_2$), 6.83 (1H, d, J 8.4Hz, ArH ortho to OMe), 6.8-7.4 (5H, m, ArH para to cyclopentyloxy + C_6H_4OMe), 7.25 (1H, s, CH=CCN), and 7.70 (1H, d, J 2.1Hz, ArH ortho to cyclopentyloxy); m/z 350 (M^+ + 1, 14%), 349 (M^+, 57) 282 (20) 281 (100), 150 (12), 129 (37), 71 (11), 70 (11), 67 (13), 57 (16), and 41 (22).

c) **(Z)-2-(4-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 4-chlorophenylacetronitrile (1.65g, 8.7mmol) and Intermediate 1 (2.00g, 9.1mmol). The crude product was recrystallised from ethanol to afford the title compound (2.74g) as pale yellow crystals m.p. 129-137°C (Found: C, 71.18; H, 5.69; N, 3.82. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 7.2-7.6 (6H, m, ArH para to cyclopentyloxy + CH=CCN + C_6H_4Cl), and 7.67 (1H, d, J 2.1Hz, ArH ortho to cyclopentyloxy); m/z 353 (M^+ + 10%), 288 (6), 287 (35), 286 (18), 285 (100), 224 (7), and 207 (10).

d) **(Z)-2-(4-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl) propenenitrile**

From 4-bromophenylacetonitrile (2.15g, 10mmol) and Intermediate 1 (2.00g, 9.1mmol). The crude product was recrystallised from ethanol to afford the title compound (3.27g) as yellow crystals m.p. 116-119°C (Found: C, 63.17; H, 5.03; N, 3.35. $C_{21}H_{20}BrNO_2$ requires C, 63.33; H, 5.06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.84 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.15-7.35 (1H, m, ArH para to cyclopentyloxy), 7.35 (1H, s, CH=CCN), 7.48 (4H, s, C_6H_4CBr), and 7.67 (1H, d, J 2.1Hz, ArH ortho to cyclopentyloxy); m/z 399 (16%), 397 (17), 332 (19), 331 (100), 329 (19), 328 (100), 235 (8), 207 (15), and 41 (17).

e) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl) propenenitrile**

From 2,6-dichlorophenylacetonitrile (8.00g, 43mmol) and Intermediate 1 (9.46g, 43mmol). The crude product was recrystallised from ethanol to afford the title compound (12.35g) as a white solid (see Example 1 o) for spectral data).

f) **(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dimethoxy-phenyl) propenitrile**

From 2,6-dimethoxyphenylacetonitrile and Intermediate 1. The crude product was recrystallised from ethanol to afford the title compound as white crystals m.p. 120.5-122°C (Found: C, 72-88; H, 6.33; N, 3.13. $C_{23}H_{25}NO_4$ requires C, 77.80; H, 6.64; N, 3.69%); δ_H ($CDCl_3$) 1.45-2.1 (8H, br m, $(CH_2)_4$), 3.84 (6H, s, $C_6H_3(OMe)_2$), 3.89 (3H, s, OMe ortho to cyclopentyloxy), 4.87 (1H, br m, OCH), 6.60 (2H, d, J 8.4 Hz, $C_6H_3(OMe)_2$), 6.87 (1H, d, J 8.4 Hz, ArH meta to OCp), 7.00 (1H, s, CH=CCN), 7.2 (1H, dd, J 8.4, 2.1 Hz, ArH para to OCp), 7.29 (1H, d, J 8.4Hz, ArH meta to 2 xOMe), and 7.79 (1H, d, J 2.1Hz, ArH ortho to OCp); m/z 379 (M^+, 20%), 312 (21), 311 (100), 280 (11), 152 (43), 151 (72), 150 (33), 137 (18), 91 (16), 85 (15), 83 (23), 43 (10), and 41 (19).

EXAMPLE 4

(Z)-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-propenenitrile

A mixture of the phenol of Example 3 (600mg, 1.79mmol), caesium carbonate (580mg, 1.79mmol), and methyl iodide (0.24mg, 3.8mmol) in DMF (10ml) was allowed to stir at ambient temperature for 18h. The reaction mixture was partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallised from ethanol to afford the title compound (490mg) as yellow crystals m.p. 102-105°C. (Found: C, 75.43; H, 6.60; N, 3.98. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.01%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.84 (1H, d, J ca. 8.6Hz, ArH meta to cyclopentyloxy), 6.89 (2H, ca.d, J 8.8Hz, 2x ArH ortho to OMe), 7.23 (1H, dd, J 8.6, 2.5Hz, ArH para to OMe), 7.27 (1H, s, CH=CCN), 7.53 (2H, ca.d, J 8.8Hz, 2x ArH meta to OMe) and 7.64 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy); m/z 349 (M^+, 32%), 282 (36), 281 (100), 266 (19), 238 (14), 220 (8), and 41 (11).

EXAMPLE 5

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

A mixture of Intermediate 1 (2.13g, 9.68mmol), 4-methyl-3-nitropyridine (2.47g, 17mmol), and ammonium acetate (1.19g, 15mmol) in acetic acid (20ml) was heated to reflux for 3h. The reaction mixture was cooled and partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (2 x 10ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to chromatography (SiO_2; Et_2O-hexane, 1:1) to afford the title compound (1.83g) as an orange solid m.p. 114-116°C. (Found: C, 66.94; H, 5.94; N, 8.01. $C_{19}H_{20}N_2O_3$ requires C, 67.05; H, 5.92; N, 8.23%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.86 (3H, s, OMe), 4.75 (1H, br m, $OCHCH_2$), 6.84 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.0-7.2 (2H, m, 2x ArH meta to OMe) 7.30 (1H, s, CH=CH), 7.38 (1H, s, CH=CH), 7.61 (1H, d, J 5.4 Hz, pyridine H_5), 8.73. (1H, d , J 5.4 Hz, pyridine H_6), and 9.09 (1H, s, pyridine H_2); m/z 340 (M^+, 15%) 308 (25), 240 (69), 226 (20), 225 (34), 152 (100), 151 (31), 149 (29), 121 (29), 68 (26), 67 (66), and 57 (22).

EXAMPLE 6

a) **(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine**

Intermediate 3a) (2.65g, 6.92mmol) was dissolved in toluene (60ml) containing p-toluenesulphonic acid (0.2g) and the mixture heated to reflux for 2.5h in a Dean-Stark apparatus. The reaction mixture was concentrated in vacuo and the residue subjected to chromatography (SiO_2; Et_2O-hexane, 1:2) to afford the title compound (1.55g) as yellow crystals m.p. 99-101°C. (Found: C, 62.68; H, 5.22; N, 3.70. $C_{19}H_{19}Cl_2NO_2$ requires C, 62.65; H, 5.26; N, 3.85%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.86 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.83 (1H, d, J 8.9Hz, ArH ortho to OMe), 6.90 (1H, d, J 16.6 Hz,CH=CH) 7.0-7.2 (2H, m, 2x ArH meta to OMe), 7.40 (1H, d, J 16.6 Hz,CH=CH), and 8.42(2H, s, pyridine H_2, H_6); m/z 365 (15%), 363 (20), 297 (67), 296 (28), 295 (100), 262 (28), 260 (79), 245 (36), 230 (22), 228 (27), 216 (23), and 152 (24).

The following compounds were prepared in a manner similar to the compound of Example 6 a.

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

From Intermediate 3b). The crude product was subjected to chromatography (SiO_2; Et_2O-hexane, 2:1) to afford the title compound (1.58g) as a pale yellow solid m.p. 76-77.5°C. (Found: C, 77.20; H, 7.20; N, 4.63. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.80 (1H, d, J 8.5Hz, ArH ortho to OMe), 6.95 (1H, d, J 15.6 Hz,CH=CH), 6.95-7.7 (5H, m, 2x ArH meta to OMe + pyridine H_3, H_4, H_5), 7.51 (1H, d, J 15.6 Hz,CH=CH), and 8.53(1H, dm, J 4.9 Hz, pyridine H_6); m/z 295 (M^+, 23%), 294 (11), 227 (21), 226 (100), 211 (18), 184 (10), and 154 (13).

c) **(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine**

From Intermediate 3 c). The crude product was subjected to chromatography (SiO_2; EtOAc) then recrystallised from Et_2O-hexane to afford the title compound (1.64g) as a pale yellow amorphous solid m.p. 83-84.5°C. (Found: C, 72.58; H, 6.81; N, 9.40. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%); δ_H (300MHz; $CDCl_3$) 1.6-1.7 (2H, br m, cyclopentyl H's), 1.8-2.1 (6H, br m, cyclopentyl H's), 3.90 (3H, s, OMe), 4.84 (1H, br m, OCHCH$_2$), 6.91 (1H, d, J 16Hz, CH=CH), 6.92 (1H, d, J 8.3 Hz, ArH ortho to OMe), 7.1-7.2 (2H, m, 2x ArH meta to OMe), 7.31 (1H, dd, J 5.3, 1.3 Hz, pyridine H_5), 7.81 (1H, d, J 16 Hz,CH=CH), 8.65 (1H, d, J 5.3 Hz, pyridine H_6), and 9.14 (1H, d, J 1.3Hz, pyridine H_2); m/z 296 (M^+, 18%), 228 (26), 227 (100), 213 (6), 212 (7), and 41 (9).

EXAMPLE 7

a) **(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine**

Intermediate 4a) was dissolved in toluene (50ml) containing 4-toluenesulphonic acid (0.1g) and the mixture heated to reflux in a Dean-Stark apparatus for 2h. The cooled reaction mixture was poured into saturated sodium hydrogen carbonate solution (25ml) and extracted with dichloromethane (1x50ml, 1x25ml). The organic extract was dried ($MgSO_4$), concentrated in vacuo and the residue subjected to chromatography (SiO_2; Et_2O-hexane, 1:1) to afford the title compound (370mg). (Found: C, 72.75; H, 6.78; N, 9.23. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, (CH$_2$)$_4$), 3.85 (3H, s, OMe), 4.82 (1H, br m, OCH), 6.75-7.7 (7H, br m, ArH ortho to OMe + 2x ArH meta to OMe + CH=CH + pyridazine H_3, H_5), 8.95 (1H, dd, J 4.3, 1.4 Hz, pyridazine H_6);

The following compounds were prepared in a manner similar to the compound of Example 7a.

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

From Intermediate 4b). The crude product was subjected to chromatography (SiO_2; EtOAc) to afford the title compound (7.47g) as pale yellow needles m.p. 108-108.5°C (from Et_2O-hexane). (Found: C, 76.92; H, 7.12; N, 4.88. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, (CH$_2$)$_4$), 3.84 (3H, s, OMe), 4.81

(1H, br m, OCHCH$_2$), 6.77 (1H, d, J 15.8 Hz, CH=CH), 6.81 (1H, d, J ca. 9 Hz, ArH ortho to OMe), 6.95-7.1 (3H, m, ArH meta to OMe + CH=CH), 7.28 (2H, dd, J 4.7, 1.6 Hz, pyridine H$_3$, H$_5$), and 8.49 (2H, dd , J 4.7, 1.6 Hz, pyridine H$_2$, H$_6$); m/z 295 (M$^+$, 35%), 228 (20), 227 (100), 226 (86), 198 (34), 184 (23), 167 (12), 166 (16), 154 (10), and 41 (20).

c) **(E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrazine**

From Intermediate 4c). The crude product was subjected to chromatography (SiO$_2$; Et$_2$O-hexane, 1:1) to afford the title compound (0.80g) as a pale brown solid m.p. 81-83°C. (Found: C, 72.94; H, 6.78; N, 9.23. $C_{18}H_{20}N_2O_2$ requires C, 72.94; H, 6.80; N, 9.45%); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, (CH$_2$)$_4$), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.81 (1H, d, J 8.8 Hz, ArH ortho to OMe), 6.93 (1H, d, J 15.9 Hz, CH=CH), 7.0-7.15 (2H, m, 2xArH meta to OMe), 7.63 (1H, d, J 15.9 Hz, CH=CH), and 8.25-8.60 (3H, m, pyrazine H$_3$, H$_5$, H$_6$).

d) **(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-propenyl] pyridine**

From Intermediate 7 (1g) using 10% NaOH solution (25ml). Chromatography (SiO$_2$; dichloromethane) followed by recrystallisation (hexane) afforded a mixture of (Z)- title compound, 4-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)propenyl]pyridine, and the title compound (247mg) as white needles m.p. 78-79°C. Found C, 77.64; H, 7.58; N, 4.41 $C_{20}H_{23}NO_2$ requires C, 77.63; H, 7.49; N, 4.52%). δ_H (80 MHz; $CDCl_3$) 1.6-2.0 (8H, br m, (CH$_2$)$_4$), 2.26 (3H, d, J 1.3Hz, CH$_3$), 3.85 (3H, s, OMe), 4.75-4.85 (1H, m, OCHCH$_2$), 6.60-7.21 (6H, m, ArH + PyH$_3$, H$_5$ + C=CH), and 8.52 (2H, br d, PyH$_2$, H$_6$). m/z (EI) 309 (M$^+$, 30%), 241 (100), 222 (21), and 212 (29).

e) **(E)-4-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-propenyl]} pyridine hydrochloride**

From Intermediate 3d (0.40g, 1.22mmol). Purification by column chromatography (SiO$_2$; EtOAc) afforded the title compound free base which was dissolved in Et$_2$O and treated with ethanolic HCl to give the title compound as a fine yellow precipitate. m.p. 197.1 - 200.6°C. (Found: C, 69.12; H, 6.92; N, 3.96 $C_{20}H_{23}NO$ HCl requires C, 69.45; H, 6.99; N,

4.05%). δ_H (80 MHz; $CDCl_3$) 1.6-2.0 (8H, br m, $(CH_2)_4$), 2.39 (3H, d, J 1.0Hz, CH_3), 3.87 (3H, s, OCH_3), 4.73-4.83 (1H, m, $OCHCH_2$), 6.93-7.0 (3H, m, ArH), 7.25 (1H, s, HC=C), 7.90 (2H, br d, PyH_3, H_5), and 8.65 (2H, br d, PyH_2, H_6). m/z (EI) 309 (M^+-HCl), 241 and 212.

EXAMPLE 8

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

A solution of sodium ethoxide [prepared from sodium (0.10g, 4.50mmol)] in ethanol (50ml) was added over 5 min to a stirred mixture of 4-pyridine carboxaldehyde (0.44g, 4.10mmol) and (3-cyclopentyloxy-4-methoxyphenyl)-methyltriphenylphosphonium chloride (2.00g, 4.08g) in ethanol (30ml). After 2h, the reaction mixture was concentrated in vacuo and the residue partitioned between EtOAc (75ml) and brine (50ml). The organic layer was separated, then dried ($MgSO_4$) and concentrated in vacuo. A ^1H n.m.r. spectrum indicated that the mixture consisted of a 3:2 mixture of (Z) : (E) title compound (and triphenylphosphine oxide). A portion (0.6g) of the mixture was subjected to chromatography (SiO_2; hexane to EtOAc) to afford pure (Z)-title compound (0.14g) as a pale yelow solid m.p. (Found: C, 77.18; H, 7.16; N, 4.63. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%); δ_H (300MHz; $CDCl_3$) 1.5-1.55 (2H, br m, cyclopentyl H's), 1.65-1.9 (6H, br m, cyclopentyl H's), 3.83 (3H, s, OMe), 4.44 (1H, br m, $OCHCH_2$), 6.40 (1H, d, J 12.2 Hz, CH=CH), 6.65-6.80 (4H, m, ArH ortho to OMe + 2xArH meta to OMe + CH=CH), 7.15 (2H, ca. d, J 6.0 Hz, pyridine H_2, H_6); m/z 295 (M^+, 22%), 228 (15), 227 (100), 226 (94), 198 (35), 184 (15), 166 (12), 43 (19), and 41 (29).

EXAMPLE 9

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(phenylmethyl) propenenitrile

A solution of Intermediate 5 (1.1g) in toluene (100ml) containing 4-toluenesulphonic acid (0.05g) was heated to reflux for 3h. The reaction mixture was partitioned between saturated sodium hydrogen carbonate solution (50ml) and dichloromethane (50ml). The organic phase was separated then dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to chromatography (SiO_2; Et_2O-hexane, 1:1) to afford the title compound (0.90g) as an off-white solid m.p. 111-112°C. (Found: C,

79.12; H, 7.00; N, 4.13. $C_{22}H_{23}NO_2$ requires C, 79.25; H, 6.95; N, 4.20%); δH ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.64 (2H, d, J 0.9Hz, $PhCH_2$), 3.83 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.78 (1H, d, J 8.3 Hz, ArH ortho to OMe), 6.82 (1H, d, J 0.9Hz, CH=CCN), 7.07 (1H, dd, J 8.6, 2.0Hz, ArH para to cyclopentyloxy), 7.2-7.3 (5H, ca. s, C_6H_5), and 7.50 (1H, d, J 1.8Hz, ArH ortho to cyclopentyloxy); m/z 333 (M^+, 16%), 266 (19), 265 (100), 264 (25), 222 (11), 137 (11), 115 (14), and 41 (13).

EXAMPLE 10

(E) and (Z) isomers of 3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4,5-dichloro-1-imidazolyl) propenenitrile (from Intermediate 1a)

4,5-dichloroimidazol-1-yl acetonitrile (purified by dissolution in CH_2Cl_2, containing florisil and SiO_2) (2.99g, 0.016mol) in THF (5ml) was added to a solution of LDA [made from diisopropylamine (190ml, 0.0135mol) and n-butyllithium (10.60ml)] in THF at 0°C. 3.75g of Intermediate 1a was added The reaction mixture was stirred at 0°C. for ca 30min, filtered and concentrated to dryness. Purification by column chromatography (SiO_2; EtOAc-hexane, 1:3) gave (1) (Z) title compound (0.218g) after trituration in hexane as a yellow solid m.p. 87.8-88.8 (Found: C, 57.05; H, 4.48; N, 10.96 $C_{18}H_{17}O_2N_3Cl_2$ requires C, 57.16; H, 4.53; N, 11.11%). δH (80MHz; $CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.84 (3H, s, OCH_3), 4.3-4.4 (1H, m, $OCHCH_2$), 6.00 (1H, s, ArH), 6.77 (2H, br s, ArH), 7.33 (1H, s, HC=C or imid CH), and 7.42 (1H, s, HC=C or imid CH). m/z (EI) 379 (M^+, 3%), 377 (5), 308 (10), 276 (11), 275 (13), 274 (41), 273 (28), 247 (11), 242 (100), 230 (22), and 214 (10).

(2) (E) title compound (0.189g) as pale yellow crystals m.p. 129.3-131.9 (from EtOH). (Found: C, 57.08; H, 4.48; N, 10.92 $C_{18}H_{17}O_2N_3Cl_2$ requires C, 57.16; H, 4.53; N, 11,11%) δH (80 MHz; $CDCl_3$) 1.6-2.0 (8H, br m, $(CH_2)_4$), 3.91 (3H, s, OCH_3), 4.78-4.86(1H, m, $OCHCH_2$), 6.88 (1H, d, J 8.5Hz, ArH_5), 7.15-7.3 (2H, m, ArH), 7.51 (1H, s, imid CH), and 7.60 (1H, d, J 2.0Hz, HC=C). m/z (EI) 379 (M^+, 63%), 377 (88), 311 (27), 310 (12), 309 (39), 276 (33), 275 (27), 274 (96), 273 (35), and 242 (100).

EXAMPLE 11

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)2-(2,6-difluorophenyl) propenenitrile

To a solution of LDA [made from butyllithium (6.70ml, 0.010mol) and diisopropylamine (1.80ml, 0.012mol)] in THF at -10°C was added 2,6-difluorophenylacetonitrile (1.20ml, 9.70mmol). The solution became yellow. Left to stir at -10°C for ca 30min before adding chlorotrimethylsilane (1.30ml, 0.010mol). The solution became colourless. Left to stir at -10°C for ca 20min before cooling to -78°c and adding butyllithium (6ml; 9.6mmol)). The solution became light orange. Left to stir ca 15 min before adding Intermediate 1 (2.13g, 9.68mmol). The reaction mixture was left to warm to RT overnight, washed with saturated sodium bicarbonate solution, extracted with dichloromethane, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (SiO_2; Et_2O-hexane, 1:4) afforded the title compound (0.301g) as white crystals. m.p. 79.1-81°C (Found C, 70.80; H, 5.39; N, 3.93. $C_{21}H_{19}F_2NO_2$ requires C, 70.97; H, 5.39; N, 3.94%). δ_H (80MHz; $CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OCH_3), 4.18-4.9 (1H, m, $OCHCH_2$), 6.78-7.4 (6H, m, ArH + HC=C), and 7.74 (1H. d, J 2.1Hz, ArH). m/z (EI) 355 (M^+, 15%), 287 (100), 244 (15) and 84 (25).

EXAMPLE 12

Ethyl cis-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl) propenoate

A mixture of Intermediate 1 (26.62g; 0.12mol), ethyl-4-pyridylacetate (19.92g; 0.12mol; 1eq) and ammonium acetate (18.63g; 0.24g; 2eq) in glacial acetic acid (200ml) was stirred at 120°C under N_2 for 20 hours. The solution was cooled to room temperature and the acid removed *in vacuo* to give an orangey/brown residue. This residue was taken up in a saturated bicarbonate solution (to pH=8.5) and extracted several times with ethyl acetate. The combined organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness to give a yellow solid. Recrystallisation from toluene/hexane (1st crop) then toluene (2nd crop) followed by column chromatography (SiO_2; hexane-EtOAc/hexane: 7/3) gave the title compound m.p. 109-111°C as a white crystalline solid. δ_H ($CDCl_3$) 1.27 (3H, t, J 7.1 Hz, CH_2CH_3), 1.45-1.8 (8H, br m, cyclopentyl H's), 3.81 (3H, s, OMe), 4.16 (1H. br m, OCH), 4.25 (2H, q, J 7.1 Hz,

CH_2CH_3), 6.43 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloixy), 6.73 (1H, d, J 8.4 Hz, ArH ortho to OMe), 6.80 (1H, dd, J 2.0, 8.4 Hz, ArH para to cyclopentyloxy), 7.22 (2H, dd, J 1.6, 4.5 Hz, pyridine H_3, H_5), 7.83 (1H, s, HC = C) and 8.64 (2H, dd, J 1.6, 4.5 Hz, pyridine H_2, H_6).

An alternative procedure is as follows:

To a stirred solution of Intermediate 1 (22g; 100mmol) and ethyl-4-pyridyl-acetate (16.5g; 100mmol) in dry toluene (150ml) at room temperature was added glacial acetic acid (2.4ml) followed by piperidine (0.8ml). The solution was heated to reflux and the water produced removed as an azeotrope, collected by a Dean Stark Apparatus. After 16 hrs, the solution was allowed to cool to room temperature, charcoal and Florisil added, stirred for 5 minutes and then filtered. The solvent was removed by evaporation *in vacuo*. The crystalline solid obtained was dissolved in dichloromethane, washed with a saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered and the solvent removed by evaporation *in vacuo*. The product was recrystallised (diisopropyl ether) to give the title compound as a white crystalline solid, with melting point and NMR consistent with the above values.

EXAMPLE 13

(E)-1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl)ethene

Potassium tert.-butoxide (197mg, 1.75mmol, 1.2eq) was added to a solution of Intermediate 10(500mg, 1.46mmol) in THF at 0°C. The mixture was stirred for 5 min then a solution of 3-pyridinecarboxaldehyde (156mg, 1.46mmol) in THF (5ml) was added dropwise. After stirring at RT for 16h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between chloroform (10ml) and water (5ml), and the organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; EtOAc-hexane, 1:1) to afford the title compound (196mg) as a pale yellow oil; δ_H (80MHz; $CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.82 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.7-7.3 (6H, m, C_6H_3 + HC=CH + pyridine H_4), 7.73 (1H, m, pyridine H_5), 8.40 (1H, dd, J 4.5, 2.0Hz, pyridine H_6), and 8.64 (1H, d, J 2.0HZ, pyridine H_2).

The title compound (185mg) was dissolved in ethanol (5ml) and treated with Et_2O-HCl. The mixture was concentrated *in vacuo* and the residue recrystallised form chloroform-hexane to afford the title compound hydrochloride (173mg) as pale yellow crystals m.p. 177-181°C (300MHz; $CDCl_3$) 1.65-2.1 (8H, br m, $(CH_2)_4$), 3.91 (3H, s, OMe), 4.87 (1H, br m, OCH), 6.91 (1H, d, J 8.0 Hz, ArH ortho to OMe), 6.93 (1H, d, J 16.2Hz, CH=CH), 7.05-7.15 (2H, m, 2 x ArH meta to OMe), 7.2-7.3 (1H, m, pyridine H_4), 7.73 (1H, d, J 16.2Hz, CH=CH), 7.85 (1H, dd, J 7.5, 5.0Hz, pyridine H_5), 8.41 (1H, d, J 7.5HZ, pyridine H_6), 8.55 (1H, d, J 5.0Hz, pyridine H_2), and 8.87 (1H, br s, NH); m/z (EI) 295 (M^+-HCl, 49%), 228 (20), 227 (100), 226 (92), 207 (28), 198 (25), 180 (39), 41 (34), 38 (27), and 36 (85).

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.

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.

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
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

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 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.

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

Phosphodiesterase activity was assayed as follows. The reaction was 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 $MgCl_2$, 0.1µM [^{3}H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30^{o}C for between 5 to 30 min. The reaction was terminated by addition of 50µl 2% trifluoroacetic acid containing [^{14}C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [^{3}H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [^{3}H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing 10ml of scintillation cocktail. Recovery of [^{3}H]-5'AMP was determined using the [^{14}C]-5'AMP and all assays were conducted in the linear range of the reaction.

Compounds according to the invention such as compounds of the 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**

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 by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated 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).

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**

Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocyto-chalasin 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.

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.

4. **Relaxation of Constricted Airway Smooth Muscle in vitro**

The effects of compounds of the invention on guinea-pig isolated tracheal smooth muscle were investigated. Isolated tracheal rings were suspended in organ baths and immersed in oxygenated Krebs' solution. The smooth muscle was contracted with sub-maximal concentrations of histamine or carbachol prior to the addition of increasing concentrations of test compound to the organ baths. The most potent compounds of the Examples caused a concentration-dependent reversal of both histamine and carbachol-induced contractions at concentrations of 1nM to 100µM. The compounds were generally more potent in reversing histamine-induced tone than carbachol-induced tone.

5. **Effects on Cardiac Muscle in vitro**

Compounds of the invention have been tested for their effects on isolated cardiac muscle. Right atrial and papillary muscles were dissected out from the hearts of guinea pigs and suspended in organ baths for measuring the rate (chronotropic) of spontaneously beating atria and force (inotropic) of the electrically stimulated papillary muscle. In these preparations, selective PDE IV inhibitors such as rolipram do not have any direct effects whereas selective PDE III inhibitors such as milrinone have positive chronotropic and inotropic effects. The non-specific PDE inhibitor theophylline, which is used in asthma as a bronchodilator, also causes significant cardiovascular changes such as tachycardia. Selective PDE IV inhibitors have advantage over theophylline, therefore, through reduced cardiovascular side effects. The most potent and selective compounds of the Examples had no direct effects on the atrial and papillary muscles in vitro at concentrations up to 10µM but in combination with PDE III inhibitors, these inhibitors showed an enhancement of chronotropic and inotropic activity, typical of selective type IV inhibitors.

6. **Anti-inflammatory Activity in vivo**

Interleukin-5 (IL-5)-induced pleural eosinophilia in the rat (*Lisle, et al, 1993, Br.J. Pharmacol. 108, 230p*) is inhibited by compounds of the

Examples given orally at doses of 0.0001 to 10.0mg/kg. The most potent compounds cause a dose-dependent reduction in migrating eosinophils with ED_{50}s of 0.003 to 0.03mg/kg p.o.

Compounds of the invention also reduce the inflammatory responses induced in rats by platelet activating factor (PAF).

7. **Anti-allergic Activity in vivo**

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later and at six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

8. **Effects on Pulmonary Dynamics**

Compounds of the invention (0.001-10mg/kg by oral or other route of administration) reduce the allergic bronchoconstruction caused by antigen in sensitized guinea pigs.

Compounds of the invention have been tested for their effects on ozone-induced hyperreactivity of the airways of guinea pigs. Following the inhalation of ozone, guinea pigs become very much

more sensitive to the bronchoconstrictor effects of inhaled histamine than naive animals (*Yeadon et al, 1992, Pulmonary Pharm., 5, 39*). There is a pronounced shift to the left (10-30 fold) of the dose response curve to histamine and a highly significant increase in the maximum increase in pulmonary resistance. Compounds of the Examples administered 1h prior to ozone by the intraperitoneal or oral (0.001-10mg/kg) route caused a dose-dependent inhibition of ozone-induced hyperreactivity.

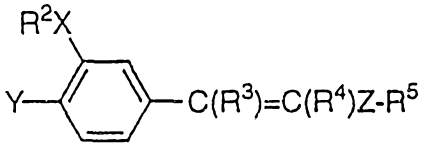
9. **Adverse Effects**

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

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

CLAIMS

1. A compound of formula (1)



(1)

wherein

Y is a halogen atom or a group $-OR^1$, wherein R^1 is an optionally substituted alkyl group;

X is -O-, -S-, or $-N(R^6)-$, wherein R^6 is a hydrogen atom or an optionally substituted alkyl group;

R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4 which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (wherein R^7 is a hydrogen atom, an optionally substituted alkyl, aralkyl or aryl group), $-CONR^8R^9$ (wherein R^8 and R^9, which may be the same or different, is as defined for R^7), $-CSNR^8R^9$, -CN or $-CH_2CN$ group;

Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

(but excluding:
methyl 3-[2-[3-cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate and 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic acid)

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

2. A compound according to Claim 1 wherein Y is a $-OR^1$ group.

3. A compound according to Claim 2 wherein R^1 is an optionally substituted straight or branched C_{1-3}alkyl group.

4. A compound according to Claim 3, where R^1 is a methyl group.

5. A compound according to any of Claims 1 to 4, wherein X is -O-.

6. A compound according to any of Claims 1 to 5 wherein R^2 is a cyclopentyl group.

7. A compound according to any of Claims 1 to 6 wherein Z is a $-(CH_2)_n$ group wherein n is zero, or an integer 1 or 2.

8. A compound according to Claim 7 wherein Z is a $-(CH_2)_n-$ group where n is zero.

9. A compound according to any of Claims 1 to 8 wherein R^3 is a hydrogen atom or a $-CH_3$ group.

10. A compound according to Claim 9 where R^3 is a hydrogen atom.

11. A compound according to any of Claims 1 to 10 wherein R^4 is a hydrogen atom or an optionally substituted alkyl or -CN group.

12. A compound according to Claim 11 wherein R^4 is a hydrogen atom or a -CN group.

13. A compound according to any of Claims 1 to 12 wherein R^5 is an optionally substituted C_{6-12}aryl group or a C_{3-9}heteroaryl group containing one, two, or three heteroatoms selected from -O-, -S- or -N- atoms.

14. A compound according to Claim 13 where R^5 is an optionally substituted phenyl, pyridyl, thienyl, imidazolyl, pyridazinyl or pyrimidinyl group.

15. A compound according to Claim 14 where R^5 is an optionally substituted phenyl or pyridyl group.

16. A compound according to Claim 15 where R^5 is a phenyl or a 2- or 3- monosubstituted or 2,6-disubstituted phenyl group.

17. A compound according to Claim 15 where R^5 is a 2-, 3- or 4- pyridyl group or a 3,5 disubstituted 4-pyridyl group.

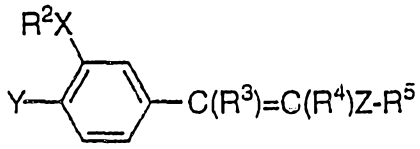
18. A compound according to any of Claims 13 to 17 wherein the aryl or heteroaryl group is substituted by one or two R^{10} substituents, where R^{10} is an atom or group R^{11} or $-Alk^1(R^{11})_m$ wherein R^{11} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-C(O)R^{7a}$, [where R^{7a} is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], $-SO_3H$, $-SO_2R^{7a}$, $SO_2N[R^{7a}R^{8a}]$, (where R^{8a} is as defined for R^{7a} and may be the same as or different to R^{7a}) $-CON[R^{7a}R^{8a}]$, $-NHSO_2R^{7a}$, $-N[SO_2R^{7a}]_2$, $-NHSO_2N[R^{7a}R^{8a}]$, $-NHC(O)R^{7a}$, or $-NHC(O)OR^{7a}$ group; Alk^1 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)p-, [where p is an integer 1 or 2] or $-N(R^6)-$ (where R^6 is a hydrogen atom or an optionally substituted alkyl group) groups; and m is zero or an integer 1, 2 or 3.

19. A compound according any of claims 13 to 17 wherein the aryl or heteroaryl group is substituted by one or two R^{10} substituents, where R^{10} is a halogen atom or a nitro, amino, alkoxy, haloalkyl, hydroxy, $-NHCOR^{7a}$, $-NHCONHR^{7a}$, or $-NHSO_2R^{7a}$ group.

20. A compound which is
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl) propenenitrile;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl) propenenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)2-(4,5-dichloro-1-imidazolyl)propenenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl) propenenitrile;

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl)propenenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl) propenenitrile;
(E)-4-{2-[1-(3-Cyclopentyloxy-4-methoxy)phenyl]-1-propenyl} pyridine;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)-propenenitrile;
N-{4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-pyridyl} phenylsulphonamide;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine;
(E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine; or
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine;
and the salts, solvates, hydrates and N-oxides thereof.

21. A pharmaceutical composition comprising a compound of formula (1)



(1)

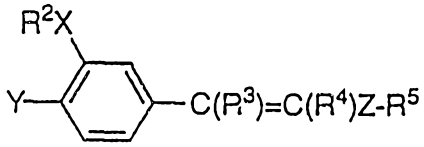
wherein
Y is a halogen atom or a group $-OR^1$, wherein R^1 is an optionally substituted alkyl group;
X is -O-, -S-, or $-N(R^6)-$, wherein R^6 is a hydrogen atom or an optionally substituted alkyl group;
R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;
R^3 and R^4 which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (wherein R^7 is a hydrogen atom, an optionally substituted alkyl, aralkyl or aryl

group), -CONR^{8}R^9 (wherein R^8 and R^9, which may be the same or different, is as defined for R^7), -CSNR^{8}R^9, -CN or -CH$_2$CN group;
Z is -(CH$_2$)$_n$- where n is zero or an integer 1, 2 or 3;
R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
(but excluding:
methyl 3-[2-[3-cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate and 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic acid)
and the salts, solvates, hydrates, progdrugs and N-oxides thereof, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

22. A composition according to Claim 21 in a form suitable for oral administration.

23. A composition according to Claim 22 where the form for oral administration is a tablet, lozenge or capsule.

24. A process for the preparation of a compound of formula (1)



(1)

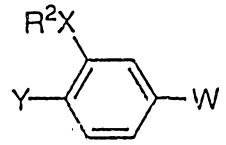
wherein
Y is a halogen atom or a group -OR^1, wherein R^1 is an optionally substituted alkyl group;
X is -O-, -S-, or -N(R^6)-, wherein R^6 is a hydrogen atom or an optionally substituted alkyl group;
R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4 which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, $-CO_2R^7$ (wherein R^7 is a hydrogen atom, an optionally substituted alkyl, aralkyl, or aryl group) $-CONR^8R^9$ (wherein R^8 and R^9, which may be the same or different, is as defined for R^7), $-CSNR^8R^9$, -CN or $-CH_2CN$ group;

Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
(but excluding:
methyl 3-[2-[3-cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate and 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic acid)
and the salts, solvates, hydrates, prodrugs and N-oxides thereof, which comprises:

i) reacting a compound of formula (3)



(3)

where

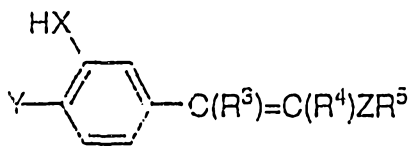
(a) W is a $-C(O)R^3$ group, where R^3 is as defined for formula (1) but is not a -CN or $-CH_2CN$ group, with a compound $R^5ZCH_2R^4$; or where

(b) W is a $-CH_2R^3$ group with an aldehyde or ketone R^5ZCOR^4, where R^4 is as just defined for R^3; or where

(c) W is a $-C(O)R^3$ group with a silane derivative $Alk_3SiCH(R^4)(R^5)$ (where Alk is an alkyl group)

in the presence of a base or an acid in a suitable solvent.

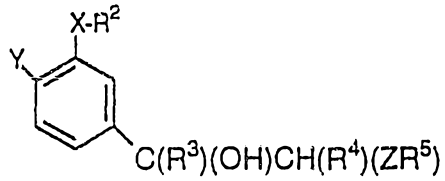
ii) alkylating a compound of formula (5)



(5)

with a halide R^2Hal, or with an alcohol R^2OH;

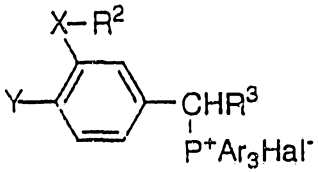
iii) dehydrating an alcohol of formula (6)



(6)

using an acid at an elevated temperature;

iv) reacting a phosphonium salt



where Ar is an aryl group and Hal is a halogen atom with a compound R^5ZCOR^4; or

v) interconverting a compound of formula (1) to yield another compound of formula (1).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/00452

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C255/36 A61K31/275 A61K31/33 C07D213/57 C07D213/61
C07D333/24 C07D213/30 C07D233/26 C07D237/14 C07D237/24
C07D239/10 C07D241/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 00968 (SMITHKLINE BEECHMAN CORPORATION) 23 January 1992 see page 4, line 1 - page 5, line 16 see claims; examples	1

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 1994	-3. 06. 94

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 94/00452

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9200968	23-01-92	AU-A-	8229291	04-02-92
		CA-A-	2086741	11-01-92
		EP-A-	0538384	28-04-93
		JP-T-	6501679	24-02-94
		CN-A-	1060652	29-04-92