Compounds of formula (1) are described wherein Y is a halogen atom, or a -XR^8 group where X is -O-, -S(O)_{n=1}-, where m is zero or an integer of value 1 or 2, or -N(R^b)- where R^b is a hydrogen atom or an optionally substituted alkyl group and R^8 is a hydrogen atom or an optionally substituted alkyl group; Z is a group -XR^2 where R^2 is an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl or heterocycloalkyl group; -C(R^3)-C(R^4)(R^5) where R^3 is a hydrogen or fluorne atom or a methyl group, and R^4 and R^5 which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkoxy, alkylthio, -CO_2R^9 where R^9 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group, -CONR^{10}R^{11} where R^{10} and R^{11}, which may be the same or different, is each as defined for R^2, -CSNR^{10}R^{11}, -CN or -NO_2 group, or R^7 and R^8 together with the carbon atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloalkyl group or -[CH(R^9)]_nCH(R^9)(R^8) where n is zero or the integer 1; R^2 is a hydrogen or a fluorine atom, an optionally substituted alkyl group, or a hydroxyl group; R^3 is a hydrogen or a fluorine atom, or an optionally substituted alkyl group; R^4 is a hydrogen or a fluorine atom, an optionally substituted alkyl group or an OR group where R^5 is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkynol, formyl, carbamido or thiocarbamido group; Ar is an optionally substituted monocylic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; Ar is a monocylic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; R^1 is a group -N(R^{12})C(-NC)NHR^{13} where R^{12} is a hydrogen atom or a C_1-salkyl group and R^{13} is a hydrogen atom, a C_1-salkyl group or an optionally substituted phenyl or phenyl(C_1-salkyl group), -N(R^{12})C(-NC)S(R^{13})_2, N(R^{12})(C(-CHNO_2))NHR^{13} or -N(R^{12})(C(-CHNO_2))SR^{13}; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. The compounds are metabolically stable phosphodiesterase type IV inhibitors and are of use in the prophylaxis and treatment of diseases such as asthma where an unwanted inflammatory response or muscular spasm is present.
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TRIARYLETHANES USEFUL AS PDE IV INHIBITORS

This invention relates to a novel series of triarylethanis, 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 mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell 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 spasmodylotic 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.

In our International Patent Specifications Nos. WO 94/14742, WO 95/35281 and WO 95/35283 we describe triarylethanes which are potent inhibitors of the PDE IV isoenzyme at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. The compounds are of use in medicine, especially in the prophylaxis and treatment of asthma.
We have now found a particular series of triarylethenes which are potent and selective PDE IV inhibitors and which also have other advantageous pharmacological properties, including especially improved metabolic stability.

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

\[
\begin{align*}
\text{Y} & \text{C(}R^2\text{)C(}R^3\text{)(}R^4\text{)Ar}^1
\end{align*}
\]

wherein
-\( Y \) is a halogen atom, or a \(-XR^a\) group where \( X \) is \(-O-, -S(O)\)\(_m^\cdot\) [where \( m \) is zero or an integer of value 1 or 2], or \(-N(R^b)\)\(-\) [ where \( R^b \) is a hydrogen atom or an optionally substituted alkyl group] and \( R^a \) is a hydrogen atom or an optionally substituted alkyl group;
-\( Z \) is a group \(-XR^5 \) [where \( R^5 \) is an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl or heterocycloalkyl group], \(-C(R^5)=C(R^7)(R^8)\) [where \( R^6 \) is a hydrogen or fluorine atom or a methyl group, and \( R^7 \) and \( R^8 \), which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkoxy, alkylthio, \(-CO_2R^9\) [where \( R^9 \) is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], \(-CONR^{10}R^{11}\) [where \( R^{10} \) and \( R^{11} \), which may be the same or different, is each as defined for \( R^9 \)], \(-CSNR^{10}R^{11}\), \(-CN \) or \(-NO_2 \) group, or \( R^7 \) and \( R^8 \) together with the carbon atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloalkyl group] or \([-\text{CH(}R^5\text{)\text{nCH(}R^7\text{)(}R^8\text{)}\text{) where } n \text{ is zero or the integer 1};
-\( R^2 \) is a hydrogen or a fluorine atom, an optionally substituted alkyl group, or a hydroxyl group;
-\( R^3 \) is a hydrogen or a fluorine atom, or an optionally substituted alkyl group;
R⁴ is a hydrogen or a fluorine atom, an optionally substituted alkyl group or an OR⁵ group where R⁵ is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group;

Ar¹ is an optionally substituted monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected form oxygen, sulphur or nitrogen atoms;

Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

R¹ is a group -N(R¹²)C(=NCN)NHR¹³ [where R¹² is a hydrogen atom or a C₁₋₃ alkyl group and R¹³ is a hydrogen atom, a C₁₋₃ alkyl group or an optionally substituted phenyl or phenylC₁₋₃ alkyl group], -N(R¹²)C(=NCN)SR¹³, N(R¹²)C(=CHNO₂)NHR¹³ or -N(R¹²)C(=CHNO₂)SR¹³;

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

It will be appreciated that certain compounds of formula (1) may have one or more chiral centres, depending for example on the nature of the groups Z, R², R³ and R⁴. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. The compounds of the invention also exist as geometric isomers and the invention is to be understood to extend to all such isomers and mixtures thereof.

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

R⁸ in the compounds of formula (1) may be, for example, a hydrogen atom or an optionally substituted straight or branched alkyl group, for example, an optionally substituted C₁₋₆ alkyl group, such as a methyl, ethyl, n-propyl or i-propyl group. Optional substituents which may be present on R⁸ groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms. Particular R⁸ groups include for example -CH₂F, -CH₂Cl, -CHF₂, -CHCl₂, -CF₃ or -CCl₃ groups.
In compounds of formula (1), X may be an oxygen or a sulphur atom, or a group \(-S(O)\), \(-S(O)_2\), \(-NH\) or \(C_{1-6}\) alkylamino, for example a \(C_{1-3}\) alkylamino, e.g. methylamino \([-N(CH_3)]\) or ethylamino \([-N(C_2H_5)]\) group.

5 Alkyl groups represented by \(R^5\), \(R^7\) or \(R^8\) in the compounds of formula (1) include optionally substituted straight or branched \(C_{1-6}\) alkyl groups. Particular examples include \(C_{1-3}\) alkyl groups such as methyl or ethyl groups. Optional substituents on these groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxy or \(C_{1-6}\) alkoxy e.g. \(C_{1-3}\) alkoxy such as methoxy or ethoxy or \(-CO_2R^9\), \(-CONR^{10}R^{11}\), \(-CSNR^{10}R^{11}\) or \(-CN\) groups. Particular examples of substituted alkyl groups include \(-CH_2F\), \(-CH_2Cl\), \(-CHF_2\), \(-CHCl_2\), \(CF_3\) or \(-CCl_3\) groups.

10 Alkenyl groups represented by \(R^5\), \(R^7\) or \(R^8\) in the compounds of formula (1) include optionally substituted straight or branched \(C_{2-6}\) alkenyl groups optionally interrupted by one or more \(-O\), \(-S(O)_m\) and/or \(-N(R^b)\) atoms or groups. Particular examples include ethenyl, propen-1-yl and 2-methylpropen-1-yl groups. Optional substituents include those described above in relation to alkyl groups represented by the groups \(R^5\), \(R^7\) or \(R^8\).

15 When \(R^7\) or \(R^8\) in compounds of formula (1) is an alkoxy or alkylthio group it may be for example an optionally substituted straight or branched \(C_{1-6}\) alkoxy or \(C_{1-6}\) alkylthio group optionally interrupted by one or more \(-O\), \(-S(O)_m\) and/or \(-N(R^b)\) atoms or groups. Particular examples include \(C_{1-3}\) alkoxy, e.g. methoxy or ethoxy, or \(C_{1-3}\) alkylthio e.g. methylthio or ethylthio groups. Optional substituents include those described above in relation to alkyl groups represented by the groups \(R^7\) or \(R^8\).

20 When \(R^5\) is, or \(R^7\) and \(R^8\) together with the carbon atom to which they are attached are, a cycloalkyl or cycloalkenyl group, the group 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-cyclo-buten-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
of said groups being optionally substituted by one, two or three
substituents selected from halogen atoms, e.g. fluorine, chlorine,
bromine or iodine atoms, straight or branched C1-6alkyl e.g. C1-3alkyl
such as methyl or ethyl, hydroxyl or C1-6alkoxy e.g. C1-3alkoxy such as
methoxy or ethoxy groups. Examples of heterocycloalkyl groups
represented by R5, and R7 and R8 together, include C3-8heterocycloalkyl
groups such as tetrahydrofuranyl or pyrrolidinyl groups. Such groups may
be substituted by one, two or three substituents as just described for
cycloalkyl and cycloalkenyl groups represented by R5, R7 and R8.

When R7 or R8 is a -CO2R9, -CONR10R11 or CSNR10R11 group or such a
group is present as a substituent in compounds of formula (1) it may be for
example a -CO2H, -CONH2 or -CSNH2 group or a group -CO2R9
-CNR10R11, -CSNR10R11, -CONHR11, or -CSNHR11 where R9, R10 and
R11 where present is a C1-3alkyl group such as methyl or ethyl group, a
C6-12aryl group, for example an optionally substituted phenyl, or a 1- or 2-
naphthyl group, or a C6-12aryl/C1-3alkyl group such as an optionally
substituted benzyl or phenethyl group. Optional substituents which may
be present on these aryl groups include R16 substituents discussed below
in relation to the group Ar1.

When the group R4 in compounds of formula (1) is an ORc group it may
be for example a hydroxyl group or a group -ORc where Rc is an optionally
substituted straight or branched C1-6alkyl group, e.g. a C1-3alkyl group
such as a methyl or ethyl group, a C2-alkenyl group such as an ethenyl or
2-propen-1-yl group, a C1-3alkoxyC1-3alkyl group such as a methoxy-
methyl, ethoxymethyl or ethoxyethyl group, a C1-6alkanoyl, e.g. C1-
3alkanoyl group such as an acetyl group, or a formyl [HC(O)-],
carboxamidoc (CONR14R15) or thiocarboxamido (CSNR14R15) group,
where R14 and R15 in each instance may be the same or different and is
each a hydrogen atom or an optionally substituted straight or branched C1-
6alkyl, e.g. C1-3alkyl group such as methyl or ethyl group. Optional
substituents which may be present on such Rc, R14 or R15 groups include
those described below in relation to the alkyl groups R3 or R4.
Alkyl groups represented by R², R³ or R⁴ in compounds of formula (1) include optionally substituted straight or branched C₁₋₆ alkyl groups, e.g. C₁₋₃ alkyl groups such as methyl, ethyl, n-propyl or i-propyl groups. Optional substituents which may be present on these groups include one or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁₋₆ alkoxy e.g. C₁₋₃ alkoxy such as methoxy or ethoxy groups.

Monocyclic or bicyclic aryl groups represented by the group Ar or Ar¹ in compounds of formula (1) include for example C₆₋₁₂ aryl groups, for example phenyl, 1- or 2-naphthyl, indenyl or isoindenyl groups. In the case of the group Ar¹, such groups may be optionally substituted, for example as described below.

When the monocyclic or bicyclic aryl group Ar or Ar¹ contains one or more heteroatoms, Ar or Ar¹ may be for example a C₁₋₉ heteroaryl group containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, Ar or Ar¹ 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. Bicyclic heteroaryl groups include for example nine- or ten- membered heteroaryl groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms. Ar¹ heteroaryl groups of these types may be optionally substituted, for example as described below.

Examples of heteroaryl groups represented by Ar or Ar¹ include pyrrolyl, furyl, thieryl, 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, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinazoliny1, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinoliny1, isoquinoliny1, tetrazolyl, 5,6,7,8-tetra-
hydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl. Example of bicyclic heteroaryl groups include quinolinyl or isoquinolinyl groups.

The heteroaryl group represented by Ar or Ar' 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 group Ar or Ar' 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. In another example, when the group Ar or Ar' is a quinolinyl group it may be a 2-, 3-, 4-, 5-, 6-, 7- or 8- quinolinyl and when it is an isoquinolinyl, it may be a 1-, 3-, 4-, 5-, 6-, 7- or 8- isoquinolinyl group.

When in compounds of formula (1) the Ar or Ar' 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 group Ar or Ar' is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

The ary1 or heteroaryl groups represented by Ar' in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents R'. The substituent R' may be selected from an atom or group R' wherein R' is a halogen atom, an amino (-NH2), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO2H), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)Alk, -SO3H, -SO2Alk2 -SO2NH2, -SO2NAlk, -SO2N[Alk]2, -CONH2, -CONHAlk, CON[Alk]2, -NHSO2H, -NAlkSO2H, -NHSO2Alk, -NAlkSO2Alk, -N[SO2Alk]2, -NHSO2NH2, -NAlkSO2NH2, -NHSO2NAlk, -NAlkSO2NAlk, -NHSO2N[Alk]2, -NAlkSO2N[Alk]2, -NHC(O)H, -NHC(O)Alk, -NAlkC(O)H, -NAlkC(O)Alk, -N[C(O)Alk]2, -NHC(O)OH, -NHC(O)OAlk, -NAlkC(O)OH, -NAlkC(O)OAlk, -NHCONH2, -NHCONAlk, -NHCON[Alk]2, -NAlkCON[Alk]2, -NAlkCONH[Alk], -NAlkCONH2, -C(S)H, -C(S)Alk, -CSNH2, -CNSNHAlk, -CSN[Alk]2, -NHC(S)H, -NHCSAlk, -NAlkC(S)H, -NAlkC(S)Alk, -N[C(S)Alk]2, -N[C(O)Alk]SO2H, -NHCSNH2,
-NHCSNHAI\text{lk}, -NHCSN[Alk]_2, -N\text{AIk}CSN[Alk]_2, -N\text{AIk}CSNHAI\text{lk},
-N\text{AIk}CSNH_2, or -N[C(O)\text{Alk}]SO_2\text{Alk} group; Alk 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)\text{p}-, [where p is
an integer 1 or 2] or -N(R^b)- groups; and m is zero or an integer 1, 2 or 3.

When in the group -\text{Alk}(R^{17})_m m is an integer 1, 2 or 3, it is to be
understood that the substituent or substituents R^{17} may be present on any
suitable carbon atom in -\text{Alk}. Where more than one R^{17} substituent is
present these may be the same or different and may be present on the
same or different carbon atom in Alk. Clearly, when m is zero and no
substituent R^{17} is present or when Alk forms part of a group such as
-SO_2\text{Alk} the alkylene, alkenylene or alkynylene chain represented by Alk
becomes an alkyl, alkenyl or alkynyl group.

When R^{17} is a substituted amino group it may be a group -\text{NH}[\text{Alk}(R^{17a})_m]
[where \text{Alk} and m are as defined above and R^{17a} is as defined above for
R^{17} but is not a substituted amino, a substituted hydroxyl or a substituted
thiol group] or a group -N[\text{Alk}(R^{17a})_m]_2 wherein each -\text{Alk}(R^{17a})_m group is
the same or different.

When R^{17} is a halogen atom it may be for example a fluorine, chlorine,
bromine, or iodine atom.

When R^{17} is a cycloalkoxy group it may be for example a C_5-7cycloalkoxy
group such as a cyclopentylxylo or cyclohexyloxy group.

When R^{17} is a substituted hydroxyl or substituted thiol group it may be a
group -O\text{Alk}(R^{17a})_m or -S\text{Alk}(R^{17a})_m respectively, where \text{Alk}, R^{17a} and m
are as just defined.

Esterified carboxyl groups represented by the group R^{17} include groups of
formula -CO_2\text{Alk}^1 wherein \text{Alk}^1 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, \text{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 C₆₋₁₂aryl group such as an optionally
substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl
group such as an optionally substituted phenyloxyethyl, phenyloxyethyl,
1-naphthloxyethyl, or 2-naphthloxyethyl group; an optionally
substituted C₁₋₈alkanoxyloxyC₁₋₈alkyl group, such as a pivaloyloxyethyl,
propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroxyloxyC₁₋₈alkyl
group such as an optionally substituted benzoyloxyethyl or benzoyloxy-
propyl group. Optional substituents present on the Alk¹ group include R¹⁶
substituents described above.

Particular examples of the chain Alk when present include methylene,
ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-utylene, ethylene, 2-propylene, 2-butenylene, 3-butenylene,
ethynylene, 2-propynylene, 2-butyne or 3-butyne chain, optionally
interrupted by one, two, or three -O- or -S-, atoms or -S(O) -, -S(O)₂-
or -N(Rᵇ)- groups.

Particularly useful atoms or groups represented by R¹⁶ include fluorine,
chlorine, bromine or iodine atoms, or C₁₋₈alkyl, e.g. methyl or ethyl,
C₁₋₈alkylamino, e.g. methylamino or ethylamino, C₁₋₈ hydroxyalkyl, e.g.
hydroxymethyl or hydroxyethyl, C₁₋₈alkylthiol e.g. methylthiol or ethylthiol,
C₁₋₈alkoxy, e.g. methoxy or ethoxy, C₅₋₇cycloalkoxy, e.g. cyclopentylloxy,
haloC₁₋₈alkyl, e.g. trifluoromethyl, C₁₋₈alkylamino, e.g. methylamino or
ethylamino, amino (-NH₂), aminoC₁₋₈alkyl, e.g. aminomethyl or aminoethyl,
C₁₋₈dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano,
hydroxyl (-OH), formyl [HC(O)⁻], carboxyl (-CO₂H), -CO₂Alk¹ [where Alk¹ is
as defined above], C₁₋₆ alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g.
thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₈alkylsulphonyl, e.g.
methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₈alkylaminosulphonyl,
e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₈dialkylaminosulphonyl,
e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NHSO₂H),
C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonyl-
amino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethyl-
sulphonylamino, aminosulphonylamino (\(-\text{NH}_2\text{SO}_2\text{NH}_2\)), \(\text{C}_1\text{-alkylamino-sulphonylamino}\), e.g. methylaminosulphonylamino or ethylaminosulphonylamino, \(\text{C}_1\text{-dialkylamino-sulphonylamino}\), e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, \(\text{C}_1\text{-alkanoylamino}\), e.g. acetylamo, \(\text{C}_1\text{-alkanoylamino}\text{C}_1\text{-alkyl}\), e.g. acetylaminoethyl or \(\text{C}_1\text{-alkoxy carbonylamino}\), e.g. methoxy carbonylamino, ethoxy carbonylamino or t-butoxycarbonylamino thiocarboxamido (\(-\text{CSNH}_2\)), \(\text{C}_1\text{-alkylamino-thiocarbonyl}\), e.g. methylaminothiocarbonyl or ethylaminothiocarbonyl, \(\text{C}_1\text{-dialkylaminothiocarbonyl}\), e.g. dimethylaminothiocarbonyl or diethylaminothiocarbonyl, \(\text{aminocarbonylamino}\), \(\text{C}_1\text{-alkylaminocarbonylamino}\), e.g. methylaminocarbonylamino or ethylaminocarbonylamino, \(\text{C}_1\text{-dialkylaminocarbonylamino}\), e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, \(\text{aminothiocarbonylamino}\), \(\text{C}_1\text{-alkylaminothiocarbonylamino}\), e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, \(\text{C}_1\text{-6 dialkylaminothiocarbonylamino}\), e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, \(\text{C}_1\text{-alklaminothiocarbonylamino}\), e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, \(\text{aminocarbonylCl}_1\text{-alkyl-amino}\), e.g. aminocarbonylmethylamino or aminocarboxylethylamino, \(\text{aminothiocarbonylCl}_1\text{-alkylamino}\), e.g. aminothiocarbonylmethylamino or aminothiocarboxylethylamino, \(\text{formylaminoC}_1\text{-alkylsulphonylamino}\), e.g. formylaminomethylsulphonylamino or formyl-aminoethylsulphonylamino, \(\text{thioformylaminoC}_1\text{-alkylsulphonylamino}\), e.g. thioformylaminomethylsulphonylamino or thioformylethylsulphonylamino, \(\text{C}_1\text{-acylamino-sulphonylamino}\), e.g. acetylaminosulphonylamino, \(\text{C}_1\text{-thio-acylamino-sulphonylamino}\), e.g. thioacetylaminosulphonylamino groups.

Where desired, two \(\text{R}^{16}\) substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a \(\text{C}_2\text{-alkylenedioxy}\) group such as ethylenedioxy.

It will be appreciated that where two or more \(\text{R}^{16}\) substituents are present, these need not necessarily be the same atoms and/or groups. The \(\text{R}^{16}\) 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 \(\text{Ar}\) or \(\text{Ar}^1\) 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 group $R^1$ in compounds of formula (1), when the group $R^{12}$ and/or $R^{13}$ is a C$_{1-3}$alkyl group it may be a straight or branched C$_{1-3}$alkyl group selected from a methyl, ethyl, n-propyl or i-propyl group. Phenyl C$_{1-3}$alkyl groups represented by the group $R^{13}$ include benzyl or phenethyl groups. These and other phenalkyl or phenyl groups represented by $R^{13}$ may be optionally substituted by one, two or more halogen atoms, e.g. chlorine, bromine, iodine or fluorine atoms or C$_{1-3}$alkyl e.g. methyl or ethyl, or C$_{1-3}$alkoxy, e.g. methoxy or ethoxy, groups.

Particular examples of $R^1$ groups include -NHC(=NCN)NHR$^{13}$, -NHC(=NCN)SR$^{13}$, -NHC(=CHNO$_2$)NHR$^{13}$ or -NHC(=CHNO$_2$)SR$^{13}$ groups, especially those wherein $R^{13}$ is a methyl, ethyl, benzyl or substituted benzyl group containing one or two halogen, C$_{1-3}$alkyl or C$_{1-3}$alkoxy substituents as just described.

In general, the groups represented by $R^1$ may be attached to the Ar group through any available ring carbon atom.

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

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

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.
Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or aminos, which are convertible \textit{in vivo} by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

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

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

\(\text{Z}\) in the compounds of formula (1) is preferably a group \(\text{XR}^5\). In compounds of this type \(\text{X}\) is especially an oxygen atom. The group \(\text{R}^5\) is in particular an optionally substituted \(\text{C}_{1-3}\)alkyl group, especially a methyl, \(-\text{CH}_2\text{F}\) or \(-\text{CHF}_2\) group, or a \(\text{C}_{3-8}\)cycloalkyl group, especially a cyclobutyl or cyclopentyl group.

Particularly useful \(\text{Ar}\) or \(\text{Ar}^1\) groups in compounds of formula (1) include those groups in which \(\text{Ar}\) or \(\text{Ar}^1\) is a monocyclic aryl group such as a phenyl group optionally containing one or more heteroatoms selected from oxygen, sulphur, or, in particular, nitrogen atoms. In these compounds, when the group represented by \(\text{Ar}\) or \(\text{Ar}^1\) is a heteroaryl group it is preferably a nitrogen-containing monocyclic heteroaryl group, especially a six-membered nitrogen-containing heteroaryl group. Thus, in one preferred example, the groups \(\text{Ar}\) and \(\text{Ar}^1\) may each be a nitrogen-containing heteroaryl group. In another preferred example \(\text{Ar}\) may be a monocyclic aryl group or a monocyclic or bicyclic heteroaryl group containing one or more oxygen, sulphur or nitrogen atoms and \(\text{Ar}^1\) may be an optionally substituted six-membered nitrogen-containing \(\text{Ar}^1\) heteroaryl group. In these examples, the six-membered nitrogen-containing \(\text{Ar}^1\) heteroaryl group may be an optionally substituted pyridyl, pyridazinyl,
pyrimidinyl, pyrazinyl or imidazolyl group. Particular examples include optionally substituted 2-pyridyl, 3-pyridyl, 5-imidazolyl, or, especially, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl or 3-pyrazinyl. The monocyclic aryl group may be a phenyl group, and the monocyclic or bicyclic heteroaryl group containing one or more oxygen, sulphur or nitrogen atoms may be an optionally substituted 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 2-benzo(b)thiophenyl, 2-benzo(b)furyl or 4-isoquinolinyl group.

In general in compounds of formula (1) when Ar\(^1\) is a substituted phenyl group it may be for example a mono-, di- or trisubstituted phenyl group in which the substituent is an atom or group R\(^{16}\) as defined above. When the group is a monosubstituted phenyl group the substituent may be in the 2-, or preferably 3-, or especially 4-position relative to the ring carbon atom attached to the remainder of the molecule. When the Ar\(^1\) group is a disubstituted phenyl group, the substituents may be in the 2,6 position relative to the ring carbon atom attached to the remainder of the molecule.

Particularly useful substituents R\(^{16}\) which may be present on Ar\(^1\) groups, especially on phenyl groups, include halogen atoms or alkyl, haloalkyl, amino, substituted amino, nitro, -NHSO\(_2\)NH\(_2\), -NHSO\(_2\)NHCH\(_3\), -NHSO\(_2\)N(CH\(_3\))\(_2\), -NHC\(_2\)CH\(_3\), -NHC(O)NH\(_2\), -NCH\(_3\)C(O)NH\(_2\), -NHC(O)NHCH\(_3\), -NHC(O)NHCH\(_2\)CH\(_3\), or -NHC(O)N(CH\(_3\))\(_2\) groups, each of said atoms or groups being optionally separated from the remainder of the Ar\(^1\) group by a group Alk as defined above.

When in compounds of formula (1) Ar\(^1\) a substituted pyridyl group it may be for example a mono- or disubstituted pyridyl group, such as a mono- or dissubstituted 2-pyridyl, 3-pyridyl or especially 4-pyridyl group substituted by one or two atoms or groups R\(^{16}\) as defined above, in particular one or two halogen atoms such as fluorine or chlorine atoms, or methyl, methoxy, hydroxyl or nitro groups. Particularly useful pyridyl groups of these types are 3-monosubstituted-4-pyridyl or 3,5-disubstituted-4-pyridyl, or 2- or 4-monosubstituted-3-pyridyl or 2,4-disubstituted-3-pyridyl groups.
A particular class of compounds according to the invention has the formula (1) wherein Ar is a phenyl group. In compounds of this type the substituent R\(^1\) may be in particular at the 3- or 4-positon relative to the phenyl carbon atom attached to the remainder of the molecule of formula (1).

In the compounds of formula (1) one preferred group of compounds are those where the group R\(^2\) is a hydrogen atom; the group R\(^3\) is a methyl group, or especially a hydrogen atom; the group R\(^4\) is a methyl group, or especially a hydrogen atom; and Y, Z, Ar, Ar\(^1\) and R\(^1\) are as defined for formula (1). In compounds of this type R\(^3\) and R\(^4\) is each especially a hydrogen atom.

One particularly preferred group of compounds of the invention has the formula (1) wherein Y is a -XR\(^a\) group, Z is a -XR\(^5\) group, R\(^2\), R\(^3\) and R\(^4\) is each a hydrogen atom, Ar\(^1\) is an optionally substituted nitrogen-containing heteroaryl group, Ar is a phenyl group and R\(^1\) is as defined for formula (1). In compounds of this type the group X in Y or Z is especially an oxygen atom; the group R\(^a\) is especially an optionally substituted C\(_{1-3}\)alkyl group, particularly a methyl, -CH\(_2\)F, -CH\(_2\)Cl, -CHF\(_2\), -CHCl\(_2\), CF\(_3\) or -CCl\(_3\) group; the group R\(^5\) is especially an optionally substituted C\(_{1-3}\)alkyl group, particularly a methyl, -CH\(_2\)F or -CHF\(_2\) group or a C\(_{3-8}\)cycloalkyl group, particularly a cyclobutyl or cyclopentyl group; and Ar\(^1\) is an optionally substituted pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or imidazolyl group, especially an optionally mono- or di-substituted 2-, 3- or 4- pyridyl group. Optional substituents include those particularly described above. In general in these compounds the group R\(^1\) is preferably attached to the Ar phenyl group at the 3- or 4-position relative to the phenyl carbon atom attached to the remainder of the molecule, and the group may be any of those R\(^1\) groups generally or particularly described above, especially a -NHC(=NCN)NHR\(^{13}\) or -NHC(=CHNO\(_2\))NHR\(^{13}\) group.

Particularly useful compounds according to the invention include those specifically described in the Examples hereinafter and especially include:

(R)-N\{[(E/Z)-1-\{3-[3-Cyclopentyloxy-4-methoxyphenyl]-2-(4-pyridinyl)-ethyl]aniilino\}-2-nitroethenyl\}-N-methylamine;
(R)-N'-Cyano-N'-[3-[3-cyclopentyloxy-4-methoxyphenyl]-2-(4-pyridinyl)-ethyl]phenyl]-N-methylamine;
(R)-N-Benzyl-N'-cyano-N'-[4-[1-[3-cyclobutyl oxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]guanidine;
5
(R)-N-[(E/Z)-1-[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]-anilino]-2-nitroethenyl]-N-benzylamine;
(R)-N-[(E/Z)-1-[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]-
anilino]-2-nitroethenyl]-N-[(4-fluorophenyl)-methyl]amine;
(R)-N-Benzyl-N'-[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)-
ethyl]phenyl]-N'-cyanoguanidine;
10
(R)-N'-[4-[1-[3,4-Bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)-ethyl]phenyl]-
N'-cyano-N-[(4-fluorophenyl)-methyl]guanidine;

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

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

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 atherosclerosis.

Compounds of the invention may 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 may also reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

Compounds of the invention may 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 may 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 may ameliorate these symptoms with a consequent enhancement of quality of life.

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

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

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.
Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

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 glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

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

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

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

In addition to the formulations described above, the compounds of formulae (1) and (2) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

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

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

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular 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 e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. In the reactions described below it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard
practice [see, for example, Green, T.W. in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1991].

Thus according to a further aspect of the invention a compound of formula (1) wherein \( R^1 \) is a -N(R\(^{12}\))C(=NCN)SR\(^{13} \) or -N(R\(^{12}\))C(=CHNO\(_2\))SR\(^{13} \) group may be prepared by reaction of an intermediate amine of formula (2):

\[
\begin{align*}
Z & \quad Y \\
\text{Y} & \quad \text{Z} \\
\text{C(R\(^2\))C(R\(^3\))(R\(^4\))Ar}^1 & \quad \text{Ar} \\
\text{Ar} & \quad \text{NH}_2 \\
\end{align*}
\]

where \( Y, Z, R^2, R^3, R^4, \text{Ar} \) and \( \text{Ar}^1 \) are as defined for formula (1), with a reagent \( R^{12} \text{SN(R}^{12}\text{)}\text{C(=NCN)SR}^{13} \) or \( R^{16}\text{SN(R}^{12}\text{)}\text{C(=CHNO}2\text{)SR}^{13} \).

The reaction may be performed in a solvent such as an alcohol, e.g. ethanol, or a nitrile, e.g. acetonitrile at around ambient up to the reflux temperature.

The intermediate starting materials of formula (1) may be prepared by any of the processes described in International Patent Specification Nos. WO94/14742, WO95/17386, WO95/35281 and WO95/35283 or from any appropriate compound described therein using standard procedures involving simple functional group manipulations.

In another process according to the invention, a compound of formula (1) wherein \( R^1 \) is a -N(R\(^{12}\))C(=NCN)NR\(^{13} \) or -N(R\(^{12}\))C(=CHNO\(_2\))NR\(^{13} \) group may be prepared from a corresponding compound of formula (1) wherein \( R^1 \) is a -N(R\(^{12}\))C(=NCN)SR\(^{13} \) or -N(R\(^{12}\))C(=CHNO\(_2\))SR\(^{13} \) group by reaction with an amine \( R^{13}\text{NH} \).
The reaction may be performed in a solvent such as an alcohol, e.g. methanol or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70° C to 80° C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at around 0° to ambient temperature.

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 or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

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

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral acid or base. Suitable chiral acids include, for example, tartaric acid and other tartrates such as dibenzoyl tartrates and ditoluoyl tartrates, sulphonates such as camphor sulphonates, mandelic acid and other mandelates and phosphates such as 1,1′-binaphthalene-2,2′-diyl hydrogen phosphate. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid or base in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography.
Alternatively, a particular enantiomer may be obtained by using an appropriate chiral intermediate of formula (2) in the process described above. Chiral intermediates may be obtained in particular by use of the enantioselective process described in International Patent Specification No. WO95/17386.

A particular geometric isomer of a compound of the invention may also be obtained from a corresponding mixture of isomers using conventional separation procedures, for examples by chromatography.

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

The starting anilines for the preparation of the compounds of Examples 1, 3, 5, 7 and 10 were prepared as described in International Patent Specification No. WO 95/17386 using 3-cyclopentyloxy-4-methoxybenzaldehyde, 3-cyclobutyloxy-4-methoxybenzaldehyde or 3,4-bis(difluoromethoxy)benzaldehyde as starting materials and the appropriate Grignard reagent (see the Examples in WO 95/177386)

EXAMPLE 1
(R)-3-[1-[3-Cyclopentyloxy-4-methoxyphenyl]-2-(4-[pyridinyl]ethyl)-N-[(E/Z)-1-(methylsulphonyl)]-2-nitroethenyl]aniline
To a solution of 3-[1-(R)-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridinyl)ethyl]aniline (880mg, 2.27mmol) in dry acetonitrile (10ml) at room temperature was added 1,1-bis(methylthio)-2-nitroethylene (1.20g, 3.2equivalents). The mixture was heated at reflux overnight and then partitioned between ethyl acetate (100ml) and water (100ml). The aqueous layer was separated and the organic layer washed with water (3x100ml), brine (100ml), dried (MgSO₄), filtered and solvent removed in vacuo to give a yellow foam. The foam was subjected to flash column chromatography (SiO₂; eluant ethyl acetate) to give the title compound as a white foam (830mg). ¹Hnmr (300MHz, d₄ methanol). δ 1.58 (2H, br), 1.76 (6H, br), 2.38 (3H, s), 3.41 (2H, d, J 8.2Hz), 3.75 (3H, s), 4.33 (1H, t, J 8.2Hz), 4.71 (1H, br), 6.78 (2H, s), 6.83 (2H, s), 7.12 (1H, d, J 7.6Hz),
7.18 (2H, d, J 6.2Hz), 7.25 (1H, br s), 7.33 (2H, m) and 8.28 (2H, dd, J 4.5, 1.6Hz). m/z (ESI, 40V) 506 (MH⁺, 100), 445 (12), 438 (10), 413 (16).

**EXAMPLE 2**

5 (R)-N-((E/Z)-1-[[3-[1-[3-Cyclopentylxloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]aniline]-2-nitroethenyl]-N-methylamine

To the compound of Example 1 (500mg, 0.99mmol) was added methyllamine in methanol (20ml of a 2M solution, 40 equivalents). The mixture was then heated at 40°C for a period of 3h. Solvent was removed in vacuo and the yellow residue subjected to column chromatography (SiO₂ eluant 23:2 dichloromethane:methanol) to give the title compound as a pale yellow solid (350mg). ¹Hnmr (300MHz, d₄ methanol). δ 1.58 (2H, br), 1.75 (6H, br), 3.01 (2H, br), 3.41 (2H, d, J 7.5Hz), 3.74 (3H, s), 4.34 (1H, dd, J 7.9-8.3Hz), 4.72 (1H, br), 6.30 (1H, br), 6.77-6.85 (3H, m), 7.05 (1H, d, J 7.5Hz), 7.17 (3H, dd, J 1.5, 3.6Hz), 7.30-7.37 (2H, m) and 8.28 (2H, dd, J 1.5, 4.6Hz). m/z (ESI, 40V) 489 (MH⁺, 100%), 421 (15), 396 (32).

**EXAMPLE 3**

20 (R)-4-((2-((Cyanooimino)(methylsulphonyl)methyl)amino)phenyl)-2-[3-cyclopentylxloxy-4-methoxyphenyl]ethyl)pyridine

To a solution of 3-[1-(R)-(3-cyclopentylxyloxy-4-methoxyphenyl)-2-(4-pyridinyl)ethyl]aniline (890mg, 2.3mmol) in ethanol (10ml) at 0°C was added dimethylcyanodithioimidocarbonate (1.0g, 3equivalents). The mixture was allowed to warm to room temperature and stirred for 72h. The mixture was partitioned between ethyl acetate (100ml) and water (100ml), the aqueous layer was separated and the organic layer washed with water (3x50ml), brine (50ml), dried (MgSO₄), filtered and solvent removed in vacuo to give a pale yellow foam. The foam was subjected to flash column chromatography (SiO₂; eluant, ethyl acetate) to yield the title compound as a white foam (685mg). ¹Hnmr (300MHz, CDCl₃). δ 1.58 (2H, br), 1.79 (6H, br), 2.44 (3H, s), 3.32 (2H, d, J 8.7Hz), 3.80 (3H, s), 4.17 (1H, t, J 8.0Hz), 4.66 (1H, br), 6.63 (1H, d, J 2.0Hz), 6.79 (1H, dd, J 8.3, 2.0Hz), 6.78 (1H, d, J 8.3Hz), 6.96 (2H, dd, J 4.5, 1.6Hz), 7.12 (1H, s), 7.15 (2H, s), 7.28 (2H, m) and 8.38 (2H, dd, J 4.5, 1.6Hz). m/z (ESI, 40V) 487 (MH⁺, 100), 445 (17), 419 (41), 377 (52).
EXAMPLE 4
(R)-N"-Cyan-N"-[3-[1-[3-cyclopentyloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]-N-methylamine

To the compound of Example 3 (521mg, 1.1mmol) was added methylamine solution in methanol (31ml of a 2M solution, 62mmol). The mixture was stirred at room temperature overnight, partitioned between ethyl acetate (100ml) and water (100ml), the aqueous layer was separated and the organic layer washed with water (2x50ml), brine (50ml), dried (MgSO₄), filtered and solvent removed in vacuo to give a crude product. This was subjected to column chromatography (SiO₂; eluant, 45:5, dichloromethane:methanol) to give the title compound as a white foam (320mg). ¹Hnmr (300MHz, d₄ methanol). δ 1.58 (2H, br), 1.73 (6H, br), 2.81 (3H, s), 3.39 (2H, dd, 1.7, 3.3Hz), 3.74 (3H, s), 4.28 (1H, t, 7.9Hz), 4.72 (1H, br), 6.78 (1H, d, 8.0Hz), 6.81 (2H, d, 0.9Hz), 7.08 (1H, d, 2.0Hz), 7.16-7.30 (4H, m) and 8.27 (2H, d, 5.0Hz). m/z (ESI, 27V), 470 (MH⁺, 100), 402 (8).

EXAMPLE 5
(R)-4-{2-[4-{[(Cyanomino)(methyl)sulphonyl]methyl}amino]phenyl}-2-[3-cyclobutyloxy-4-methoxyphenyl]ethyl]pyridine

The title compound was prepared from 4-{1-(R)-(3-cyclobutyloxy-4-methoxyphenyl)-2-(4-pyridinyl)ethyl]aniline (2.0g) and dimethylcyanodithioimidocarbonate (4.0g) as a near white glass (2.63g) using a similar procedure to the preparation of the compound of Example 3. ¹Hnmr (CDCl₃) δ 1.58-1.70 (1H, br m), 1.76-1.87 (1H, br m), 2.10-2.46 (4H, br m), 2.46 (3H, s), 3.32 (2H, d, 7.9Hz), 3.83 (3H, s), 4.14 (1H, t, 7.9Hz), 4.52 (1H, p), 6.46 (1H, d, 2.1Hz), 6.68 (1H, dd, 2.1, 8.3Hz), 6.76 (1H, d, 8.3Hz), 6.96 (2H, d, 5.3Hz), 7.20 (4H, m), 8.27 (-0.75H, br s) and 8.40 (2H, d, 5.3Hz). m/z (ESI, 27V) 473.3 (MH⁺, 100%).

EXAMPLE 6
(R)-N-Benzyl-N"-cyano-N"-[4-{1-[3-cyclobutyloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]guanidine

The title compound was prepared from the compound of Example 5 (0.5g) and benzylamine (1.16ml) in tetrahydrofuran (20ml) as a white glass
(0.56g) using a similar procedure to the preparation of the compound of Example 4. ¹H NMR (CDCl₃) δ  1.60-1.70 (1H, br m), 1.75-1.9 (1H, br m), 2.1-2.5 (4H, br m), 3.27 (2H, d, J 7.9Hz), 3.81 (3H, s), 4.11 (1H, t, J 7.91Hz), 4.47 (2H, d, J 5.4Hz), 4.52 (1H, p (J=5.4Hz)), 5.15 (1H, br m), 6.46 (1H, d, J 2.1Hz), 6.66 (1H, dd, J 2.1, 8.3Hz), 6.75 (1H, d, J 8.3Hz), 6.90 (2H, d, J 5.5Hz), 7.11 (2H, d, J 8.4Hz), 7.24 (4H, br m), 7.34 (3H, br m) and 8.36 (2H, d, J 5.5Hz).  m/z (ESI 27V) 532.2 (MH⁺, 100%).

**EXAMPLE 7**

(R)-4-[1-[3,4-Bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]-N-(1-[methylsulphonyl]-2-nitroethyl)aniline

To a solution of 4-[1-(R)-(3,4 bis(difluoromethoxy)phenyl)-2-(4-pyridinyl)ethyl]aniline (3.0g, 7.44mmol) in dry acetonitrile (30ml) at room temperature was added 1,1-bis(methylthio)-2-nitroethylene (2.5g, 2 equivalents). The mixture was heated at reflux overnight, cooled and the solvent removed in vacuo to give a yellow foam. The foam was subjected to flash chromatography (SiO₂, eluant 95% dichloromethane/5% ethanol) to give the title compound. ¹H NMR (300MHz CDCl₃) δ 2.36 (3H, s), 3.31 (2H, d, J 7.99Hz), 4.25 (1H, t, J 7.94Hz), 6.45 (1H, t, J 7.35Hz), 6.48 (1H, t, J 7.35Hz), 6.67 (1H, s), 6.91 (2H, d, J 6.0Hz), 7.01-7.07 (2H, c), 7.15-7.25 (4H, c), 8.41 (2H, d, J 6.0Hz) and 11.75 (1H, br).

**EXAMPLE 8**

(R)-N-[(E/Z)-1-[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]anilino]-2-nitroethenyl]-N-benzylamine

To a solution of the compound of Example 7 (900mg, 1.72mmol) in dry acetonitrile (10ml) at room temperature was added benzylamine (900mg, 8.44mmol). The mixture was heated at reflux overnight, cooled and the solvent and volatiles removed in vacuo. The residue was subjected to flash chromatography (SiO₂; eluent ethyl acetate) to yield the title compound as a yellow foam (590mg). ¹H NMR (300 MHz CDCl₃) δ 3.3 (2H, d), 3.9 (1H, br), 4.2 (2H, m), 4.6 (1H, br), 5.1 (1H, br), 6.4 (1H, t), 6.5 (1H, t), 6.9 (2H, d), 7.0-7.5 (12H, c) and 8.4 (2H, d).  m/z (ESI, 60V) 583 (MH⁺, 100), 537 (21), 490 (70), 444 (74).

The following compound was prepared using a similar procedure:
EXAMPLE 9
R-\textit{N}[(E/Z)-1-{[4-[3.4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)-ethyl]anilino}-2-nitroethenyl]-\textit{N}-(4-fluorophenyl)-methyl]amine

From the compound of Example 7 (700mg, 1.3mmol) and 4-fluorobenzylamine (700mg, 5.6mmol) to yield the title compound as a yellow foam (560mg). $^1$Hnmr (300 MHz, d$_4$ methanol) $\delta$ 3.56 (2H, d, $\downarrow 8.21$Hz), 4.49-4.55 (3H, c), 6.75 (2H, t, $\downarrow 73.69$Hz), 7.09-7.27 (8H, c), 7.35-7.44 (6H, c) and 8.41 (2H, d, $\downarrow 4.84$). m/z (ESI, 60V), 601 (MH$^+$, 100%) 508 (73), 462 (61), 314 (30).

EXAMPLE 10
(R)-4-{[2-[3.4-Bis(difluoromethoxy)phenyl]-2-(4-[[cyanoimino](methyl- sulphanyl)methyl]amino)phenyl]ethyl}pyridine

To a solution of 4-[1-(R)-(3.4 bis(difluoromethoxy)phenyl)-2-(4-pyridinyl)ethyl]aniline (1.8g, 4.4mmol) in ethanol (20ml) at room temperature was added dimethylcyanodithioimidocarbonate (1.3g, 8.9mmol). The mixture was heated at 70$^\circ$ for 72h, cooled and the solvent removed in vacuo to give a yellow foam. The foam was subjected to flash chromatography (SiO$_2$; eluant ethyl acetate) to give the title compound as a yellow foam (1.2g). $^1$Hnmr (300 MHz, CDC$_3$) $\delta$ 2.46 (3H, s), 3.30 (2H, d, $\downarrow 7.98$Hz), 4.23 (1H, t, $\downarrow 7.84$Hz), 6.46 (1H, t, $\downarrow 73.58$Hz), 6.48 (1H, t, $\downarrow 73.51$Hz), 6.90 (2H, d, $\downarrow 6.0$Hz), 7.02 (1H, d, $\downarrow 8.38$Hz), 7.06 (1H, br), 7.16 (1H, d, $\downarrow 3.0$Hz), 7.16 (1H, d, $\downarrow 3.0$Hz), 7.18-7.25 (3H, c), 8.10 (1H, br) and 8.40 (2H, d, $\downarrow 6.03$Hz).

EXAMPLE 11
(R)-\textit{N-Benzyl-N'}-[4-[3.4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]phenyl]-\textit{N''}-cyanoguanidine

To the compound of Example 10 (400mg, 0.79mmol) in anhydrous tetrahydrofuran (10ml) was added benzylamine (1ml, excess). The mixture was stirred at room temperature for 72h. The solvent and volatiles were removed in vacuo to yield the title compound as a white solid (300mg). $^1$Hnmr (300 MHz, CDC$_3$) $\delta$ 3.28 (2H, d, $\downarrow 7.99$Hz), 4.21 (1H, t, $\downarrow 7.98$Hz), 4.47 (2H, d, $\downarrow 5.69$Hz), 5.27 (1H, br), 6.43 (1H, t, $\downarrow 73.58$Hz), 6.47 (1H, t, $\downarrow 73.39$Hz), 6.89 (2H, d, $\downarrow 6.03$Hz), 6.99-7.34 (12H, c) and
8.38 (2H, d, J 6.04Hz). For C_{29}H_{23}N_{5}O_{7}F_{4} requires C, 63.94%; H, 4.47%; N, 12.43%; Found C, 63.87%; H, 4.48%; N, 12.52%.

The following compound was prepared in a similar manner:

**EXAMPLE 12**

(R)-N'-(4-[3,4-Bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)-ethyl]phenyl)-N''-cyano-N-[4-fluorophenyl]methyl]guanidine

From the compound of Example 10 (400mg, 0.79mmol) and 4-fluorobenzylamine (1ml, excess) as a white solid (300mg). \(^1\)Hnmr (300 MHz, CDCl₃) δ 3.29 (2H, d, J 8.0Hz), 4.23 (1H, t, J 7.99Hz), 4.43 (2H, d, J 5.67Hz), 5.10 (1H, br), 6.44 (1H, t, J 73.57Hz), 6.48 (1H, t, J 73.34Hz), 6.90 (2H, d, J 5.89Hz), 7.02-7.06 (2H, c), 7.10 (1H, br), 7.13-7.26 (8H, c) and 8.39 (2H, d, J 5.97Hz). m/z (ESI, 60V) 582 (MH⁺, 100), 562 (21), 540 (39), 489 (15), 447 (12).

**EXAMPLE 13**

(R)-4-[2-[3,4-Bis(difluoromethoxy)phenyl]-2-[[cyanoimino][4-[[fluorophenyl]methyl]]methyl][amino]phenyl]ethyl]pyridine-N-oxide

To the compound of Example 12 (280mg, 0.5mmol) in dichloromethane (5ml) at 5° was added 50% m-chloroperbenzoic acid (170mg, 1 equivalent). The mixture was stirred at 5° for 2h, then quenched with saturated sodium bisulphite (2ml). The aqueous layer was separated and the organic layer washed with saturated sodium bisulphite (3 x 2ml), dried (Na₂SO₄), filtered and solvent removed in vacuo to yield the title compound as a white solid (160mg). \(^1\)Hnmr (300 MHz, CDCl₃) δ 3.28 (2H, d, J 8.0Hz), 4.15 (1H, t, J 7.9Hz), 4.44 (2H, d, J 5.78Hz), 5.20 (1H, br), 6.48 (2H, t, J 73.43Hz), 6.86 (2H, d, J 7.12Hz), 6.99-7.26 (11H, c), 7.38 (1H, br) and 8.00 (2H, d, J 7.11Hz). m/z (ESI, 60V) 598 (MH⁺, 100), 556 (82), 447 (19).

The following compound was prepared in a similar manner:

**EXAMPLE 14**

(R)-4-[2-[(Benzylamino)(cyanoimino)methyl]amino]phenyl][3,4-bis(difluoromethoxy)phenyl]ethyl]pyridine-N-oxide

From the compound of Example 11 (340mg, 0.62mmol) and 50% m-chloroperbenzoic acid as a white solid (200mg). \(^1\)Hnmr (300 MHz, CDCl₃)
δ 3.27 (2H, d, J 8.0Hz), 4.14 (1H, t, J 7.86Hz), 4.48 (2H, d, J 5.72Hz), 5.29 (1H, br), 6.48 (2H, t, J 73.49Hz), 6.85 (2H, d, J 7.02Hz), 7.00 (1H, dd, J 2.19, 8.43Hz), 7.06 (1H, br), 7.12-7.34 (10H, c), 7.50 (1H, br) and 7.98 (2H, d, J 7.03Hz). m/z (ESI, 60V) 580 (MH+, 85), 538 (100), 429 (41).

The advantageous pharmacological properties of the compounds according to the invention may be demonstrated in the following in vitro and ex vivo tests:

1. **Isolated Recombinant Human PDE IVA Enzyme**

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 Reifsnnyder, 1990, TIPS, 11, 150). These recombinant enzymes, particularly the human eosinophil recombinant PDE IVA, 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-ethanesulphonic acid (TES)-NaOH buffer (pH 7.5), 10mM MgCl₂, 0.1µM [³H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30°C for between 5 to 30 min. The reaction was terminated by addition of 50µl 2% trifluoroacetic acid containing [¹⁴C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [³H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [³H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing 10ml of scintillation cocktail. Recovery of [³H]-5'AMP was determined
using the $[^{14}C]-5'AMP$ and all assays were conducted in the linear range of
the reaction. Results were expressed as IC$_{50}$ values.

For example, using this procedure with a recombinant PDE IVA enzyme
the compounds of the Examples had IC$_{50}$ values of 3.3nM (the compound
of Example 2) and 0.5nM (the compound of Example 4).

The compounds of the Examples had little or no activity against other
isolated PDE isoenzymes (specifically PDE I, II, III or V - see WO
94/14742 for experimental details) at concentrations up to 100$\mu$M, thus
illustrating the selectivity of their action against PDE IV.

2. Rat Hepatocyte Metabolism
The improved metabolic stability of the compounds according to the
invention was demonstrated in a conventional rat hepatocyte model in
which rat hepatocytes were cultured in the presence of test compound.
The quantity of compound remaining after a fixed period of time was then
determined using mass spectroscopy.

In this test, for example, the compounds of the Examples remain
substantially unmetabolised after 3h with 80% and over of each compound
remaining at the end of this period. This compares favourably with related
compounds, for example compounds without any substitution present on
Ar, which are extensively metabolised in 3h.
CLAIMS

1. A compound of formula (1):

\[
\begin{align*}
\text{Y} & \text{C(R}^2\text{)}\text{C(R}^3\text{)}\text{(R}^4\text{)}\text{Ar}^1 \\
\text{Ar} & \text{R}^1
\end{align*}
\]

(1)

wherein
Y is a halogen atom, or a -XR^a group where X is -O-, -S(O)\text{m}^- [where
m is zero or an integer of value 1 or 2], or -N(R^b)- [ where R^b is a
hydrogen atom or an optionally substituted alkyl group] and R^a is a
hydrogen atom or an optionally substituted alkyl group;
Z is a group -XR^5 [where R^5 is an optionally substituted alkyl, alkenyl,
cycloalkyl, cycloalkenyl or heterocycloalkyl group], -C(R^6)=C(R^7)(R^8)
[where R^6 is a hydrogen or fluorine atom or a methyl group, and R^7
and R^8, which may be the same or different, is each a hydrogen or
fluorine atom or an optionally substituted alkyl, alkenyl, alkoxy,
alkylthio, -CO_2R^9 [where R^9 is a hydrogen atom or an optionally
substituted alkyl, aralkyl or aryl group], -CONR^{10}R^{11} [where R^{10}
and R^{11}, which may be the same or different, is each as defined for R^9],
-CSNR^{10}R^{11}, -CN or -NO_2 group, or R^7 and R^8 together with the
carbon atom to which they are attached are linked to form an
optionally substituted cycloalkyl, cycloalkenyl or heterocycloalkyl
group] or [-CH(R^6)]_nCH(R^7)(R^8) where n is zero or the integer 1;
R^2 is a hydrogen or a fluorine atom, an optionally substituted alkyl
group, or a hydroxyl group;
R^3 is a hydrogen or a fluorine atom, or an optionally substituted alkyl
group;
R^4 is a hydrogen or a fluorine atom, an optionally substituted alkyl
group or an OR^c group where R^c is a hydrogen atom or an optionally
substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl,
carboxamido or thiocarboxamido group;
Ar^1 is an optionally substituted monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
R^1 is a group -N(R^{12})C(=NCN)NHR^{13} [where R^{12} is a hydrogen atom or a C_{1-3}-alkyl group and R^{13} is a hydrogen atom, a C_{1-3}-alkyl group or an optionally substituted phenyl or phenyl[C_{1-3}-alkyl group], -N(R^{12})C(=NCN)SR^{13}, N(R^{12})C(=CHNO_2)NHR^{13} or -N(R^{12})C(=CHNO_2)SR^{13};
and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

2. A compound according to Claim 1 wherein each of R^2, R^3 and R^4 is a hydrogen atom.

3. A compound according to Claim 1 or Claim 2 wherein Y is a -XR^a group, Z is a -XR^5 group, Ar^1 is an optionally substituted nitrogen-containing heteroaryl group and Ar is a phenyl group.

4. A compound according to Claim 3 wherein Y is an -OR^a group where R^a is an optionally substituted C_{1-3}-alkyl group, and Z is an -OR^5 group where R^5 is an optionally substituted C_{1-3}-alkyl group or a C_{3-8}cycloalkyl group.

5. A compound according to any one of the preceding claims wherein Ar^1 is an optionally substituted pyridyl, pyrazinyl, pyrimidinyl, pyrazinyl or imidazolyl group.

6. A compound according to Claim 5 wherein Ar^1 is an optionally mono- or di-substituted 2-, 3- or 4- pyridyl group.

7. A compound according to any one of Claim 1 to Claim 6 wherein R^1 is a -NHC(=NCN)NHR^{13} or -NHC(=CHNO_2)NHR^{13} group.
8. A compound according to Claim 7 wherein R¹³ is a methyl, ethyl, benzyl or substituted benzyl group containing one or two halogen, C₁₋₃alkyl or C₁₋₃alkoxy substituents.

9. A compound which is:
   (R)-N⁺{[(E/Z)-1-[[3-[1-[3-Cyclopentyloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]anilino]-2-nitroethenyl]-N-methylamine;
   (R)-N'-Cyanobenzyl-N'-[[3-[1-[3-cyclopentyloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]-N-methylamine;
   (R)-N-Benzyl-N'-cyano-N'-[4-[1-[3-cyclobutyloxy-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]guanidine;
   (R)-N⁺{[(E/Z)-1-[[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethy]anilino]-2-nitroethenyl]-N-benzylamine;
   R⁻N⁺{[(E/Z)-1-[[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]anilino]-2-nitroethenyl]-N-{[4-fluorophenyl]-methyl}amine;
   (R)-N-Benzyl-N'-[4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]phenyl]-N'-cyano-N'-[4-[fluorophenyl]methyl]guanidine;
   (R)-N⁻{[4-[1-[3,4-Bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]phenyl]-N'-cyano-N'-[4-[fluorophenyl]methyl]guanidine;
   and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

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

\[
\begin{array}{c}
\text{Y} \\
\text{C(R²)C(R³)(R⁴)Ar} \\
\text{Ar} \\
\text{C(R⁴)C(R⁵)Ar} \\
\text{R¹} \\
\end{array}
\]

\[\text{(1)}\]

wherein
Y is a halogen atom, or a -XR² group where X is -O⁻, -S(O)ₓ⁻ [where m is zero or an integer of value 1 or 2], or -N(R³⁻)⁻ [where R³ is a hydrogen atom or an optionally substituted alkyl group] and R² is a hydrogen atom or an optionally substituted alkyl group;
Z is a group -XR⁵ [where R⁵ is an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl or heterocycloalkyl group], -C(R⁶)=C(R⁷)(R⁸)
[where R\(^6\) is a hydrogen or fluorine atom or a methyl group, and R\(^7\) and R\(^8\), which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkoxy, alkylthio, -CO\(_2\)R\(^9\) [where R\(^9\) is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], -CONR\(^{10}\)R\(^{11}\) [where R\(^{10}\) and R\(^{11}\), which may be the same or different, is each as defined for R\(^9\)], -CSNR\(^{10}\)R\(^{11}\), -CN or -NO\(_2\) group, or R\(^7\) and R\(^8\) together with the carbon atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloalkyl group] or [-CH(R\(^6\))]\(_n\)CH(R\(^7\))(R\(^8\)) where n is zero or the integer 1; R\(^2\) is a hydrogen or a fluorine atom, an optionally substituted alkyl group, or a hydroxyl group; R\(^3\) is a hydrogen or a fluorine atom, or an optionally substituted alkyl group; R\(^4\) is a hydrogen or a fluorine atom, an optionally substituted alkyl group or an OR\(^c\) group where R\(^c\) is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; Ar\(^1\) is an optionally substituted monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; R\(^1\) is a group -N(R\(^{12}\))C(=NCN)NH\(_R\(^{13}\) [where R\(^{12}\) is a hydrogen atom or a C\(_{1-3}\)-alkyl group and R\(^{13}\) is a hydrogen atom, a C\(_{1-3}\)-alkyl group or an optionally substituted phenyl or phenylC\(_{1-3}\)-alkyl group], -N(R\(^{12}\))C(=NCN)SR\(^{13}\), N(R\(^{12}\))C(=CHNO\(_2\))NH\(_R\(^{13}\) or -N(R\(^{12}\))C(=CHNO\(_2\))SR\(^{13}\); and the salts, solvates, hydrates, prodrugs and N-oxides thereof; together with one or more pharmaceutically acceptable carriers, excipients or diluents.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/38 A61K31/44

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 6 C07D 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

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Date of the actual completion of the international search 26 February 1998

Date of mailing of the international search report 3.03.98

Name and mailing address of the ISA
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

Authorized officer
Gettins, M
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