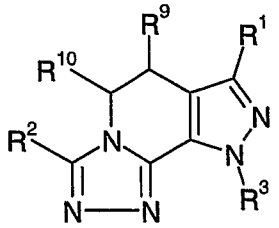
INHALATION COMPOSITIONS COMPRISING TRICYCLIC 5,6-DIHYDRO-9H-PYRAZOLO (3,4-C) -1, 2, 4-TRIAZOLO (4, 3-alpha) PYRIDINES.

The present invention relates to an inhaled formulation, comprising a compound selected from a particular class of 5,6-dihydro-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridines, which is capable of delivering the compound as fine, solid particles to the lung and the use of such a formulation in the treatment of certain diseases such as respiratory diseases.

The compounds that are useful in the invention are the compounds of the formula (I)

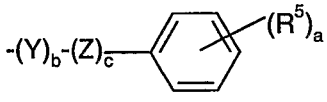


(I)

and the pharmaceutically acceptable salts thereof; wherein

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_4)$alkenyl, phenyl, dimethylamino, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_6)$acyl wherein the alkyl, phenyl or alkenyl groups may be substituted with up to two hydroxy, $(C_1\text{-}C_3)$alkyl, or trifluoromethyl groups, or up to three halogens;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_{14})$alkyl, $(C_1\text{-}C_7)$alkoxy$(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_{14})$alkenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_2)$alkyl, a saturated or unsaturated $(C_4\text{-}C_7)$heterocyclic$(CH_2)_n$ group wherein n is 0, 1 or 2, containing as the heteroatom one or two of the group consisting of oxygen, sulphur, sulphonyl, nitrogen and NR^4 wherein R^4 is hydrogen or $(C_1\text{-}C_4)$alkyl; or a group of the formula



wherein a is an integer from 1 to 5; b and c are 0 or 1; R^5 is hydrogen, hydroxy, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_1-C_5) alkoxy, (C_3-C_6)cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C_1-C_4)alkyl; wherein Z is oxygen, sulphur, SO_2, CO or NR^8 wherein R^8 is hydrogen or (C_1-C_4)alkyl; and Y is (C_1-C_5)alkylene or (C_2-C_6)alkenyl optionally substututed with up to two (C_1-C_7)alkyl or (C_3-C_7)cycloalkyl groups; wherein each of the alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic groups may be substituted with one to fourteen of the group consisting of (C_1-C_2)alkyl, trifluoromethyl or halogen; and

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryl and (C_6-C_{10})aryloxy.

These compounds, which are selective PDE4 inhibitors, are described in International Patent Application WO-A-96/39408. Conditions which may be treated by inhalation of the tricyclic 5,6-dihydro-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridines described therein include respiratory diseases such as asthma and chronic obstructive airways disease (COAD, also known as chronic obstructive pulmonary disease (COPD)).

The aforementioned application refers to the optimum therapeutic dose for the compounds described therein as generally in the range of from 0.1 to 400mg daily for an average adult patient. It is indicated that a dosage for inhaler administration is generally formulated as a 0.1 to 1% (w/v) solution. Although not stated, a typical dosage form for the administration of such a solution would be a metered dose inhaler (MDI).

On the basis of multiple dose patient studies using a solution MDI (administered *via* a 'spacer') to administer small amounts of said compounds at frequent intervals throughout the day, it has been calculated that a daily inhaled dose of up to 3mg of active compound would be efficacious in the treatment of both asthma and COAD. However, attempts to administer such a quantity by solution MDI

using a more reasonable number of doses, typically not more than four per day, invariably produced an immediate cough response in most subjects. Cough severity varied but during the course of the treatment some asthma patients developed worsening of symptoms which was associated with more severe cough responses. Cough responses can prevent the drug being taken on board in a quantity sufficient for the desired therapeutic effect and, perhaps most importantly, have serious consequences for patient compliance.

It has been surprisingly found that when the active compound is administered in the form of fine, solid particles, specifically using a dry powder inhaler, subjects manifest little or no cough response at doses which caused cough with the solution MDI. Subjects are able to accept the full therapeutic dose of active compound or a significant proportion thereof in a reasonable, *i.e.* patient-compliant, number of doses (typically not more than four per day). This is unexpected since the cough response would normally be associated with the compounds *per se* and a powder or suspension formulation is potentially irritant.

Thus, the present invention provides an inhaled formulation comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined above, characterised in that the formulation is capable of delivering the compound as fine, solid particles to the lung.

Further, the present invention provides the use of such an inhaled formulation in the manufacture of a medicament for the treatment of a disease treatable by the inhibition of PDE4, particularly a respiratory disease such as asthma or chronic obstructive pulmonary disease.

Further, the present invention provides a method of treatment of a disease treatable by the inhibition of PDE4, particularly a respiratory disease such as asthma or chronic obstructive pulmonary disease, comprising the administration of such an inhaled formulation to a mammal.

Preferred compounds for use in the invention have an aqueous solubility at physiological pH of less than 0.15mg/ml. Compounds having an aqueous

solubility of less than 0.05mg/ml are especially preferred. For the purposes of the invention, "physiological pH" is defined as a pH of from 6.0 to 8.0. Solubility may be measured by diluting a weighed amount of test compound with a suitable pH buffer, shaking the mixture for 24 hours, filtering the mixture and measuring the saturated solubility of the filtrate using LC-MS (liquid chromatograhy-mass spectrometry).

Preferred compounds of the formula (I) include those wherein each of the alkyl, alkenyl, cycloalkyl, alkoxyalkyl and heterocyclic groups may be substituted with 1 to 5 of the group consisting of (C_1-C_2)alkyl, trifluoromethyl and hydrogen.

Preferably, R^1 is methyl, ethyl or isopropyl.

Preferably, R^3 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_2)alkyl or phenyl optionally substituted with 1 or 2 of the group consisting of hydrogen, hydroxy, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_1-C_5)alkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C_1-C_4)alkyl.

Preferred individual compounds of the formula (I) are:

9-cyclopentyl-5,6-dihydro-7-ethyl-3-phenyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopenyl-5,6-dihydro-7-ethyl-3-(furan-2-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-pyridyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(4-pyridyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(3-thienyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3-benzyl-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-propyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3,9-dicyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(1-methylcyclohex-1-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3-(*tert*-butyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-methylphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-methoxyphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]1,2,4-triazolo[4,3-α]pyridine;

3-(2-chlorophenyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-iodophenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-trifluoromethylphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine; and

5,6-dihydro-7-ethyl-9-(4-fluorophenyl)-3-(1-methylcyclohex-1-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

and the pharmaceutically acceptable salts thereof.

Particularly preferred compounds of the formula (I) are 3-(*tert*-butyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]1,2,4-triazolo[4,3-α]pyridine, and the pharmaceutically acceptable salts thereof.

Most preferred are 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]1,2,4-triazolo[4,3-α]pyridine, and the pharmaceutically acceptable salts thereof, especially the free base.

For the purposes of the present invention, 'fine', solid drug particles may be taken to be those which are less than 20 micrometers in diameter. Preferably, the powdered drug used will have a particle size range wherein 90% of particles are less than 10 micrometers in diameter and 50% of particles are less than 5 micrometers in diameter. Even more preferably, the powdered drug used will have a particle size range wherein 90% of particles are less than 6 micrometers in diameter and 50% of particles are less than 3 micrometers in diameter. Most preferably, the powdered drug used will have a particle size range wherein 95% of particles are less than 5 micrometers in diameter and 50% of particles are less than 2.5 micrometers in diameter.

A suitable particle size distribution may be obtained by micronising (milling) the bulk drug substance or by particle engineering. Examples of particle engineering are super critical fluid crystallisation and the preparation of microspheres (e.g. by spray drying).

Devices which are capable of delivering fine, solid particles produced by the techniques outlined above to the lung of a patient include dry powder inhalers, suspension metered dose inhalers, suspension nebulisers and suspension atomisers. Dry powder inhalers are preferred. Suitable dry powder inhalers for use in the invention include capsule devices such as Spinhaler (trade mark), Rotahaler (trade mark), Handihaler (trade mark), Aerohaler (trade mark), Eclipse (trade mark), Turbospin (trade mark) and the Flowcaps (trade mark) inhaler. Other suitable dry powder inhalers for use in the invention include multidose inhalers such as Accuhaler (trade mark), Turbuhaler (trade mark), Ultrahaler (trade mark), Diskhaler (trade mark), Novoliser (trade mark), Easyhaler (trade mark), Taifun (trade mark), Clickhaler (trade mark), Twisthaler (trade mark) and Aspirair (trade mark).

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the chosen means of inhalation and standard pharmaceutical practice.

In the case of an aerosol suspension spray presentation from a pressurised container, pump, spray, atomiser (e.g. an atomiser using electrohydrodynamics to produce a fine mist) or nebuliser a suitable propellant may be used such as e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubron (trade mark) or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The drug will be dispersed in a suitable agent such as water or aqueous ethanol. A lubricant such as sorbitan trioleate may also be included.

Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler may be formulated to contain a powder mix of a compound of the formula (I), a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, trehalose or magnesium stearate. For the purposes of the present invention, a preferred dry powder formulation consists of a dry powder blend of the compound of the formula (I), or salt thereof, and lactose (preferably as lactose monohydrate). The lactose should be of sufficiently fine grade that 90% of the lactose particles are less than 1000 micrometers in diameter and 50% of the lactose particles are less than 500 micrometers in diameter. Preferably, 90% of the lactose particles are less than 300 micrometers in diameter and 50% of the lactose particles are less than 100 micrometers in diameter. Most preferably, 90% of the lactose particles are less than from 100 to 200 micrometers in diameter, 50% of the lactose particles are less than from 40 to 70 micrometers in diameter and 10% of the lactose particles are less than 10 micrometers in diameter. Drug loading may vary from 0.1 to 100% w/w of the dry powder blend and is preferably from 5 to 100% w/w, most preferably from 5-40% w/w.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 10000 μg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1μg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

A further method of delivering fine, solid particles of drug to the lung is use of microspheres comprising poly(D,L-lactic-co-glycolic acid) wherein such microspheres are generated *in situ* after delivery from a solution metered dose inhaler.

The fine, solid particles of drug to be delivered according to the invention may optionally be delivered in the form of liposomes to modify their release characteristics.

The formulations of the present invention may comprise one or more further pharmacologically active agents including:

(a) an A2a agonist such as one of the compounds generally and specifically disclosed in WO-A-00/23457, WO-A-00/77018, WO-A-01/27131, WO-A-01/27130, WO-A-01/60835, WO-A-02/00676 and WO-A-01/94368, preferably 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide or a pharmaceutically acceptable salt or solvate thereof or 6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[1-(2-pyridinyl)-4-piperidinyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide or a pharmaceutically acceptable salt or solvate thereof;

(b) an anticholinergic agent, such as a tiotropium, ipratropium or oxitropium salt or a solvate thereof;

(c) a β2 adrenergic receptor agonist such as salmeterol or formoterol or a pharmaceutically acceptable salt or solvate thereof;

(d) a corticosteroid; or

(e) a dopamine D2 receptor agonist.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Examples

In each of Examples 1 to 3, the lactose monohydrate particle size distribution was 90% less than 190 micrometers in diameter, 50% less than 55 micrometers in diameter and 10% less than 6 micrometers in diameter and the drug particle size distribution was 90% less than 5.8 micrometers in diameter, 50% less than 2.9 micrometers in diameter and 10% less than 1.0 micrometers in diameter.

Example 1 - Dry powder inhaler capsule (0.5mg)

A mixture of 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine (0.5mg, micronised by spiral air-jet milling) and lactose monohydrate (9.5mg, Pharmatose 150M (DMV) Ph.Eur) were blended by hand and filled into a size 3 opaque white capsule shell (supplied by Capsugel, product code 1505).

Example 2 - Dry powder inhaler capsule (1mg)

A mixture of 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine (1.0mg, micronised by spiral air-jet milling) and lactose monohydrate (19mg, Pharmatose 150M (DMV) Ph.Eur) were blended by hand and filled into a size 3 opaque white capsule shell (supplied by Capsugel, product code 1505).

Example 3 - Dry powder inhaler capsule (2mg)

A mixture of 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine (2.0mg, micronised by spiral air-jet milling) and lactose monohydrate (38mg, Pharmatose 150M (DMV) Ph.Eur) were blended by

hand and filled into a size 3 opaque white capsule shell (supplied by Capsugel, product code 1505).

Example 4 - Dry powder inhaler

The capsules manufactured in accordance with Examples 1 to 3 were loaded into a monodose inhaler (supplied by Plastiape SpA) for administration to human subjects.

Example 5 - Clinical data

The formulations of Examples 1 to 3 were tested for tolerance and safety in a clinical trial using healthy volunteers. Volunteers were dosed using a dry powder inhaler, as described in Example 4, with capsules containing the 0.5mg, 1mg and 2mg doses of Examples 1, 2 and 3, respectively, or with placebo capsules containing only lactose. A dose escalation was used and any coughs were assessed as to their number, severity, duration and quality. Some of the results are shown in Table 1.

Table 1 - Cough toleration

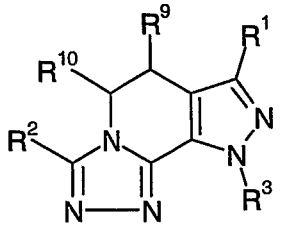
Dose	Percentage of subjects coughing in the first 5 minutes following dosing	
	Placebo (dry powder)	Active (dry powder)
1 x 0.5mg	-	0 (0/9)
2 x 0.5mg	-	11 (1/9)
1 x 1mg	0 (0/6)	22 (2/9)
2 x 1mg	0 (0/6)	22 (2/9)
1 x 2mg	0 (0/3)	33 (3/9)
2 x 2mg	0 (0/3)	11 (1/9)
3 x 2mg	0 (0/3)	29 (2/7)

When a dose equivalent to the 1 x 0.5 mg dry powder dose is administered via a solution MDI, approximately 80-100% of subjects experience cough in the first 5

minutes following dosing. Not only is the percentage of cough greatly reduced by use of the dry powder inhaler as compared with the solution metered dose inhaler but the severity of those coughs is also greatly reduced. Furthermore, with the dry powder inhaler the incidence of cough remains acceptable at doses in the therapeutic range.

Claims

1. An inhaled formulation comprising a compound of the formula (I)

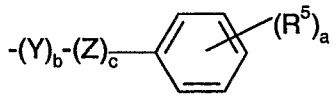


(I)

or a pharmaceutically acceptable salt thereof; wherein

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_4)$alkenyl, phenyl, dimethylamino, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_6)$acyl wherein the alkyl, phenyl or alkenyl groups may be substituted with up to two hydroxy, $(C_1\text{-}C_3)$alkyl, or trifluoromethyl groups, or up to three halogens;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_{14})$alkyl, $(C_1\text{-}C_7)$alkoxy$(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_{14})$alkenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_2)$alkyl, a saturated or unsaturated $(C_4\text{-}C_7)$heterocyclic$(CH_2)_n$ group wherein n is 0, 1 or 2, containing as the heteroatom one or two of the group consisting of oxygen, sulphur, sulphonyl, nitrogen and NR^4 wherein R^4 is hydrogen or $(C_1\text{-}C_4)$alkyl; or a group of the formula



wherein a is an integer from 1 to 5; b and c are 0 or 1; R^5 is hydrogen, hydroxy, $(C_1\text{-}C_5)$alkyl, $(C_2\text{-}C_5)$alkenyl, $(C_1\text{-}C_5)$ alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_4)$alkyl; wherein Z is oxygen, sulphur, SO_2, CO or NR^8 wherein R^8 is

hydrogen or (C_1-C_4)alkyl; and Y is (C_1-C_5)alkylene or (C_2-C_6)alkenyl optionally substututed with up to two (C_1-C_7)alkyl or (C_3-C_7)cycloalkyl groups; wherein each of the alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic groups may be substituted with one to fourteen of the group consisting of (C_1-C_2)alkyl, trifluoromethyl or halogen; and

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryl and (C_6-C_{10})aryloxy;

characterised in that the formulation is capable of delivering the compound as fine, solid particles to the lung.

2. An inhaled formulation according to claim 1 wherein each of the alkyl, alkenyl, cycloalkyl, alkoxyalkyl and heterocyclic groups may be substituted with 1 to 5 of the group consisting of (C_1-C_2)alkyl, trifluoromethyl and hydrogen.

3. An inhaled formulation according to claim 1 or claim 2 wherein R^1 is methyl, ethyl or isopropyl.

4. An inhaled formulation according to any preceding claim wherein R^3 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_2)alkyl or phenyl optionally substituted with 1 or 2 of the group consisting of hydrogen, hydroxy, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_1-C_5)alkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C_1-C_4)alkyl.

5. An inhaled formulation according to claim 1 wherein the compound of the formula (I) is selected from:

9-cyclopentyl-5,6-dihydro-7-ethyl-3-phenyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopenyl-5,6-dihydro-7-ethyl-3-(furan-2-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-pyridyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(4-pyridyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(3-thienyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3-benzyl-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-propyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3,9-dicyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(1-methylcyclohex-1-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

3-(*tert*-butyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-methylphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-methoxyphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]1,2,4-triazolo[4,3-α]pyridine;

3-(2-chlorophenyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-iodophenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;

9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-trifluoromethylphenyl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine; and
5,6-dihydro-7-ethyl-9-(4-fluorophenyl)-3-(1-methylcyclohex-1-yl)-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine;
and the pharmaceutically acceptable salts thereof.

6. An inhaled formulation according to claim 1 wherein the compound of the formula (I) is 3-(*tert*-butyl)-9-cyclopentyl-5,6-dihydro-7-ethyl-9*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-α]pyridine.

7. An inhaled formulation according to claim 1 wherein the compound of the formula (I) is 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9*H*-pyrazolo[3,4-*c*]1,2,4-triazolo[4,3-α]pyridine.

8. An inhaled formulation according to claim 1 wherein the compound of the formula (I) has an aqueous solubility at physiological pH of less than 0.15mg/ml.

9. An inhaled formulation according to claim 8 wherein the compound of the formula (I) has an aqueous solubility at physiological pH of less than 0.05mg/ml.

10. An inhaled formulation according to any one of the preceding claims wherein the fine, solid drug particles have a size distribution of 90% less than 10 micrometers in diameter and 50% less than 5 micrometers in diameter.

11. An inhaled formulation according to claim 10 wherein the fine, solid drug particles have a size distribution of 90% less than 6 micrometers in diameter and 50% less than 3 micrometers in diameter.

12. An inhaled formulation according to any one of the preceding claims wherein the fine, solid particles are delivered to the lung by a dry powder inhaler.

13. An inhaled formulation according to claim 12 wherein the dry powder blend comprises lactose, preferably in its monohydrated form.

14. An inhaled formulation according to any one of claims 1 to 11 wherein the fine, solid particles are delivered by a suspension metered dose inhaler, a suspension atomiser or a suspension nebuliser.

15. An inhaled formulation according to any one of claims 1 to 11 wherein the fine, solid particles consist of microspheres, said microspheres comprising poly(D,L-lactic-co-glycolic acid).

16. An inhaled formulation according to any preceding claim for use as a medicament.

17. The use of an inhaled formulation according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of a disease treatable by the inhibition of PDE4.

18. The use according to claim 17, wherein the disease is a respiratory disease.

19. The use according to claim 18 wherein the respiratory disease is asthma or chronic obstructive pulmonary disease.

20. A method of treatment of a disease treatable by the inhibition of PDE4 comprising the administration of an inhaled formulation according to any one of claims 1 to 15 to a mammal.

21. A method of treatment according to claim 20 wherein the disease is a respiratory disease.

22. A method of treatment according to claim 21 wherein the respiratory disease is asthma or chronic obstructive pulmonary disease.

23. The use of a compound of the formula (I), as defined in claim 1, having an aqueous solubility at physiological pH of less than 0.15mg/ml in the manufacture of a medicament for administration by inhalation, characterised in that said medicament is in the form of a dry powder inhaler or other device capable of delivering low solubility particles.

24. Use according to Claim 23 wherein said medicament is in the form of a device other than a dry powder inhaler which is capable of delivering low solubility particles, which device is a suspension metered dose inhaler or a device capable of delivering liposomes, micronised/engineered particles, or microspheres.

25. Use according to Claim 24 wherein said device is a device capable of delivering microspheres, which microspheres comprise poly(D,L-lactic-co-glycolic acid).

26. A dry powder inhaler containing a compound of formula (I) as described in Claim 23.

27. A device other than a dry powder inhaler which is capable of delivering low solubility particles, which device contains a compound of formula (I) as described in Claim 23.