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650679

Patents Act 1990

NOTICE OF ENTITLEMENT

We, **Beecham Group p.l.c.** the applicant in respect of Application No. 86458/91, state the following:-

The Nominated person(s) is/are entitled to the grant of the patent because the Nominated person(s) would, on the grant of a patent for the invention, be entitled to have the patent assigned to him/her/them/it.

The Nominated person(s) is/are entitled to claim priority from the application(s) listed in the declaration under Article 8 of the PCT because the Nominated person made the application(s) listed in the declaration under Article 8 of the PCT.

The application(s) listed under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

Dated this 20th day of December, 1993

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

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(56) Prior Art Documents
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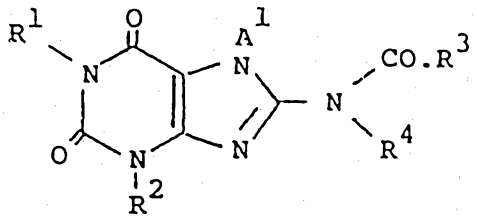
(57) Claim

1. A compound of formula (1):



(I)

or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m\text{-}A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;
R^3 represents substituted or unsubstituted aryl or a substituted alkyl group;
R^4 represents hydrogen or a group -CO.R^5 wherein R^5 represents substituted or unsubstituted alkyl or substituted or unsubstituted aryl; or

.../2

R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain; and

A^1 represents hydrogen or substituted or unsubstituted alkyl.

13. A method for the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, and allergic disorders associated with atopy comprising administering a therapeutically effective amount of a compound of formula (I) as defined in claim 1; or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof.

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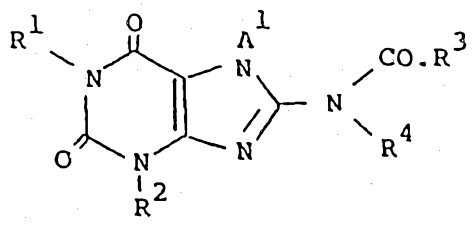


(I)

(57) Abstract

A compound of formula (I) or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a): $-(CH_2)_m$-A, wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical; R^3 represents substituted or unsubstituted aryl or a substituted alkyl group; R^4 represents hydrogen or a group $-CO.R^5$, wherein R^5 represents substituted or unsubstituted alkyl or substituted or unsubstituted aryl; or R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain; and A^1 represents hydrogen or substituted or unsubstituted alkyl; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound or composition in medicine.

Xanthines.

The present invention relates to certain novel compounds having pharmacological activity, to a process for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Molecular Pharmacology, Volume 6, No. 6, 1970, p.597-603 discloses 1,3-dimethyl-8-nitro-xanthine. This compound is disclosed as having lipolytic activity. Ann Chim, 47, 362-365 (1957) discloses 1,3-dimethyl-8-amino-xanthine and a process by which it may be prepared. No pharmacological utility is disclosed for this compound. Drug Res. 27(1) Nr 19, 1977, pages 4-14, Van K.H. Klingler discloses certain 1,3-dimethyl-8-substituted xanthines as intermediates solely in the synthesis of phenylethyl aminoalkyl xanthines. Drug Res. 31 (11), Nr. 12, 1981, R.G. Werner et al, pages 2044-2048 discloses certain 1,3-dimethyl-8-substituted xanthines. No pharmacological activity is disclosed for these compounds.

European Patent Application, Publication Number 0369744 also discloses certain 1,3- or 1,3,7- 8-H cycloalkylalkylene xanthines, for use inter alia as bronchodilators in the treatment of asthma.

European Patent Application, Publication Number 0389282 also discloses certain 1,3-cycloalkylalkylene 8-substituted xanthines for use inter alia in the treatment or prophylaxis of disorders associated with increased numbers of eosinophils.

It has now surprisingly been discovered that a novel series of substituted xanthines are indicated to be particularly effective as inhibitors of induced blood eosinophilia and that they are therefore potentially of particular use in the treatment and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

In addition these compounds show activity as phosphodiesterase inhibitors:

These compounds are indicated to have bronchodilator activity and thus to

be of potential use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

These compounds have a protective effect against the consequences of cerebral metabolic inhibition. The said compounds improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated with Parkinson's disease.

These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the compound is indicated to be of benefit for the treatment of functional disorders resulting from disturbed brain function following ischaemia.

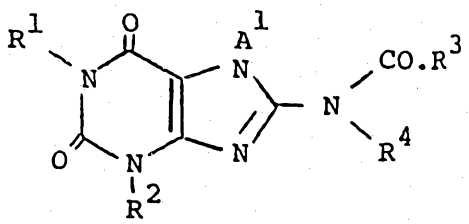
These compounds are also active in increasing the oxygen tension in ischaemic skeletal muscle. This property results in an increase in the nutritional blood flow through ischaemic skeletal muscle which in turn indicates that the compounds of the invention are of potential use as agents for the treatment of peripheral vascular disease such as intermittent claudication.

These compounds are also of potential use in the treatment of proliferative skin disease in human or non-human mammals.

In addition these compounds may also have potential as inhibitors of the production of tumour necrosis factor (TNF) and hence have potential for the treatment of human immunodeficiency virus (HIV), acute immune deficiency syndrome (AIDS), rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria,

pulmonary inflammatory disease, bone resorption diseases, reperfusion injury, graft vs. host reaction, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to AIDS, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

Accordingly, the invention provides a compound of formula (I):



(I)

or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof; wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m-A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;
R^3 represents substituted or unsubstituted aryl or a substituted alkyl group;
R^4 represents hydrogen or a group $-CO.R^5$ wherein R^5 represents substituted or unsubstituted alkyl or substituted or unsubstituted aryl; or R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain; and
A^1 represents hydrogen or substituted or unsubstituted alkyl.

Suitably, A is unsubstituted. Favourably, A represents a substituted or unsubstituted C_{3-8} cycloalkyl group, especially a C_{3-6} cycloalkyl group.

In particular, A represents a substituted or, preferably, unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

Favourably, A represents a cyclopropyl group or a cyclobutyl group.

Preferably, A represents a cyclopropyl group.

Suitably R^3 represent a substituted alkyl group. In particular an alkyl group substituted by a carboxy group. Favourably, R^3 represents a terminally substituted alkyl group, especially a terminally substituted ethyl or propyl group.

A preferred example of R^3 is the substituted alkyl group 2-carboxyethyl.

In another aspect, one example of R^3 is the substituted aryl group, o-carboxyphenyl.

In one aspect R^4 represents hydrogen.

In a further aspect R^4 represents -CO.R^5 wherein R^5 represents substituted or unsubstituted alkyl or substituted or unsubstituted aryl; or R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain.

Suitable optional substituents for the C_{2-3} polymethylene chain include up to five, preferably up to three, of the substituents mentioned below in relation to the aryl group and, especially for the C_2 polymethylene chain, substituents of adjacent carbon atoms of the C_{2-3} polymethylene chain form a residue of a substituted or unsubstituted phenylene group.

When R^3 together with R^5 represent a substituted or unsubstituted polymethylene chain it is suitably a substituted or unsubstituted C_{2-} polymethylene chain for example -CH_2CH_2- or a substituted or unsubstituted phenylene group.

When A^1 represents a substituted alkyl group it may be substituted as mentioned hereinafter in relation to alkyl groups.

Suitable substituted alkyl groups, represented by A^1, include aralkyl groups wherein the aryl group may be substituted or unsubstituted.

A suitable substituted aralkyl group represented by A^1, is a substituted benzyl group, suitably a methoxybenzyl group, for example a 4-methoxybenzyl group.

Preferably A^1 represents hydrogen.

Suitably, m represents zero or the integer 1.

Favourably, m represents 1.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable base salts of the compounds of formula (I) include 7-N base salts including metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Suitable acid addition salts of the compounds of formula (I) are the acid addition salts including pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphonate, α-keto glutarate, α-glycerophosphate and glucose-1-phosphate. Preferably the acid addition salt is a hydrochloride salt.

Pharmaceutically acceptable solvates include conventional solvates such as hydrates.

The pharmaceutically acceptable salts or solvates of the compounds of formula (I) are prepared using conventional procedures.

When used herein the term 'cyclic hydrocarbon radical' includes single ring and fused ring, alicyclic hydrocarbons comprising up to 8 carbon atoms in each ring, suitably up to 6 carbon atoms, for example 3, 4, 5 or 6 carbon atoms.

Suitable optional substituents for any cyclic hydrocarbon radical includes a C_{1-6} alkyl group or a halogen atom.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, halo alkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl,alkylcarbonyloxy, or alkylcarbonyl groups. Optional substituents for any phenylene group include up to three of the substituents mentioned in relation to the aryl group.

When used herein the term 'alkyl' whether used alone or when used as part of another group (for example as in an alkylcarbonyl group) includes straight and branched chain alkyl groups, containing from 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, for example methyl, ethyl, propyl or butyl. Suitable optional substituents for any alkyl group include up to five, preferably up to three of the substituents mentioned above in relation to the aryl group.

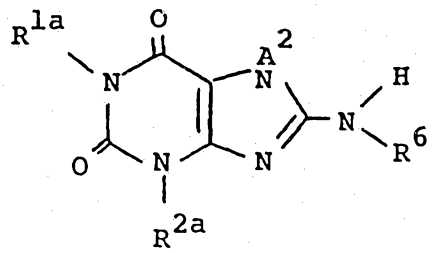
When used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

The compounds of formula (I) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (I) or where appropriate a pharmaceutically

acceptable salt thereof or a pharmaceutically acceptable solvate thereof, which process comprises:

a) for compounds of formula (I) wherein R^3 is substituted or unsubstituted aryl or substituted alkyl and R^4 is hydrogen or -CO.R^5 wherein R^5 is substituted or unsubstituted alkyl or substituted or unsubstituted aryl, by reacting a compound of formula (II):



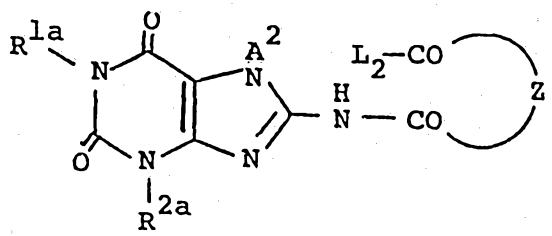
(II)

wherein R^{1a} represents R^1, as defined in relation to formula (I), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (I), or a group convertible thereto, A^2 represents A^1 as defined in relation to formula (I) or a group convertible thereto and R^6 represents hydrogen, a group -CO.R^{5a}, wherein R^{5a} represents unsubstituted alkyl, or a group -COR^{5b}, wherein R^{5b} is substituted alkyl or substituted or unsubstituted aryl, with a compound of formula (III):

$$R^7.CO.L^1 \qquad \text{(III)}$$

wherein, when R^6 in compound (II) is hydrogen or a group CO.R^{5a} then R^7 represents substituted alkyl or substituted or unsubstituted aryl, or when R^6 is a group -CO.R^{5b} then R^7 represents substituted or unsubstituted aryl or substituted or unsubstituted alkyl, and L^1 represents a leaving group; or

b) for compounds of formula (I) wherein R^3 together with R^5 represent a substituted or unsubstituted C_{2-3} polymethylene chain, by cyclising a compound of formula (IV):



(IV)

wherein R^{1a}, R^{2a} and A^2 are as defined in relation to formula (II), Z represents the substituted or unsubstituted C_{2-3} polymethylene chain as defined in relation to formula (I) or a protected form thereof, and L^2 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or A^2 to A^1;

(ii) converting a compound of formula (I) into a further compound of formula (I);

(iii) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

A suitable leaving group L^1 is a halo atom for example a bromine or chlorine atom.

Suitably, L^2 represents a halo atom, for example a bromine or chlorine atom, or a hydroxyl group.

Favourably, L^2 represents a hydroxyl group.

A compound of formula (II) wherein R^6 represents -CO.R^{5a} wherein R^{5a} is unsubstituted alkyl may be prepared by reacting a compound of formula (II) wherein R^6 is hydrogen with an appropriate compound of abovedefined formula (III).

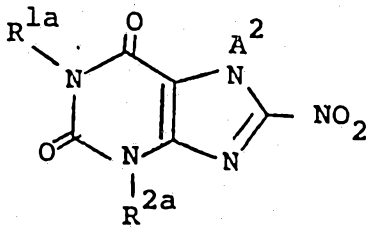
The reaction between compounds of formulae (II) and (III) may be carried out using conventional acylation conditions, for example in an aprotic solvent, such as dimethylformamide or tetrahydrofuran, at any temperature providing a suitable rate of formation of the required product, for example in the range of from 0°C to 100°C, conveniently at ambient temperature.

In the reaction between compounds (II) and (III), the 8-amino group of compound (II) is suitably in an activated form, favorably in an anionic form such as a salted form, for example an alkali metal salted form.

Alternatively and preferably, the reaction between compounds of formulae (II) and (III) is carried out in an aprotic solvent, such as tetrahydrofuran, at a temperature in the range of 0°C to 100°C, in the presence of a base such as triethylamine.

The cyclisation of compound (IV) may be carried out under analogous conditions as appropriate to the reaction between compounds (II) and (III), a favoured aprotic solvent being tetrahydrofuran.

A compound of formula (II) wherein R^6 is hydrogen, may be prepared by reducing a compound of formula (V):

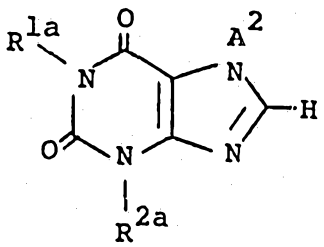


(V)

wherein R^{1a}, R^{2a} and A^2 are as defined in relation to formula (II); and thereafter if required converting R^{1a} into R^1 and/or R^{2a} into R^2 and/or A^2 into A^1.

The reduction of compound (V) may be carried out by using any suitable, conventional reduction method, for example using tin powder and concentrated hydrochloric acid at ambient temperature or by using sodium dithionite in aqueous methanol at ambient temperature.

A compound of formula (V) may be prepared by nitrating a compound of the above defined formula (VI):

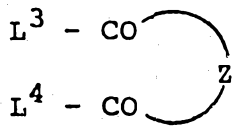


(VI)

wherein R^{1a}, R^{2a} and A^2 are as defined in relation to formula (II), and thereafter, if required, converting R^{1a} into R^1 and/or R^{2a} into R^2 and/or A^2 into A^1.

The nitration of compound (VI) may be carried out using any suitable, conventional nitrating agent, for example a nitric acid/acetic acid mixture in an inert solvent, such as dichloromethane, at any temperature providing a convenient rate of formation of the required product, conveniently at ambient temperature.

A compound of formula (IV), may be prepared by reacting a compound of formula (II) wherein R^6 is hydrogen, with a compound of formula (VII):



(VII)

wherein Z is as defined in relation to formula (IV), L^3 and L^4 each independently represent leaving groups or L^3 together with L^4 represents an oxygen atom; and thereafter, if required, converting R^{1a} into R^1 and/or R^{2a} into R^2 and/or A^2 into A^1.

When L^3 and L^4 represent leaving groups each may represent the group L^2 as hereinbefore defined.

The reaction between compounds of formulae (II) wherein R^6 is hydrogen, and (VII) wherein L^3 and L^4 independently represent leaving groups may be carried out under analogous conditions to that used in the cyclisation of the compounds of formula (IV).

The reaction between the compound of formula (II) wherein R^6 is hydrogen and the compound of formula (VII) wherein L^3 together with L^4 is an oxygen atom may be carried out in an aprotic solvent, such as tetrahydrofuran at any temperature providing a suitable rate of formation of the required product, such as in the range of from 20 to 80°C, suitably at 60°C and preferably in the presence of a base such as triethylamine.

Favourably, the compound of formula (IV) is not isolated from the reaction

between compounds of formulae (II), wherein R^6 is hydrogen, and (VII), but is converted in situ into a compound of formula (I).

A compound of formula (VII), especially when L^3 together with L^4 is an oxygen atom, may also be reacted with a compound of formula (II), wherein R^6 is hydrogen, to provide a compound of formula (I) wherein R^1 and R^2 are as defined above, R^4 is hydrogen and R^3 is a substituted or unsubstituted phenyl group having a carboxyl group attached ortho to the carbon atom bonding R^3 to the carbonyl of the N-CO.R^3 group.

Conversions of one compound of formula (I) into another compound of formula (I) includes:

i) converting a compound of formula (I) wherein A^1 represents hydrogen into a compound of formula (I) wherein A^1 represents substituted or unsubstituted alkyl; or

ii) hydrolysing compounds wherein R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain, for example when R^3 together with R^5 represents $-CH_2CH_2-$ the resulting compound of formula (I) is that wherein R^4 is hydrogen and R^3 is $-CH_2CH_2-CO_2H$, or when R^3 and R^5 together represent a phenylene group then the resulting compound of formula (I) is that wherein R^4 is hydrogen and R^3 is o-carboxyphenyl.

Alkylation reaction (i) may be effected by conventional alkylation methods, for example by treatment of the appropriate compound of formula (I) with an alkyl halide of a compound of formula (VII) described below and wherein A^3 is A^1.

In the hydrolysis (ii) hydrolysis of the appropriate compound of formula (I) may be effected by any suitable hydrol procedure, for example treatment with lithium hydroxide in aqueous tetrahydrofuran at ambient temperature.

Suitable values for R^{1a}, R^{2a} and A^2 include R^1, R^2 and A^1 respectively or nitrogen protecting groups such as benzyl groups.

When R^{1a}, R^{2a} or A^2 represents other than R^1, R^2 or A^1 repectively, the abovementioned conversions of R^{1a} into R^1, R^{2a} to R^2 and A^2 into A^1 may be carried out using the appropriate conventional procedure. For example when R^{1a}, R^{2a}, or A^2 represents a nitrogen protecting group, such as a benzyl group, the protecting group may be removed using the appropriate conventional procedure, such as catalytic hydrogenation, and the resulting product reacted with a compound of formula (VIII):

$$X\text{-}A^3 \qquad \text{(VIII)}$$

wherein A^3 represents R^1 or R^2 (for converting R^{1a} into R^1 or R^{2a} into R^2) or A^3 represents A^1 (for converting A^2 into A^1) wherein R^1, R^2 and A^1 are as defined in relation to formula (I) and X represents a leaving group, such as halide, for example bromide or iodide.

The protection of any reactive group or atom, such as the xanthine nitrogen atom may be carried out at any appropriate stage in the aforementioned process. Suitable protecting groups include those used conventionally in the art for the particular group or atom being protected, for example suitable protecting groups for the xanthine nitrogen atoms are benzyl groups.

In the circumstances when variable A^1 represents a benzyl group or a substituted benzyl group and R^{1a} and/or R^{2a} represents a nitrogen protecting group, the particular protecting groups chosen will be those which may be prepared and removed without affecting A^1, examples of such protecting groups are trialkyl silyl groups such as t-butyl dimethyl silyl or trimethyl silyl groups.

Preferably for compounds of formula (I) wherein A^1 represents benzyl or substituted benzyl then R^{1a} is R^1 and R^{2a} is R^2.

Protecting groups may be prepared and removed using the appropriate conventional procedure:

For example, N-benzyl protecting groups may be prepared by treating the appropriate compound of formula (II) with benzyl chloride in the presence of a base such as triethylamine, bases such as potassium t-butoxide may

also be used . The N-benzyl protecting groups may be removed by catalytic hydrogenation over a suitable catalyst, such as palladium on activated charcoal, in a suitable solvent, such as ethanol conveniently at an elevated temperature, or by treatment with anhydrous aluminium chloride in dry benzene at ambient temperature. Trialkylsilyl protected nitrogen groups may be prepared by treating the appropriate compound with a trialkylsilyl halide, for example trimethylsilyl chloride, in the presence of a base such as potassium t-butoxide. The N-trialkylsilyl protecting group may be removed by mild basic hydrolysis or by treatment with a source of fluoride ions such as tetrabutylammoniumfluoride.

Compounds of formulae (II) especially those wherein A^2 and/or R^6 are other than hydrogen, (IV) and (V) especially those wherein A^2 is other than hydrogen are novel compounds and as such form part of the present invention. The compounds of formula (VI) wherein A^2 is other than hydrogen are novel compounds and accordingly form part of the present invention.

Compounds of formula (VI) wherein A^2 is hydrogen are known compounds and may be prepared according to methods disclosed in EP 0369744.

Compounds of formula (VII) and (VIII) are known compounds or are prepared according to methods used to prepare known compounds for example those disclosed in J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: the present invention accordingly provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

In a further aspect the present invention also provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as a phosphodiesterase inhibitor.

In a particular aspect, as indicated hereinbefore, the present invention provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

In a further particular aspect, the present invention provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatments mentioned hereinbefore, such as cerebral vascular and neuronal denerative disorders associated with learning, memory and cognitive dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events or for the inhibition of the production of tumour necrosis factor in for example the treatment of human immunodeficiency virus.

A compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical,

parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats;

emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (I) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05,

0.06, 0.08, 0.1 or 0.2 mg/kg/day; and such therapy may extend for a number of weeks or months.

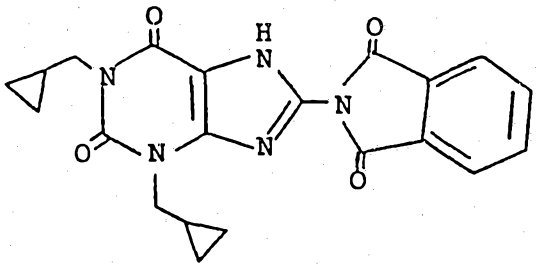
When used herein the term 'pharmaceutically acceptable' encompasses materials suitable for both human and veterinary use.

No toxicological effects have been established for the compounds of formula (I) in the abovementioned dosage ranges.

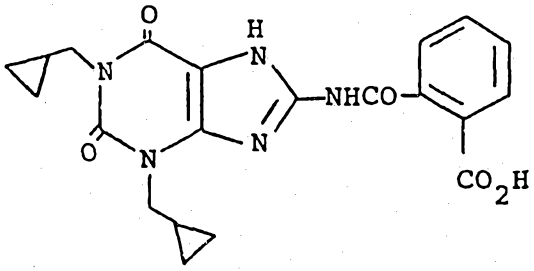
The following pharmacological data and examples illustrate the invention. The following preparations illustrate the preparation of intermediates to the novel compounds of formula (I).

Examples 1 and 2

1,3-Di(cyclopropylmethyl)-8-(N-phthalimido)xanthine and
1,3-di(cyclopropylmethyl)-8-(2-carboxybenzoyl)amino xanthine



(Ex. 1)



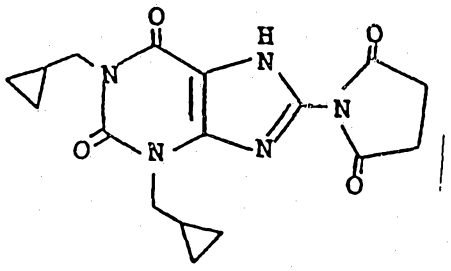
(Ex.2)

8-Amino-1,3-di(cyclopropylmethyl)xanthine (2.7g,10mmole), phthalic anhydride (1.48g,10mmole)and triethylamine (3ml,2.2eq) were stirred together in THF(40ml)at 60^{0}C for 48hr. After cooling the mixture was added to ethyl acetate (200ml) and the organic solution, washed with dilute HCl (2X30ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue on silica (acetone/hexane gradient) gave 1,3-di(cyclopropylmethyl)-8-(N-phthalimido)xanthine (1.06g,26%) m.p.244-5^{0}C, νmax(KBr)1745(s),1705(s),1652(s)and 1504(s)cm^{-1}; δ($CDCl_3$) 0.14-0.19 (2H, m), 0.22-0.29 (2H,m), 0.32-0.54 (4H,m), 1.11-1.19 (1H,m), 1.34-1.44 (1H,m), 3.77 (2H,d,J=7.0Hz), 4.05 (2H,d,J=7.5Hz) 7.90 (2H,dd,J=5.5, 3.OHz), 8.04 (2H,dd, J=5.5,3.0Hz), 12.60 (1H, brs); m/e 405 (M+,100%), 267 (50), 281 (34), 377 (33);
Found C, 62.28; H, 4.65; N, 17.35 $C_{21}H_{19}N_5O_4$
requires C, 62.21; H, 4.72; N, 17.28%.

followed by 1,3-di(cylopropylmethyl)-8-(2-carboxybenzyol)aminoxanthine (0.79g, 19%) m.p. 185-8^{0}C (d); ν max (KBr) 3428 (m), 1706(s), 1645(s), 1634(s) and 1535 (m) cm^{-1}; δ (CD[illegible] d_6-DMSO), 0.39-0.47 (8H,m), 1.26-1.38 (2H,m), 3.86 (4H,t (overlapping d), J=6.5 Hz), 5.86 (2H,brs), 7.53 (2H, dd, J=6.0, 3.5Hz), 7.72 (2H, dd, J=6.0, 3.5 H_z), 10.91 (1H, brs); m/e 185 (100%), 93 (78), 276 (76), 424 (MH^+,40);
Found C, 57.15; H, 5.12; N, 15.75. $C_{21}H_{21}N_5O_5.H_2O$
requires C, 57.13; H, 5.25; N, 15.87%.

Example 3

1,3-Di(cyclopropylmethyl)-8-(N-succinimido)xanthine



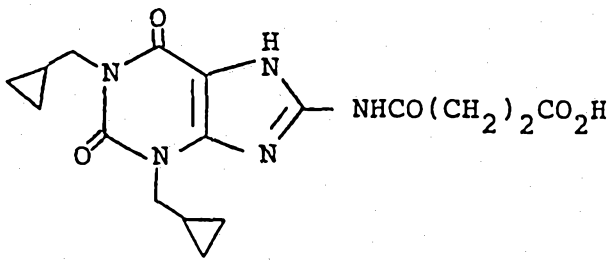
8-Amino-1,3-di(cyclopropylmethyl)xanthine (2.7g, 10mmole), succinic anhydride (2.4g, 20mmole) and tri-ethylamine (3ml, 2.2eq) were stirred together in THF (40ml) at 60°C for 48hr. After cooling the solvent was removed under reduced pressure and the residue chromatographed on silica ($MeOH/CHCl_3$ 1:20) to give 1,3-di(cyclopropylmethyl)-8-(N-succinimido)xanthine (2.46g, 70%) m.p. 235-6°C, ν max (KBr) 1739 (s), 1703 (s), 1653 (s), 1605 (w) and 1505 (s) cm^{-1}; δ ($CDCl_3$) 0.35-0.56 (8H,m), 1.22-1.44 (2H,m), 3.00 (4H,s), 3.92 (2H,d,J=7.0Hz), 4.03 (2H,d,J=7.OHz), 12.25 (1H, br);

m/e 358 (M+,100%), 35(67), found 358.1518, $C_{17}H_{19}N_5O_4$ requires 358.1516;

Found C, 57.29, H, 5.19; N, 19.57; $C_{17}H_{19}N_5O_4$ requires C, 57.13; H, 5.36; N, 19.60%.

Example 4

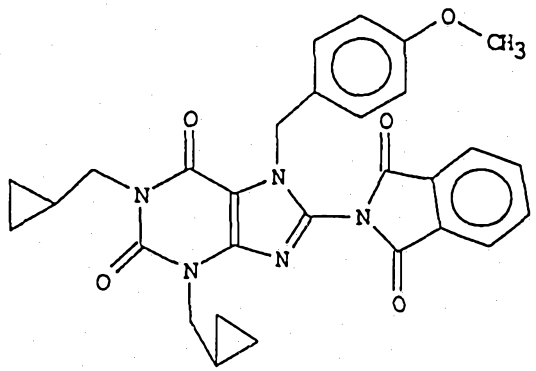
1,3-Di(cyclopropylmethyl)-8-(3-carboxypropanoyl)amino-xanthine



1,3-di(cyclopropylmethyl)-8-(N-succinimido)xanthine (0.18g, 0.5mmole) and lithium hydroxide monohydrate (0.042g, 1mmole) were stirred together in a water/THF mixture (1:1, 3ml). After 0.5h at ambient temperature the solution was neutralized with dilute hydrochloric acid and filtered to give 1,3-di(cyclopropylmethyl)-8-(3-carboxy-propanoyl)aminoxanthine (0.19g, 100%) m.p. 183-4°C, ν max (KBr) 3441 (s), 3051 (m), 1709 (s), 1700 (s), 1633 (s) and 1523 (s) cm^{-1}; δ (d_6 DMSO) 0.30-0.50 (8H,m), 1.13-1.29 (2H,m), 2.49-2.67 (4H,m), 3.77 (2H,d,J=7.0Hz), 3.83 (2H,d,J=7.0Hz), 11.77 (1H,br), 12.13 (2H, br); m/e 35(100%), 358 (35), 276 (8), 376 (MH^+,4), found 376.2399, $C_{17}H_{22}N_5O_5$ requires 376.1621.

Example 5

1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(N-phthalimido)xanthine

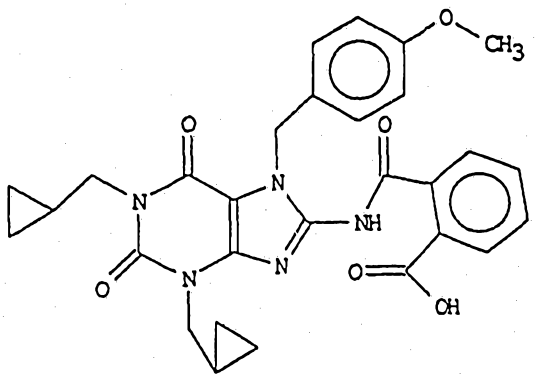


1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(N-phthalimido)xanthine, m.p. 190-192°C, was prepared in 82% yield from 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine in a similar manner to that of Example 1, δ ($CDCl_3$) 0.44-0.51 (8H,m), 1.29-1.58 (2H,m), 3.67 (3H,s), 3.95 (2H,d,J=7.2Hz), 4.00 (2H,d,J=7.4Hz), 5.49 (2H,s), 6.66 (2H,d,J=8.8Hz), 7.07 (2H,d,J=8.8Hz) and 7.80-7.94 (4H,m); ν_{max} (KBr) 1795 (w), 1742 (s), 1702 (s), 1663 (s), 1513 (s) and 724 (m) cm^{-1}; m/e 121 (100%), 525 (M^+,30);

Found C, 66.08; H, 5.16; N, 13.12; $C_{29}H_{27}N_5O_5$ requires C, 66.27; H, 5.18; N, 13.33%.

Example 6

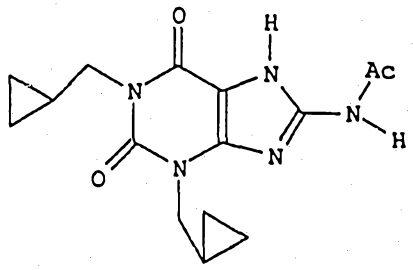
8-(2-Carboxybenzoylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine



8-(2-Carboxybenzoylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine, m.p. 165-6°C, was prepared in 90% yield from 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(N-phthalimido)xanthine in a similar manner to that of Example 4. δ ($CDCl_3$) 0.09-0.12 (2H,m), 0.25-0.26 (2H,m), 0.37-0.49 (4H,m), 0.91-0.96 (1H,m), 1.21-1.30 (1H,m), 3.67 (2H,d,J=7.4Hz), 3.78 (3H,s), 3.92 (2H,d,J=7.2Hz), 5.89 (2H,brs), 6.86 (2H,d,J=8.5Hz), 7.32 (2H,d,J=8.5Hz), 7.53-7.91 (4H,m) and 10.69 (1H,brs); ν_{max} (KBr) 3359 (w), 2950 (w), 1740 (s), 1695 (s), 1650 (s), 1603 (s), 1519 (m), 1459 (m) and 1232 (m) cm^{-1}; m/e (FAB,Na) 154 (100%), 176 (80), 136 (76), 239 (25), 121 (24), 89 (20), 307 (18), 566 (MNa^+,4);
Found C, 63.68; H, 5.31; N, 12.78; $C_{29}H_{29}N_5O_6$
requires C, 44.08; H, 5.38; N, 12.89%.

Example 7

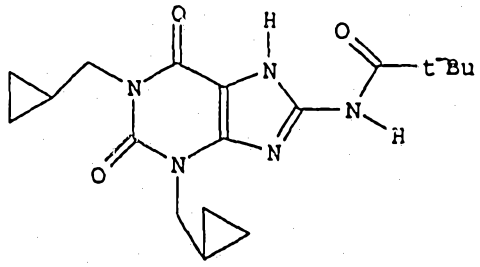
8-(2-Carboxybenzoylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine



8-(2-Carboxybenzoylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine, m.p. 165-6°C, was prepared in 90% yield from 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(N-phthalimido)xanthine in a similar manner to that of Example 4. δ ($CDCl_3$) 0.09-0.12 (2H,m), 0.25-0.26 (2H,m), 0.37-0.49 (4H,m), 0.91-0.96 (1H,m), 1.21-1.30 (1H,m), 3.67 (2H,d,J=7.4Hz), 3.78 (3H,s), 3.92 (2H,d,J=7.2Hz), 5.89 (2H,brs), 6.86 (2H,d,J=8.5Hz), 7.32 (2H,d,J=8.5Hz), 7.53-7.91 (4H,m) and 10.69 (1H,brs); ν_{max} (KBr) 3359 (w), 2950 (w), 1740 (s), 1695 (s), 1650 (s), 1603 (s), 1519 (m), 1459 (m) and 1232 (m) cm^{-1}; m/e (FAB,Na) 154 (100%), 176 (80), 136 (76), 239 (25), 121 (24), 89 (20), 307 (18), 566 (MNa^+,4);
Found C, 63.68; H, 5.31; N, 12.78; $C_{29}H_{29}N_5O_6$

requires C, 44.08; H, 5.38; N, 12.89%.

Example 8

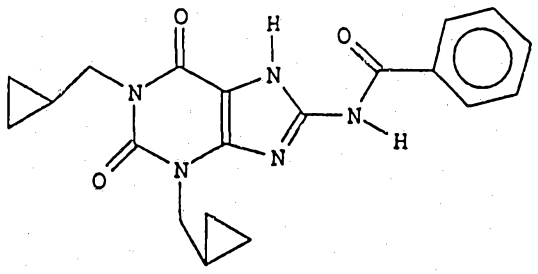


8-t-Butylamido-1,3-di(cyclopropylmethyl)xanthine

Potassium t-butoxide (1.12g 10mmole) was added to a stirred solution of 8-amino-1,3-di(cylcopropylmethyl)xanthine (2.7g, 10mmole) in dimethyl formamide (40ml) at ambient temperature. After 2 h, a solution of chloromethyl-pivaloate (1.52g, 10mmole) in DMF (5ml) was slowly added and stirring continued overnight. The mixture was added to ethyl acetate (200ml) and was washed with dilute hydrochloric acid (50ml) and water (50ml). After drying over $MgSO_4$ the solvent was removed under vacuum and the residue extracted with acetone. Chromatography of the extract on silica (hexane/acetone gradient) yielded:- 8-t-butylamino-1,3-di(cyclopropylmethyl)-7-pivaloyloxymethyl xanthine (0.40g, 8%), m.p. 157-8°C; δ ($CDCl_3$) 0.42-0.51 (8H,m), 1.22 (9H,s), 1.22-1.45 (2H,m), 1.39 (9H,s), 3.93 (2H,d,J=7.2Hz), 3.99 (2H,d,J=7.2Hz), 6.02 (2H,s), and 9.28 (1H,s); ν_{max} (KBr) 1699 (s), 1647 (s), 1522 (m), 1456 (m), 1263 (m) and 1092 (m) cm^{-1}; m/e (CI,NH_3) 372 (100%), 474 (MH^+,47), 360 (28); MH^+ observed 474.2690, $C_{24}H_{36}N_5O_5$ requires 474.2717;
Found C, 60.77; H, 7.55; N, 14.65; $C_{24}H_{35}N_5O_5$
requires C, 60.87; H, 7.45; N, 14.79%,
followed by:- 8-t-butylamido-1,3-di(cyclopropylmethyl)xanthine, (0.52g, 14.5%), m.p. 178-9°C; δ ($CDCl_3$) 0.42-0.51 (8H,m), 1.27-1.57 (2H,m), 1.33 (9H,s), 3.86 (2H,d,J=7.2Hz), 3.92 (2H,d,J=7.2Hz), 8.77 (1H,s) and 11.24 (1H,s); ν_{max} (KBr) 1707 (s), 1649 (s), 1501 (s) and 1157 (m) cm^{-1}; m/e (CI,NH_3) 360 (MH^+,100%) MH^+ observed 360.2036, $C_{18}H_{26}N_5O_3$ requires 360.2036;
Found C, 60.10; H, 7.17; N, 19.51; $C_{18}H_{25}N_5O_3$
requires C, 60.15; H, 7.01; N, 19.49%.

Example 9

8-Benzamido-1,3-di(cyclopropylmethyl)xanthine



Sodium hydride (0.30g of a 60% dispersion in oil, 7.6mmole) was added to a suspension of 8-amino-1,3-di(cyclopropylmethyl)xanthine (1.0g,3.6mmole) in tetrahydrofuran (10ml). After 0.5h benzoyl chloride (0.56g, 1.1eq) was added and stirring continued for a further 16 h. The reaction mixture was poured into water (50ml) and neutralised. The precipitate was collected by filtration, washed with benzene and dried for 16 h under vacuum to afford 8-benzamido-1,3-di(cyclopropylmethyl)xanthine (1.2g, 87%). m.p. >250°C ($CHCl_3$/MeOH); δ ($CDCl_3$) 0.37-0.55 (8H,m), 1.23-1.42 (2H,m), 3.88 (2H,d,J=7.1Hz), 3.95 (2H,d,J=6.9Hz), 7.46-7.63 (3H,m), 8.11-8.14 (2H,m); 11.86 (1H,bs), and 12.13 (1H,s), ν_{max} (KBr) 3227 (s), 1709 (s), 1649 (s), 1633 (s), 1583 (s), 1493 (s), 1258 (s), 1095 (m), 703 (m) cm^{-1}; m/e (CI) 330 (MH^+,100%) Found C, 63.14; H, 5.71; N, 18.37; $C_{20}H_{21}N_5O_3$ requires C, 63.30; H, 5.58; N, 18.46%.

Procedure 1

1,3-Di-cyclopropylmethyl-8-nitro xanthine

1,3-Di-cyclopropylmethyl xanthine (20g, 0.076mol) was dissolved in acetic acid (33ml) and then treated with concentrated nitric acid (13.2g) at 87°C. After 1 hour, the mixture was cooled to 5°C and the resulting yellow precipitate filtered off. The yellow crystals were dissolved in dichloromethane and washed with water. The separated organic layer was then dried over anhydrous sodium sulphate and concentrated in vacuo. The product crystallized from the concentrate to yield a yellow

crystalline product yield 12.2g, (56.5%), m.pt. 207°C (with decomposition).

^{1}H NMR ($CDCl_3$):

ppm: 0.35-0.7 (m, 8H), 1.1-1.7 (m, 2H), 3.95-4.2 (m, 4H), 9.0-11.0 (br. exchanges with D_2O, 1H).

Procedure 2

1,3-Di-cyclopropylmethyl-8-amino xanthine

1,3-Di-cylopropylmethyl-8-nitro xanthine (4g, 0,014mol), suspended in 50ml of concentrated hydrochloric acid,was treated with small portions of tin (8g) at room temperature. The mixture was then stirred at room temperature for two hours.

The resulting precipitate was filtered off and crystallised from ethanol to give white crystals of the title product, yield 0.9g (23%), m.pt. 281°C.

In an alternative procedure, using sodium dithionite as reducing agent (in methanol-water mixture) The yield was 36%.

^{1}H NMR ($CDCl_3$):

δ: 0.3-0.6 (m,8H), 1.0-1.6 (m,2H), 3.7-4.0 (m,4H), 5.75 (br,2H), 10.84 (br. exchanges with D_2O, 1H).

Procedure 3

8-Amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-xanthine

Potassium t-butoxide(1.34g,12mmole)was added to a solution of 8-amino-1,3-di(cyclopropylmethyl)xanthine (2.7g,10mmole)in DMF(25ml)and the resulting mixture was stirred for 0.5hr at ambient temperature. 4-Methoxybenzyl chloride(1.56g,1.35ml,10mmole) was added to the red solution which lightened to an orange colour. After stirring for 1hr at ambient temperature the mixture was added to ethyl acetate (200ml), washed with dilute hydrochloric acid(50ml),water(50ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid which was chromatographed on silica (hexane/acetone, gradient)to give 8-amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl) xanthine (2.55,64%) m.p.176°C, νmax (KBr) 3434(w), 1691(m),1639(s),1527(m) and 1456(m)cm^{-1}; δ($CDCl_3$)0.43-0.53(8H,m), 1.26-1.35(2H,m),3.79(3H,s),3.89 (4H,t(overlapping d), J=7.0H_z), 4.55(2H,brs), 5.32(2H,s), 6.90(2H,d,J=9.0H_z), 7.30(2H,d,J=9.0H_z); m/e 121(100%), 395(M^+,20); Found C, 63.64; H, 6.36; N, 17.77. $C_{21}H_{25}N_5O_3$ requires C, 63.78; H, 6.37; N, 17.71%.

PHARMACOLOGICAL DATA

1) Induction of blood eosinophilia and the effects of drugs.

Animals

Male Charles River Sprague Dawley rats weighing between 270 to 400g were used.

The method used was a modification of that described by Laycock et al (Int. Arch. Appl. Immunol, (1986). 81, 363).

Sephadex G200, particle size 40 to 120 micron, was suspended in isotonic saline at 0.5mg/ml, and stored for 48h at 4°C. 1ml of the suspension was given intravenously to rats on days 0,2 and 5. A control group received saline. The test compound was givenbefore the Sephadex on each occasion, with a contact time expected to give maximum activity at the time of the Sephadex administration. Blood was taken from the tail vein of the rats on day 7 for the determination of total and differential leucocyte counts.

A control group of at least 6 animals was included each time a compound was evaluated. The control group received Sephadex and the vehicle without test compound. The results in the drug treated animals were compared with the control group.

Total and differential leucocyte counts.

20ml samples of blood, taken from the tail vein of the rats, were added to 10ml of Isoton II and, within 30min, Zaponin (3 drops) was added, to lyse the erythrocytes. Five minutes later the total cell count was determined using a Coulter Counter Model DN. Differential leucocyte counts were carried out by fixing and staining a blood smear on a microscopic slide with May-Grunwald and Giemsa stains. A minimum of 400 cells were counted on each slide.

Statistics

Probability values were calculated using the Student's t test.

Results

The effect of the test compound upon Sephadex induced eosinophilia in the rat is set out below. The test compound was given orally 30 minutes before each injection of Sephadex.

Test Compound	Dose mg/kg (orally - 30 mins)	% of Control Mean ± SEM (n=16
Vehicle dosed control + sephadex i.v	-	100 ± 13
Negative control saline i.v.	-	14 ± 1 ***
Example 2	10	49 ± 13*
Example 3	20	60± 12*

Notes

* $p < 0.05$

*** $p < 0.001$

2) Inhibition of Phosphodiesterase

Isolation of phosphodiesterases

The Ca^{2+}/calmodulin-stimulated PDE (PDE I, see Table 1 and Beavo and Reifsynder (1990) for nomenclature) was prepared from bovine cardiac ventricle. Following chromatography on a Mono Q column, the fractions showing stimulation of PDE activity by Ca^{2+} and calmodulin were pooled and further purified on a calmodulin-affinity column. cGMP-stimulated PDE (PDE II), cGMP-inhibited PDE (PDE III) and cAMP-specific PDE (PDE IV) were all isolated from guinea-pig cardiac ventricle. Initial chromatography on a 20 ml Mono Q column resolved PDE III from a peak that contained both PDE II and PDE IV. The latter were separately rechromatographed on a 1 ml Mono Q column. cGMP-selective PDE (PDE V) was obtained from porcine lung using chromatography on DEAE-cellulose and Mono Q columns; a calmodulin-affinity column was used to remove residual PDE I activity.

Characteristics of phosphodiesterase isoenzymes

With the exception of PDE II, which displayed positive cooperativity, all the preparations showed simple Michaelis-Menton kinetics (see Table 1).

PDE I The activity of this isoenzyme was stimulated by the Ca^{2+}-calmodulin complex. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate.

PDE II The activity of this isoenzyme with cAMP as a substrate was stimulated by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate under basal conditions. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

PDEIII The activity of this isoenzyme with cAMP as a substrate was inhibited by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the former was the preferred substrate. The activity of this isoenzyme was unaffected by the Ca^{2+} calmodulin complex.

PDE IV This isoenzyme had high affinity for cAMP, the hydrolysis of which was not inhibited by cGMP. The activity of this isoenzyme was unaffected by the Ca2-calmodulin complex.

PDE V This isoenzyme had high affinity for cGMP. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

Assay of phosphodiesterase activity

PDE activity was assayed by the boronate column method as previously described (Reeves et. al., 1987). The enzymes were assayed by incubation at 37°C for 4-30 min. in 50 mM Tris, 5 mM $MgCl_2$, pH 7.5 with ^3H-labelled cyclic nucleotide (4×10^5 disintegrations min^{-1}) and ^{14}C-labelled nucleotide 5'-monophosphate (3×10^3 disintegrations min^{-1}). The assay was stopped by boiling and the ^3H-labelled 5'-monophosphate product separated from substrate on boronate columns. The reaction mixture was diluted with 0.5 mL 100 mM HEPES [N-(2-hydroxyethyl)piperazine-N^1-2-ethanesulfonic acid], 100 mM NaCl, pH 8.5, and applied to the column. The column was extensively washed with the same buffer, and the 5'-nucleotide eluted with 6 mL of 0.25 M acetic acid. The recovery of product as judged by ^{14}C-recovery was approximately 80%. All assays were linear with time of incubation and concentration of enzyme over the range used in these experiments. IC_{50} values (the concentration of inhibitor required for 50% inhibition of activity) were obtained by incubation of the isoenzyme using 1 mM cGMP as a substrate for PDE I (in the absence of Ca^{2+} and calmodulin), PDE II and PDE V and with 1 mM cAMP as a substrate for PDE III and PDE IV.

A range of inhibitor concentrations from 0.1 x IC_{50} to 100 x IC_{50} was used.

References

BEAVO, J.A. and D.H. REIFSNYDER, Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. Trends. Pharmacol. Sci. 11, 150-155 (1990).

REEVES M.L., B.K. LEIGH and P.J. ENGLAND, The identification of a new cyclic nucleotide phosphodiesterase activity in human and guinea-pig cardiac ventricle. Biochem. J. 241, 535-541 (1987).

Table 1: Kinetic properties of phosphodiesterase isoenzymes

Isoenzyme		Km (μM) cAMP	Km (μM) cGMP	Vmax cAMP / Vmax cGMP
I.	Ca^{2+}/calmodulin-stimulated	36	5	5
II.	cGMP-stimulated	45	14	1
III.	cGMP-inhibited	0.5	0.1	5
IV.	cAMP-specific	2	>	n.d.
V.	cGMP-specific	>	1	N.d.

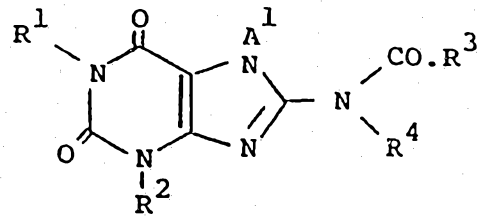
a enzyme displayed positive cooperativity
> Km > 100 mM
n.d. not determined, due to inability of PDE to hydrolyse one of the substrates.

RESULTS

Example No.	Inhibition of: PD IV IC_{50}(μM)	PDE V IC_{50}(μM)
1	10	0.05
2	6	0.2
3	44	3
4	50	13

Claims

1. A compound of formula (1):



(I)

or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m-A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;
R^3 represents substituted or unsubstituted aryl or a substituted alkyl group;
R^4 represents hydrogen or a group $-CO.R^5$ wherein R^5 represents substituted or unsubstituted alkyl or substituted or unsubstituted aryl; or R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain; and
A^1 represents hydrogen or substituted or unsubstituted alkyl.

2. A compound according to claim 1, wherein A represents a substituted or unsubstituted C_{3-8} cycloalkyl group.

3. A compound according to claim 1 or claim 2, wherein A represents an unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

4. A compound according to any one of claims 1 to 3, wherein A represents a cyclopropyl group.

5. A compound according to any one of claims 1 to 4, wherein R^3 represents a substituted alkyl group.

6. A compound according to any one of claims 1 to 5, wherein R^3 represents a terminally substituted ethyl or propyl group.

7. A compound according to any one of claims 1 to 6, wherein R^3 is 2-carboxyethyl.

8. A compound according to any one of claims 1 to 4, wherein R^3 together with R^5 represents a substituted or unsubstituted C_{2-3} polymethylene chain substituted with one, two or three selected from the list consisting of: halogen, alkyl, phenyl, alkoxy, halo alkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy and alkylcarbonyl groups or substituents of adjacent carbon atoms of the C_{2-3} polymethylene chain form a residue of a substituted or unsubstituted phenylene group.

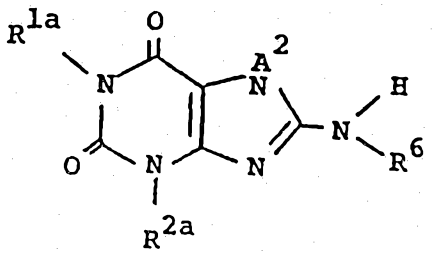
9. A compound according to any one of claims 1 to 8, wherein R^4 represents hydrogen.

10. A compound according to claim 1, selected from the group consisting of:
1,3-di(cyclopropylmethyl)-8-(N-phthalimido)xanthine;
1,3-di(cyclopropylmethyl)-8-(2-carboxybenzoyl)amino xanthine;
1,3-di(cyclopropylmethyl)-8-(N-succinimido)xanthine;
1,3-di(cyclopropylmethyl)-8-(3-carboxypropanoyl)amino xanthine;
1,3-di(cyclopropyl methyl)-7-(4-methoxybenzyl)-8-(N-phthalimido)xanthine;
8-(2-carboxybenzoylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine;
8-t-butylamido-1,3-di(cyclopropylmethyl)xanthine; and
8-benzamido-1,3-di(cyclopropylmethyl)xanthine; or if appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof.

as defined in claim 1;

~~10.~~ 11. A process for the preparation of a compound of formula (I) or where appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, which process comprises:

a) for compounds of formula (I) wherein R^3 is substituted or unsubstituted aryl or substituted alkyl and R^4 is hydrogen or -CO.R^5 wherein R^5 is substituted or unsubstituted alkyl or substituted or unsubstituted aryl, by reacting a compound of formula (II):



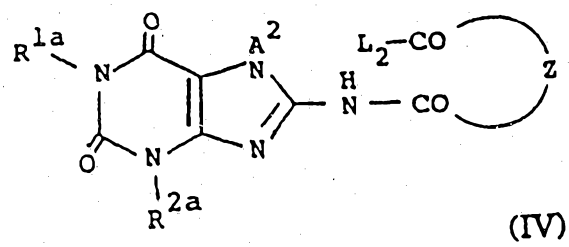
(II)

wherein R^{1a} represents R^1, as defined in relation to formula (I), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (I), or a group convertible thereto, A^2 represents A^1 as defined in relation to formula (I) or a group convertible thereto and R^6 represents hydrogen, a group -CO.R^{5a}, wherein R^{5a} represents unsubstituted alkyl, or a group -COR^{5b}, wherein R^{5b} is substituted alkyl or substituted or unsubstituted aryl, with a compound of formula (III):

$$R^7.CO.L^1 \qquad \text{(III)}$$

wherein, when R^6 in compound (II) is hydrogen or a group CO.R^{5a} then R^7 represents substituted alkyl or substituted or unsubstituted aryl, or when R^6 is a group -CO.R^{5b} then R^7 represents substituted or unsubstituted aryl or substituted or unsubstituted alkyl, and L^1 represents a leaving group; or

b) for compounds of formula (I) wherein R^3 together with R^5 represent a substituted or unsubstituted C_{2-3} polymethylene chain, by cyclising a compound of formula (IV):



(IV)

wherein R^{1a}, R^{2a} and A^2 are as defined in relation to formula (II), Z represents the substituted or unsubstituted C_{2-3} polymethylene chain as defined in relation to formula (I) or a protected form thereof, and L^2 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or A^2 and A^1;

(ii) converting a compound of formula (I) into a further compound of formula (I);

(iii) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1; or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

13. A method for the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, and allergic disorders associated with atopy comprising administering a therapeutically effective amount of a compound of formula (I) as defined in claim 1; or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof.

14. Use of a compound of formula (I) as defined in claim 1; or where appropriate

a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament.

15. Compounds of formula (I), processes for their preparation, pharmaceutical compositions containing them or methods involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 3rd day of May, 1994
Beecham Group p.l.c.
By Its Patent Attorneys
DAVIES COLLISON CAVE

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01634

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D473/06; A61K31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 386 683 (POLI INDUSTRIA CHIMICA) 12 September 1990 *Complete document*	1-16
A	EP,A,0 258 191 (SANDOZ-PATENT-GMBH) 2 March 1988 *Complete document*	1-16
P,A	EP,A,0 389 282 (BEECHAM WUELFING) 26 September 1990 cited in the application *Complete document*	1-16

° Special categories of cited documents :[10]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 JANUARY 1992	14. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101634 SA 51593

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/01/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP-A-0258191	02-03-88	AU-B- 600021	02-08-90
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		AT-B- 392968	25-07-91
		WO-A- 8805775	11-08-88
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