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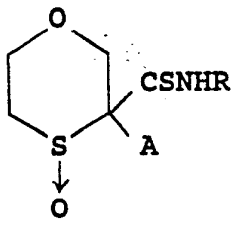

(I)

(57) Abstract

Oxathiane derivatives of formula (I) in which R represents alkyl and A represents optionally substituted phenyl or a heteroaromatic group containing 1 or 2 nitrogen atoms optionally substituted by alkyl, alkoxy or halogen, and salts thereof possess pharmacological activity and are also useful in inhibiting head hair loss.

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"OXATHIANE DERIVATIVES"

This invention relates to new therapeuticaliy useful oxathiane derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

The new oxathiane derivatives of the present invention are those compounds of formula (I), hereinafter depicted wherein:-

R represents an alkyl group; and

A represents:-

(1) a phenyl or naphthyl group which is optionally substituted by one or more substituents selected from halogen atoms and cyano, nitro, trifluoromethyl, carbamoyl, carboxyl, alkoxycarbonyl, alkylsulphonyl, alkyl and phenylalkyl groups; or

(2) a heteroaromatic group containing 1 or 2 nitrogen atoms, for example selected from pyrid-3-yl, quinolin-3-yl, isoquinolin-4-yl, pyridazin-4-yl, pyrimidin-5-yl, pyrazin-3-yl, indol-3-yl and thiazol-5-yl, optionally substituted by an alkyl or alkoxy group, or a halogen atom;

wherein all alkyl groups and moieties, including those in alkoxy and alkoxycarbonyl groups, are straight-chain or branched, and, unless otherwise specified, contain one to about six carbon atoms; and pharmaceutically acceptable salts thereof.

Preferred values for A include 3,4-dichloro-

phenyl and 3-pyridyl and R is preferably methyl.

When A represents an optionally substituted phenyl group it is preferably a phenyl group which is unsubstituted or substituted on the 3-position or on the 3- and 5-positions by substituents selected from halogen atoms and cyano, nitro, trifluoromethyl, carbamoyl, carboxyl, alkoxycarbonyl and alkylsulphonyl groups.

It is also preferred that the sulphoxide oxygen and the -CSNHR group are in the trans relationship.

In certain cases the substituents A and R can contribute to stereoisomerism. All such forms are embraced by the present invention.

Particularly important compounds of the present invention include the following:-

A (±)-trans-3-(3,4-dichlorophenyl)-N-methyl-1,4-oxathiane-3-carbothioamide 4-oxide

B (±)-trans-N-methyl-3-(3-pyridyl)-1,4-oxathiane-3-carbothioamide 4-oxide.

as well as their stereoisomeric forms and pharmaceutically acceptable salts thereof.

Letters A and B are allocated to compounds for ease of reference in other parts of the specification.

The compounds have valuable pharmacological properties, in particular properties which are indicative of utility in the treatment and/or prophylaxis of disorders associated with:-

(1) vascular smooth muscle contraction

including hypertension and other cardiovascular disorders such as congestive heart failure, and conditions associated with tissue ischaemia such as angina, peripheral vascular disease and cerebrovascular disease;

(2) respiratory smooth muscle contraction including reversible airways obstruction and asthma;

(3) contraction of smooth muscle of gastro-intestinal tract, urinary bladder and uterus, including peptic ulcers, irritable bowel syndrome and diverticular disease; irritable bladder syndrome; and premature labour.

The compounds also have utility in the inhibition of head hair loss associated with male pattern baldness, by topical application.

Compounds within the scope of the present invention exhibit positive pharmacological activities as demonstrated by in vitro tests which are believed to correlate to pharmacological activity in humans and other animals.

For example, compounds of general formula (I) were submitted to:-

Vaso-relaxant Activity Test.

The test method used was adapted from those described by Winslow et al [Eur.J.Pharmacol., 131, 219-228 (1986)] and Karaki [J.Pharmacol. Methods, 18, 1-21 (1987)] for differentiating vaso-relaxant activity.

Thoracic aorta was removed from rats and transverse strips, denuded of endothelium, were suspended in a bath containing Krebs solution. The tension was recorded and a contraction induced by addition of 20mM K^+ (potassium ion) to the bathing solution. The test compound was added to the bath as a solution in increasing cumulative concentration. The concentration in the bathing solution of the test compound which reduced the K^+-induced contraction by 90% was determined and expressed in μM as the effective concentration (EC_{90}), given in Table 1.

Table 1

Compound	EC_{90} μM
A	0.3
B	2

The compounds of general formula (I) can be prepared by the application and adaptation of known methods, for example as hereinafter identified. By the term "known methods" as used in this specification is

meant methods heretofore used or described in the literature.

According to a feature of the present invention, the compounds of general formula (I), wherein A and R are as hereinbefore defined, are prepared by the reaction of a compound of formula (II), wherein A is as hereinbefore defined and R^1 is alkyl, as hereinbefore defined, or a benzyl or carboxymethyl radical, with a compound of formula:

$$R\text{-}NH_2 \qquad (III)$$

wherein R is as hereinbefore defined.

The reaction is generally carried out using an excess of amine (III), without a solvent, or in an inert organic solvent such as an ether, an aromatic hydrocarbon, an alcohol (e.g. ethanol) or dimethyl-sulphoxide, or a mixture of these solvents normally at room temperature, optionally under pressure and optionally in the presence of thiol acceptor, such as a heavy metal salt (e.g. mercuric chloride). The amine may be added as a solution in an alcohol (e.g. ethanol).

Compounds of formula (II), wherein A and R^1 are as hereinbefore defined, can be prepared by the reaction of compounds of formula (IV), wherein A is as hereinbefore defined, with carbon disulphide, followed by reaction with a compound of formula:

$$R^1 - X \qquad (V)$$

wherein R^1 is as hereinbefore defined and X is halogen, preferably iodine or a readily displaceable ester groups such as methanesulphonyloxy or 4-toluene-sulphonyloxy.

The reaction is generally carried out in an anhydrous, inert, organic solvent such as dimethyl-formamide, at a temperature from -70°C to room temperature, and in the presence of an organic base such as a potassium alkoxide (e.g. the tert-butoxide), or an organolithium compound, or sodium hydride.

Compounds of formula (IV), wherein A is as hereinbefore defined, can be made by oxidation of the corresponding compounds of formula (VI). This is typically by reaction with a peroxy acid (e.g. meta-chloroperbenzoic acid) in an inert solvent, such as dichloromethane, at or below room temperature.

Compounds of formula (VI), wherein A is as hereinbefore defined, can be prepared by the reaction of a compound of formula:

$$AMgBr \qquad (VII)$$

wherein A is as hereinbefore defined (usually prepared from the corresponding bromide by conventional means), with 3-chloro-1,4-oxathiane.

This is typically carried out in an inert solvent such as benzene, at or below room temperature.

Alternatively, compounds of formula (IV) can be prepared by the reaction of compounds of formula:

$$A\text{-}CH_2\text{-}S(O)\text{-}(CH_2)_2\text{-}OH \qquad (VIII)$$

wherein A is as hereinbefore defined, with formaldehyde.

This reaction is generally carried out in an inert solvent such as dimethylformamide, in the presence of an organic base, such as potassium tert-butoxide, and under ice cooling.

Compounds of formula (VIII), wherein A is as hereinbefore defined, can be prepared by the oxidation of the corresponding compounds of formula:

$$A\text{-}CH_2\text{-}S\text{-}(CH_2)_2\text{-}OH \qquad (IX)$$

wherein A is as hereinbefore defined, generally under conditions similar to those described above for the conversion of compounds of formula (VI) to those of formula (IV).

Compounds of formula (IX), wherein A is as hereinbefore defined, can be prepared by the reaction of a compound of formula:

$$A - CH_2 - X^1 \qquad (X)$$

or a salt thereof, wherein A is as hereinbefore defined and X^1 is a halogen, preferably chlorine, atom, with 2-mercaptoethanol.

This reaction is typically carried out in an inert organic solvent such as an alcohol (e.g.

ethanol), in the presence of an organic base (e.g. sodium ethoxide), at temperatures up to reflux.

Compounds of formulae (III), (V), (VII) and (X) can be made by application or adaptation of known methods or are readily available.

It will be understood that it may be desirable to change one or more of the substituents on the aryl groups at an appropriate stage during the synthesis of the compounds of the invention. For example, the compounds of general formula (I) wherein A represents a phenyl group substituted by a carbamoyl group may be alternatively prepared from the corresponding compounds of general formula (I) wherein A represents a phenyl group substituted by a cyano group by the application or adaptation of known methods for such conversion.

By the term "pharmaceutically acceptable salts" as used in this specification is meant salts the anions or cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmaceutical properties of the parent compounds of general formula (I) capable of forming salts are not vitiated by side-effects ascribable to those anions or cations.

It is to be understood that, where in this specification reference is made to compounds of formula

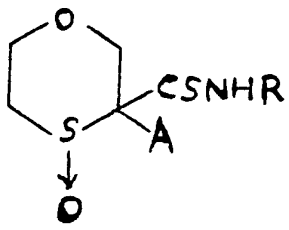
(I), it is intended to refer also, where the context so permits, to their pharmaceutically acceptable salts.

Suitable acid addition salts for use in pharmaceuticals may by selected from salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates, sulphates and nitrates, and organic acids, for example oxalates, lactates, tartrates, acetates, salicylates, citrates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates and di-p-toluoyltartrates.

Suitable salts with bases include alkali metal (e.g. sodium and potassium), alkaline earth metal (e.g. calcium and magnesium), ammonium and amine (e.g. diethanolamine, triethanolamine, octylamine, morpholine and dioctylmethylamine) salts.

As well as being useful in themselves as active compounds, pharmaceutically acceptable salts of the compounds of general formula (I) capable of forming salts with acids or bases are useful for the purposes of purification of the parent compounds of general formula (I), for example by exploitation of the solubility differences between the salts and the parent compounds, by techniques well known to those skilled in the art.

The thioformamide derivatives of general formula (I) obtained by the aforedescribed processes can be purified by the usual physical methods, in particular crystallisation and chromatography, especially to resolve mixtures of enantiomers using a chiral column.



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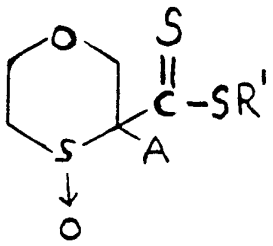

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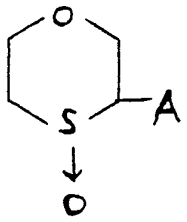

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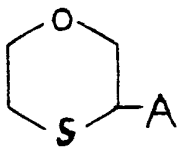


(VI)

The following Examples illustrate the preparation of compounds according to the present invention.

EXAMPLE 1

Compound A

A suspension of (±)-trans-3-(3,4-dichlorophenyl)-3-methylthiothiocarbonyl-1,4-oxathiane 4-oxide (730mg, 2mmol) in ethanol (20ml) and dimethylsulphoxide (2.8 ml) was treated with methylamine solution (1.5ml, 33% in ethanol, 15.7 mmol) and the mixture stirred for 1.5 hrs at room temperature. The mixture was then evaporated in vacuo and partitioned between dichloromethane (25ml) and water (25ml). The organic layer was dried ($MgSO_4$) evaporated in vacuo and purified by flash chromatography on silica, eluting with ethyl acetate to give (±)-trans-3-(3,4-dichlorophenyl)-N-methyl-1,4-oxathiane-3-carbothioamide 4-oxide (220mg), as colourless crystalline solid, m.p. 213-214°C;

[Found:- C, 43.0; H, 4.07; Cl, 19.6%

Calculated for $C_{12}H_{13}Cl_2NO_2S_2$:- C, 42.6; H, 3.87; Cl, 20.7%].

EXAMPLE 2

Compound B

A stirred solution of (±)-trans-3-(3-pyridyl)-3-methylthiothiocarbonyl-1,4-oxathiane 4-oxide

(560mg, 1.9 mmol) in ethanol (30ml) at room temperature was treated with a solution of methylamine (33% in ethanol, 4 ml) and the mixture stirred at room temperature for 30 mins. The mixture was evaporated in vacuo and purified by flash chromatography on silica, eluting with 5% methanol in dichloromethane, to give (±)-trans-N-methyl-3-(3-pyridyl)-1,4-oxathiane-3-carbothioamide 4-oxide (220mg), m.p. 159-161°C;

[Found:- C, 48.9; H, 5.29; N, 10.4%

Calculated for $C_{11}H_{14}N_2O_2S_2$:- C, 48.86; H, 5.21; N, 10.36%].

REFERENCE EXAMPLE 1

A stirred solution of 3-(3,4-dichlorophenyl)-1,4-oxathiane 4-oxide (a mixture of cis/trans isomers) (265mg, 1mmol) in dimethylformamide (5ml), under argon, was cooled to -40°C and treated with potassium tert-butoxide (0.12g, 1.1mmol). After 40 mins at this temperature a solution of carbon disulphide (84mg, 1.1mmol) in dimethylformamide (0.5ml) was added and the resulting red solution stirred for a further 1 hour. A solution of methyl iodide (156mg, 1.1mmol) in dimethylformamide (0.5 ml) was added and the resulting solution stirred for a further 2 hours. The reaction mixture was then poured into a mixture of dichloromethane (25ml) and aqueous ammonium chloride solution (25ml). The organic layer was separated,

dried ($MgSO_4$) and evaporated in vacuo to provide an orange oil which was purified by flash chromatography on silica, eluting with 25% ethyl acetate in toluene, to give (±)-trans-3-(3,4-dichlorophenyl)-3-methylthio-thiocarbonyl-1,4-oxathiane 4-oxide (0.11g), as orange crystals m.p. 147-150°C.

REFERENCE EXAMPLE 2

A stirred solution of 3-(3,4-dichlorophenyl)-1,4-oxathiane (1g, 4mmol) in dichloromethane (10ml) at 0°C was treated with a solution of meta-chloroperoxy-benzoic acid (85%, 860 mg, 4mmol) in dichloromethane (10ml) and stirred at 0°C for 30 mins then at room temperature for 3 hrs. The mixture was shaken with aqueous sodium bicarbonate solution and the organic phase separated, dried ($MgSO_4$) and evaporated to give a solid which was triturated with hexane / toluene (1:1) to give 3-(3,4-dichlorophenyl)-1,4-oxathiane 4-oxide (860mg), as a colourless crystalline solid, m.p. 100-103°C;

[Found:- C, 45.5; H, 3.8; Cl, 26.9%

Calculated for $C_{10}H_{10}Cl_2OS$:- C, 45.3; H, 3.8; Cl, 26.7%].

REFERENCE EXAMPLE 3

A stirred solution of 3,4-dichlorophenyl-magnesium bromide [prepared from 3,4-dichlorobromo-benzene (10.2g, 45mmol) and magnesium (1.1g, 45mmol) in

the usual fashion] was treated with a solution of 3-chloro-1,4-oxathiane [prepared from 1,4-oxathiane (2.6g, 25mmol) using the method of Tuleen and Bennet J. Het. Chem. 1969, 6, 115] in benzene (30ml), maintaining the temperature of reaction below 10°C. The mixture was allowed to stand at room temperature overnight. It was then poured into ammonium chloride solution (50ml), the organic phase was separated and the aqueous washed with ether (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography on silica eluting with toluene / hexane (1:1) to give 3-(3,4-dichlorophenyl)-1,4-oxathiane (4.5g), as colourless crystals, m.p. 65-68°C;

[Found:- C, 48.6; H, 4.05; Cl, 28.3; S, 12.7%

Calculated for $C_{10}H_{10}Cl_2OS$:- C, 48.32; H, 4.05; Cl, 28.5; S, 12.9%].

REFERENCE EXAMPLE 4

A solution of carbon disulphide (216mg, 2.8 mmol) and 3-(3-pyridyl)-1,4-oxathiane 4-oxide (280mg, 1.4 mmol) in dimethylformamide (1ml) was cooled and added to a solution of potassium tert-butoxide (320mg, 2.8 mmol) in dimethylformamide (20ml) in a dry ice / acetone bath at -70°C. After 5 mins a solution of methyl iodide (403mg, 2.8 mmol) in dimethylformamide (1ml) was added. After 30 min the mixture was poured

into ethanol (50ml) and evaporated in vacuo. The residue was purified by flash chromatography eluting with 3% methanol in dichloromethane to give (±)-trans-3-(3-pyridyl)-3-methylthiothiocarbonyl-1,4-oxathiane 4-oxide (180mg), as an orange oil.

REFERENCE EXAMPLE 5

A stirred solution of 2-(3-pyridylmethyl-sulphinyl)ethanol (0.25g, 1.35 mmol) in dimethyl-formamide (25ml) at 0°C was treated portionwise with potassium tert-butoxide (0.15g, 1.35mmol) and stirred for 10 mins. Formaldehyde gas [generated by heating paraformaldehyde (45mg, 1.5 mmol) at 150°C] was passed into the reaction mixture in a rapid stream of argon whilst cooling in an ice bath. When addition of the formaldehyde was completed the cooling bath was removed and the mixture allowed to warm to room temperature over 15 mins. The solution was poured into ethanol (30ml), neutralised with concentrated hydrochloric acid and filtered to give a clear solution which was evaporated in vacuo and the residue was purified by flash chromatography on silica, eluting with 7% methanol in dichloromethane, to give 3-(3-pyridyl)-1,4-oxathiane 4-oxide (900mg), as a colourless crystalline solid, m.p. 74-76°C.

REFERENCE EXAMPLE 6

A stirred solution of 2-(3-pyridylmethylthio)-ethanol (3.38g, 20 mmol) in dichloromethane (50ml) at 0°C was treated dropwise with a solution of m-chloroperoxybenzoic acid in dichloromethane (50ml). The mixture was stirred at 0°C for 1 hr and at room temperature for 3 hrs. The mixture was evaporated in vacuo and purified by flash chromatography on silica eluting with 20% methanol in ethyl acetate to give 2-(3-pyridylmethylsulphinyl)ethanol (3.5g), as colourless crystals, m.p. 84-86°C;

[Found:- C, 51.9; H, 6.14; N, 7.6; S, 17.2%

Calculated for $C_8H_{11}NO_2S$:-C, 51.85; H, 5.98; N, 7.6; S, 17.3%].

REFERENCE EXAMPLE 7

A stirred solution of sodium ethoxide (4.6g of sodium in 100ml ethanol) was treated with 2-mercapto-ethanol (7.8g, 0.1 mol) followed by 3-chloromethyl-pyridine hydrochloride (16.4g, 0.1 mol). The mixture was then refluxed under argon for 3.5 hours, filtered and evaporated in vacuo and the residue purified by flash chromatography on silica, eluting with 3% methanol in ethyl acetate, to give 2-(3-pyridyl-methylthio)ethanol (13g), as a yellow oil;

[Found:- C, 56.3; H, 6.6; N, 8.2; S, 18.8%

Calculated for $C_8H_{14}NOS$:- C, 56.8; H, 6.55; N, 8.27; S, 18.9%].

The present invention includes within its scope pharmaceutical compositions which comprise a compound of general formula (I) or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered rectally, but are preferably administered parenterally, by inhalation if appropriate, or, more preferably, orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose.

The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting,

and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Compositions according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilizing agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Compositions for inhalation may be sterile aqueous solutions which are then nebulised or dry powders formulated in accordance with known methods.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing one or more of the compounds of formula (I) or a pharmaceutically acceptable salt thereof.

The percentage of active ingredient in the composition of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration, the duration of the treatment and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably from about 0.01 to about 5, mg/kg body weight per day by oral administration. By inhalation, either as a nebulised solution or as a formulated dry powder, the preferred daily dosage is from about 0.001 to about 5, preferably from about 0.01 to about 0.5, mg/kg body weight.

The compounds may also be applied topically for inhibition of head hair loss associated with male pattern baldness, the preferred daily dosage being from 0.1 to 10 mg/kg body weight applied, for example, in 5ml portions two or three times per day.

The following Example illustrates pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE

No. 2 size gelatin capsules each containing:-

(±)-trans-3-(3,4-dichlorophenyl)-N-methyl-1,4-oxathiane-3-carbothioamide 4-oxide.....20mg

lactose.....100mg

starch.....60mg

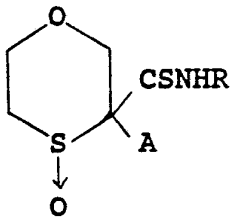
dextrin.....40mg

magnesium stearate.....1mg

were prepared in accordance with the usual procedure.

CLAIMS

1. An oxathiane derivative of formula (I)



(I)

in which

R represents an alkyl group; and

A represents:-

(1) a phenyl or naphthyl group which is unsubstituted or substituted, by one or more substituents selected from a halogen atom and a cyano, nitro, trifluoromethyl, carbamoyl, carboxyl, alkoxycarbonyl, alkylsulphonyl, alkyl and phenylalkyl group, or

(2) a heteroaromatic group containing 1 or 2 nitrogen atoms, which is unsubstituted or substituted by an alkyl or alkoxy group, or a halogen atom;

wherein all the alkyl groups and moieties, including those in alkoxy and alkoxycarbonyl groups, are straight-chain or branched and contain one to six carbon atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which the -CSNHR group is <u>trans</u> to the oxygen atom attached to sulphur.

3. A compound according to claim 1 or 2 in which R represents methyl.

4. A compound according to claim 1, 2 or 3

in which A represents

(1) a phenyl group which is unsubstituted or substituted at the 3-position or at the 3- and 5- positions by substituents selected from a halogen atom and a cyano, nitro, trifluoromethyl, carbamoyl, carboxyl, alkoxycarbonyl and alkylsulphonyl group; or

(2) a heteroaromatic group containing 1 or 2 nitrogen atoms, selected from pyrid-3-yl, quinolin-3-yl, isoquinolin-4-yl, pyridazin-4-yl, pyrimidin-5-yl, pyrazin-3-yl, indol-3-yl and thiazol-5-yl, which is unsubstituted or substituted by an alkyl or alkoxy group, or a halogen atom.

5. A compound according to claim 4 in which A represents 3,4-dichlorophenyl or pyridyl-3-yl.

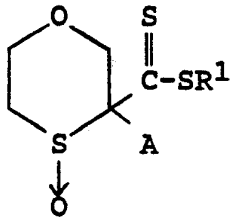
6. A compound according to claim 5 which is

(±)-trans-3-(3,4-dichlorophenyl)-N-methyl-1,4-oxathiane-3-carbothioamide 4-oxide,

(±)-trans-N-methyl-3-(3-pyridyl)1,4-oxathiane-3-carbothioamide 4-oxide,

or a pharmaceutically acceptable salt thereof.

7. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 6 which process comprises reacting a compound of formula (II)



(II)

wherein A and R are as hereinbefore defined and R^1 is a

straight or branched alkyl group of 1 to 6 carbon atoms, or a benzyl or carboxylmethyl group, with a compound of formula (III):

$$R - NH_2 \qquad (III)$$

wherein R is as hereinbefore defined;

and, if desired, converting the product thus obtained to a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 6 in association with a pharmaceutically acceptable carrier or diluent.

9. A cosmetic composition suitable for topical application to the human scalp, which composition comprises a compound as claimed in any one of claims 1 to 6 and a cosmetically acceptable carrier or diluent.

10. A method of inhibiting head hair loss which comprises applying topically to the scalp an effective amount of a compound as claimed in any one of claims 1 to 6.

11. A pharmaceutical composition suitable for use in the treatment or prophylaxis of a disorder associated with vascular, respiratory, gastro-intestinal tract, urinary bladder or uterus smooth muscle contraction which composition comprises an amount effective to combat the said disorder of a compound of formula (I) as claimed in claim 1 in association with a pharmaceutically acceptable carrier or diluent.

12. A method for the prophylaxis or treatment

of a disorder associated with vascular, respiratory, gastro-intestinal tract, urinary bladder or uterus smooth muscle contraction in a patient which method comprises administering to the patient an amount effective to combat said disorder of a compound as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00075

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

IPC[5]: C 07 D 327/06, A 61 K 31/39, A 61 K 7/06

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 327/00

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 [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	DE, A1, 3 808 024 (UNIROYAL CHEMICAL LTD) 22 September 1988 (22.09.88), see claims 1,13,20. --	1,7-9
A	FR, A, 1 494 186 (CHIMETRON S.A.R.L.) 08 September 1967 (08.09.67), see claims 1,13. ----	1,7-9

* 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
09 April 1991	05.06.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 10,12 because they relate to subject matter not required to be searched by this Authority, namely:

see PCT Rule 39.1(iv) (Method for treatment of the human or animal body by therapy)

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

SA44051

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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		AU-B2- 597478	31-05-90
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		JP-A2-63264580	01-11-88
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