607485

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

I/We LILLY INDUSTRIES LIMITED,
Kingsclere Road,
Basingstoke,
Hampshire RG21 2XA,
England

LODGED AT SUB-OFFICE
21 APR 1988
Melbourne

hereby apply for the grant of a Standard Patent for an invention entitled:

"PHARMACEUTICAL USE OF AROMATIC THIOETHERS"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

Number	Convention Country	Date
8709546	United Kingdom	22nd April 1987

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 4.12.90

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 21st day of April 19 88

AUSTRALIAN PATENT OFFICE

THE COMMISSIONER OF PATENTS

K. M. Rimington

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

CASE: G.1246

DAVIES & COLLISON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF A
CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled: PHARMACEUTICAL USE OF ORGANIC COMPOUNDS

I, Terence Roger Crowther of Erl Wood Manor, Windlesham, Surrey GU20 6PH, England do solemnly and sincerely declare as follows:

1. I am authorized by LILLY INDUSTRIES LIMITED the applicant for the patent to make this declaration on its behalf.

2. Stephen Richard BAKER of 16 Whitley Road, Yateley, Camberley, Surrey, England, and

John Robert BOOT of 45 Beech Hill Road, Sunningdale, Berkshire, England

~~XX~~/are the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:-

by an assignment dated 28th March 1988 the said applicant is the assignee of the actual inventor in respect of the invention.

3. The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made in the United Kingdom on the 22nd April 1987 by said LILLY INDUSTRIES LIMITED.

4. The basic application~~(s)~~ referred to in paragraph 3 of this Declaration was/~~were~~ the first application~~(s)~~ made in a Convention country in respect of the invention~~(s)~~ the subject of the said application.

DECLARED at Windlesham, Surrey, England
this 29th day of March 1988

LILLY INDUSTRIES LIMITED
BY THEIR ATTORNEY

T.R. Crowther

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

(12) PATENT ABRIDGMENT (11) Document No. AU-B-15034/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 607485

(54) Title
PHARMACEUTICAL USE OF AROMATIC THIOETHERS

International Patent Classification(s)
(51)[4] C07D 257/04 A61K 031/19 A61K 031/41 C07C 149/273

(21) Application No. : 15034/88 (22) Application Date : 21.04.88

(30) Priority Data

(31) Number	(32) Date	(33) Country
8709546	22.04.87	GB UNITED KINGDOM

(43) Publication Date : 27.10.88

(44) Publication Date of Accepted Application : 07.03.91

(71) Applicant(s)
LILLY INDUSTRIES LIMITED

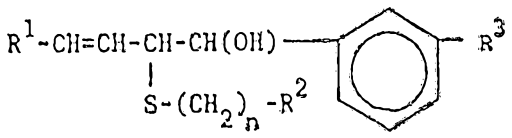
(72) Inventor(s)
STEPHEN RICHARD BAKER; JOHN ROBERT BOOT

(74) Attorney or Agent
DAVIES & COLLISON, 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 575575 31304/84 C07C 149/36 C07D 257/04 A61K 31/155
AU 576926 51321/85 C07D A61K 31/41
AU 31598/89 C07D 257/04 C07C 149/42 A61K 31/41

(57) Claim

1. A method for the treatment of a vascular disease which comprises administering to a patient in need of such treatment



(I)

in which R^1 is C_{7-20} alkyl or C_{7-20} alkenyl containing 1 to 3 double bonds, the alkyl or alkenyl group being optionally substituted by phenyl, R^2 and R^3 are carboxyl or tetrazolyl, and n is 1 to 6; or a pharmaceutically-acceptable salt thereof.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

607485

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

CLASS INT. CLASS

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

This document contains the amendments made under Section 49 and is correct for printing.

Priority:

Related Art:

NAME OF APPLICANT: LILLY INDUSTRIES LIMITED

ADDRESS OF APPLICANT: Kingsclere Road,
Basingstoke,
Hampshire RG21 2XA,
England.

NAME(S) OF INVENTOR(S) Stephen Richard BAKER
John Robert BOOT

ADDRESS FOR SERVICE: DAVIES & COLLISON, Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

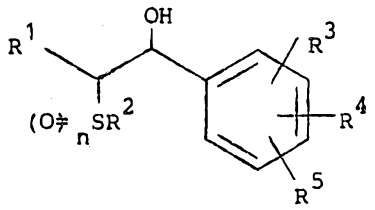
"PHARMACEUTICAL USE OF AROMATIC THIOETHERS"

The following statement is a full description of this invention, including the best method of performing it known to us :-

AUSTRALIAN PATENT OFFICE

This invention relates to the use of pharmaceutical compounds in the treatment of disease.

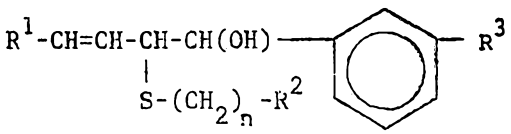
British Patent 2 144 422 discloses some compounds of having the following formula



where n, R^1, R^2, R^3, R^4 and R^5 take various values. These compounds are described as useful in diseases such as for example allergic disorders.

We have now discovered that certain of these compounds are strongly indicated for use in the treatment of vascular diseases.

The invention comprises the use of a compound of the formula



(I)

in which R^1 is C_{7-20} alkyl or C_{7-20} alkenyl containing 1 to 3 double bonds, the alkyl or alkenyl group being optionally

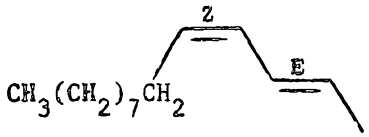
substituted by phenyl, R^2 and R^3 are carboxyl or tetrazolyl, and n is 1 to 6; or a pharmaceutically-acceptable salt thereof; for the manufacture of a medicament for the treatment of a vascular disease.

The compounds of formula (I) above and their pharmaceutically-acceptable salts are active in tests which indicate that they have potential in the treatment of cardiovascular diseases such as shock and ischaemic heart diseases for example coronary artery disease and myocardial infarction, cerebrovascular diseases, and renal diseases for example renal ischaemia.

In the above general formula, R^1 can be an alkyl group containing from 7 to 20 carbon atoms, and is preferably alkyl containing from 8 to 13 carbon atoms, such as for example 10 to 13 carbon atoms. The alkyl group is preferably straight chained. When R^1 is alkenyl it contains from 7 to 20 carbon atoms and preferably from 8 to 13 carbon atoms, such as for example 10 to 13 carbon atoms. Preferably the alkenyl group is unbranched and contains 1 or 3 double bonds. Particularly preferred alkenyl groups are those of formula $R^4CH=CH-$ where R^4 is C_{6-11} alkyl such as $CH_3(CH_2)_m$ where m is 5 to 10, or $CH_3(CH_2)_4CH=CHCH_2CH=CH_2-$. When R^1 is substituted by phenyl, the phenyl group is preferably attached to the terminal carbon atom, for example, a group of the formula $PhCH_2(CH)_mCH=CH-$ where m is 5 to 10.

It will be appreciated that such double bonds, and the double bond between the 3 and 4 carbon atoms, provide opportunities for cis-trans isomeric forms. It is preferred that the R^1 group is arranged in trans configuration about the double bond at the 3 and 4 carbon atoms. It will also be appreciated that the compounds of formula (I) possess chiral centres at the carbon atoms bearing the hydroxyl and thio groups and, accordingly, stereoisomeric forms exist R,R; S,S; R,S; and S,R. The use of all such stereoisomers, and racemic mixtures thereof, is included within the scope of the invention. The preferred compounds are of S,R configuration.

Examples of particularly preferred compounds for use in the invention are those in which the moiety $R^1CH=CH$ in formula (I) above is

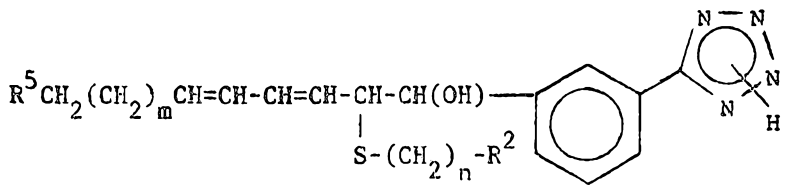


and

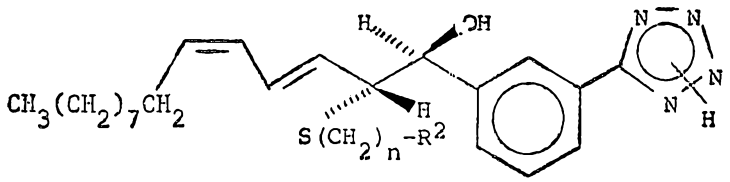
In formula (I) above the value of n in the formula can be from 1 to 6. It is preferably 1, 2 or 3 and in the most preferred compounds n is 2. The values of R^2 and R^3 can, of course, be different and R^3 is preferably tetrazolyl.

The compound of formula (I) bears two acidic functions and base addition salts can thus be prepared. The use of these salts is also included as part of the present invention. Examples of such salts are those derived from alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as salts derived from aliphatic and aromatic amines, aliphatic diamines and hydroxy alkylamines. The potassium and sodium salt forms are particularly preferred.

A particular group of compounds according to formula (I) for use in the treatment of vascular diseases, are those of the formula:



in which R^5 is hydrogen or phenyl, m is 5 to 10, n is 1, 2 or 3 and R^2 is carboxyl or tetrazolyl; and pharmaceutically-acceptable salts thereof. A further preferred group is of the formula



in which n is 1, 2 or 3; and pharmaceutically-acceptable salts thereof. Such compounds exhibit 1S, 2R chirality.

Specific examples of compounds for use in the invention are:

(1S,2R)-5-{3-[2-(2-Carboxyethylthio)-1-hydroxypentadeca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole,

(1S,2R)-5-{3-[2-(2-1H-tetrazol-5-ylethylthio)-1-hydroxypentadeca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole,

(1S,2R)-5-{3-[2-(2-carboxyethylthio)-1-hydroxy-13-phenyltrideca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole,

(1S,2R)-5-{3-[2-1H-tetrazol-5-ylethylthio)-1-hydroxy-17-phenyl-heptadeca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole,

(1S,2R)-3-[2-(2-carboxyethylthio)-1-hydroxypentadeca-3(E),5(Z)-dienyl]benzoic acid,

(1S,2R)-5-{3-[2-1H-tetrazol-5-ylethylthio)-1-hydroxy-13-phenyl-trideca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole,

(1S,2R)-3-[2-(2-carboxyethylthio)-1-hydroxy-16-phenylhexadeca-3(E),5(Z),13(Z)-trienyl]benzoic acid,

(1S,2R)-3-[2-(2-carboxyethylthio)-1-hydroxy-16-phenylhexadeca-3(E),5(Z)-dienyl]benzoic acid;

and their pharmaceutical salts.

The compounds of formula (I) can be prepared by methods which are fully described in British Patent 2 144 422 and British Patent Application 2 168 704. The first two compounds referred to above are, for example, disclosed in Example 45 of British Patent 2 144 422 and Example 1 of British Patent Application 2 168 704, respectively.

The pharmaceutical properties of the compounds of formula (I) and their potential in the treatment of vascular diseases have been demonstrated in the test described by Shipley R.E. and Tilden J.H. Proc. Soc. exp. Biol. Med. 64, 453-455 (1947). This test employs the pithed rat as model and measures the effect of a compound in restoring blood pressure after challenge with LTD_4. The following list gives the ED_{50} value in this test for the named compounds:

(1S,2R)-5-{3-[2-(2-1H-tetrazol-5-ylethylthio)-1-hydroxypentadeca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole, 0.7 mg/kg I.V.

(1S,2R)-5-{3-[2-(2-carboxyethylthio)-1-hydroxy-13-phenyltrideca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole, 3.6 mg/kg I.V.

(1S,2R)-5-{3-[2-1H-tetrazol-5-ylethylthio)-1-hydroxy-17-phenyl-heptadeca-3(E),5(Z)-dienyl]phenyl}-1H-tetrazole, 2.2 mg/kg I.V.

(1S,2R)-3-[2-(2-carboxyethylthio)-1-hydroxypentadeca-3(E),5(Z)-dienyl]benzoic acid, 9.6 mg/kg I.V.

The compounds may be administered by various routes, for examples by the oral or rectal route, topically, by inhalation, and especially parenterally, for example by intravenous injection or infusion. They are usually employed in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and normally comprise at least one active compound. In making the compositions, the active ingredient will usually be in salt form mixed with a carrier, or diluted by a carrier, which may

be a solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of injection solutions, suspensions, ointments, tablets, lozenges, sachets, cachets, elixirs, aerosols (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, and sterile packaged powders.

For preferred, parenteral, administration forms of presentation include injectible solutions and suspensions, and infusions. Injectible solutions preferably comprise a complexing agent for example a modified starch such as β-cyclodextrin or a protein such as human serum albumin, or a lecithin. For example a typical 5 ml injection contains 1 to 5 per cent of active compound and 5 to 30 per cent of β-cyclodextrin in 0.9 per cent saline solution. A typical infusion (500 ml) contains 0.01 to 1 per cent of active compound and 0.01 to 1 per cent sodium bicarbonate in 5 per cent dextrose solution.

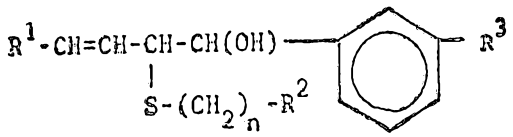
When compositions for use in the invention are formulated in unit dosage form, it is preferred that each unit dosage form contains from 1 mg to 500 mg, for example, from 5 mg to 100 mg.

The active compounds are effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.01 to 50 mg/kg, more usually in the range of from 0.05 to 10 mg/kg. However, it will be understood that the amount administered will be determined by the physician in the light of the relevant circumstances including

the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for the treatment of a vascular disease which comprises administering to a patient in need of such treatment



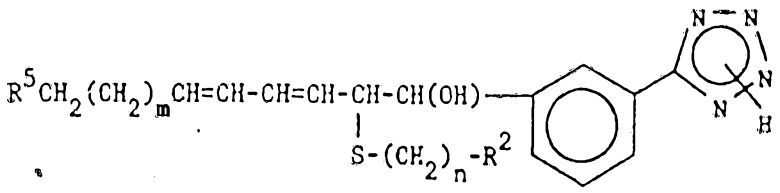
(I)

in which R^1 is C_{7-20} alkyl or C_{7-20} alkenyl containing 1 to 3 double bonds, the alkyl or alkenyl group being optionally substituted by phenyl, R^2 and R^3 are carboxyl or tetrazolyl, and n is 1 to 6; or a pharmaceutically-acceptable salt thereof.

2. A method according to claim 1, in which R^1 is $R^4CH=CH-$ where R^4 is C_{6-11} alkyl.

3. A method according to either of claims 1 and 2, in which n is 2 and R^3 is tetrazolyl.

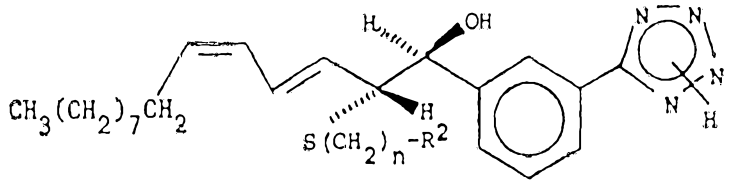
4. A method according to claim 1, in which the compound has the formula



in which R^5 is hydrogen or phenyl, m is 5 to 10, n is 1, 2 or 3 and R^2 is carboxyl or tetrazolyl; or is a pharmaceutically-acceptable salt thereof.

5. A method according to claim 4 in which the compound

has the formula



in which R^2 is carboxyl or tetrazolyl and n is 1, 2 or 3, or is a pharmaceutically-acceptable salt thereof.

6. A method for the treatment of a vascular disease substantially as hereinbefore described with reference to the Examples.

DATED this 31st day of October 1990.

LILLY INDUSTRIES LIMITED
By Its Patent Attorneys
DAVIES & COLLISON