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PERIPHERAL CIRCULATION IMPROVING AGENT

BACKGROUND OF THE INVENTION

The present invention relates to a peripheral circulation improving agent. More particularly, the present invention relates to a peripheral circulation improving agent which has an improving activity on peripheral circulation and is useful as a curing and/or prophylactic agent of chronic arterial obstruction, Raynoud's disease, Buerger's disease and the like.

It has been known that 1,5-benzothiazepine derivatives such as 2-(4-lower alkylphenyl)-3-lower alkanoyloxy (or hydroxy)-5-(2-di-lower alkylaminoethyl)-8-lower alkyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one and 2-(4-lower alkylphenyl)-3-lower alkanoyloxy (or hydroxy)-5-(2-mono-lower alkylaminoethyl)-8-lower alkyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one have an antihypertensive, cerebral and coronary vasodilating and/or platelet aggregation-inhibiting activities (for example, EP-A-0 154 838 and EP-A-0 158 340).

SUMMARY OF THE INVENTION

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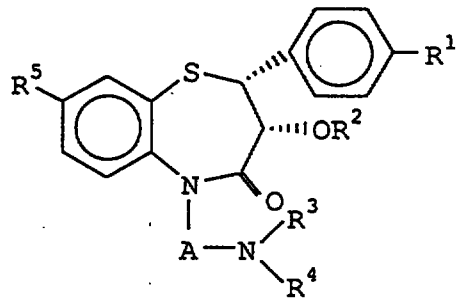
The present invention is to provide a peripheral circulation improving agent.

The inventors of the present invention have found that a (-)-cis isomer of the above 1,5-benzothiazepine derivative has a specific peripheral circulation improving activity and accomplished the present invention.

That is, the present invention relates to a peripheral circulation improving agent comprising, as an active ingredient, the (-)-cis-1,5-benzothiazepine derivative, represented by the following formula:



(I)

wherein R^1 represents a lower alkyl group or a lower alkoxy group; R^2 represents hydrogen atom or a lower alkanoyl group; R^3 represents a lower alkyl group; R^4 represents hydrogen atom or a lower alkyl group; R^5 represents hydrogen atom, a lower alkyl group or a hydroxy lower alkyl group; and A represents a lower alkylene group,

or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The (-)-cis-1,5-benzothiazepine derivative (I) and the pharmaceutically acceptable salt thereof, the active component of the present invention have an outstanding advantage that it exhibits a high improving activity on peripheral circulation, i.e., it remarkably increases a

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femoral arterial blood flow, and that the activity continues for a long period of time.

Furthermore, the (-)-cis-1,5-benzothiazepine derivative (I) has a low toxicity and a high safety. For example, the above described test compound A was orally given to a mouse in a dosage of 1000 mg/kg, no dead case was observed even after 2 days.

Accordingly, the (-)-cis-1,5-benzothiazepine derivative (I) or the pharmaceutically acceptable salt thereof of the present invention is useful as a peripheral circulation improving agent, and can be effectively used for curing and/or prophylaxis of chronic arterial obstruction, Raynoud's disease, Buerger's disease and the like in warm-blooded animals including human beings.

As a compound having an excellent therapeutic activity among the above (-)-cis-1,5-benzothiazepine derivatives (I), there may be mentioned a compound in which R^1 is a lower alkyl group, R^2 is a lower alkanoyl group, R^4 is a lower alkyl group, and R^5 is a lower alkyl group.

According to the present invention, as preferred examples of the lower alkyl group, the lower alkylene group and the lower alkoxy group, there may be mentioned those having 1 to 6 carbon atoms, particularly those having 1 to 4 carbon atoms, more specifically methyl, ethylene and methoxy groups, respectively; and as preferred examples of the lower alkanoyl group, there may be mentioned those having 2 to 6 carbon atoms, particularly those having 2 to 4 carbon atoms, more specifically acetyl group.

As another preferred example of the above (-)-cis-1,5-benzothiazepine (I) derivatives, there may be mentioned those in which R^1 is methyl group or methoxy group; R^2 is

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hydrogen atom or acetyl group; R^3 is methyl group; R^4 is hydrogen atom or methyl group; R^5 is hydrogen atom, methyl group or hydroxymethyl group; and A is ethylene group.

The (-)-cis-1,5-benzothiazepine derivative (I) as the active ingredient of the present invention can be used for a medical use of either in free form or in the form of a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt may include, for example, an inorganic acid addition salt such as hydrochloride, hydrobromide, hydroiodide, perchlorate, sulfonate and phosphate; or an organic acid addition salt such as oxalate, maleate, fumarate, tartarate and methanesulfonate.

The dosage of the (-)-cis-1,5-benzothiazepine derivative (I) or the pharmaceutically acceptable salt thereof may vary depending on the age, the body weight and the health condition of patient, or on the severity of disease, but is about 0.1 to 300 mg/kg per day, preferably 1 to 30 mg/kg per day for oral administration; and about 0.001 to 10 mg/kg per day, preferably 0.01 to 0.3 mg/kg per day for parenteral administration.

The (-)-cis-1,5-benzothiazepine derivative (I) or the pharmaceutically acceptable salt thereof can be used by way of either oral administration or parenteral administration.

The (-)-cis-1,5-benzothiazepine derivative (I) or the pharmaceutically acceptable salt thereof can be orally administered in a dosage form of a solid preparation such as tablets, pills, capsules and powder, and a liquid preparation such as solutions and suspensions, together with a pharmaceutical carrier suitable for oral administration as a pharmaceutical preparation. Such a carrier may include, for example, conventional binders (e.g. syrup, gum arabic, gelatin, sorbitol, tragacanth and polyvinylpyrrolidone),

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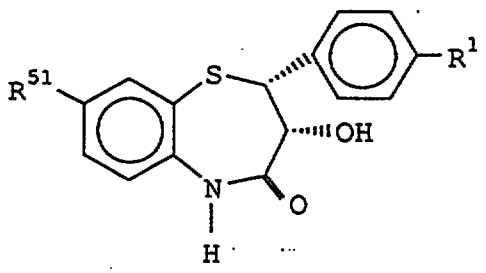
excipients (e.g. lactose, sugar, corn starch, potassium phosphate, sorbitol and glycine), lubricants (e.g. magnesium stearate, talc, polyethyleneglycol and silica), disintegrators (e.g. potato starch), or humectants (e.g. sodium lauryl sulfate).

On the other hand, in the case of parenteral administration, the composition may be preferably used as an injection or injection for drip infusion, by using, for example, distilled water for injection, physiological saline and glucose aqueous solution.

The (-)-cis-1,5-benzothiazepine derivative (I) as the active component of the present invention can be prepared according to a conventional method (for example, methods disclosed in U.S. Patent No. 3,562,257, EP-A-0 154 838, EP-A-0 158 340, and Italian Patent No. 1,227,852).

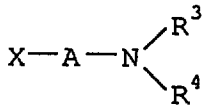
For example, the derivative can be prepared by reacting a compound represented by the formula (II):



(II)

wherein R^{51} represents hydrogen atom, a lower alkyl group or a hydroxy lower alkyl group having a protective group; and the other symbols have the same meanings as defined above,

with a compound represented by the formula (III):



(III)

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wherein X represents a halogen atom; and the other symbols have the same meanings as defined above,

in the presence of a salt (e.g., an alkali metal salt of carbonic acid),
and, if necessary, reacting the resulting compound with an acid anhydride of a compound represented by the formula (IV):

$$R^{21}—OH \qquad (IV)$$

wherein R^{21} represents a lower alkanoyl group,

in the presence of a deacidifying agent (e.g., an organic amine);
and when R^{51} is a hydroxy lower alkyl group having a protective group, removing said protective group according to a conventional method.

EXAMPLES

Experimental example 1

(Test Compounds)

The compounds listed in the following Table 1 were used as the test compounds.

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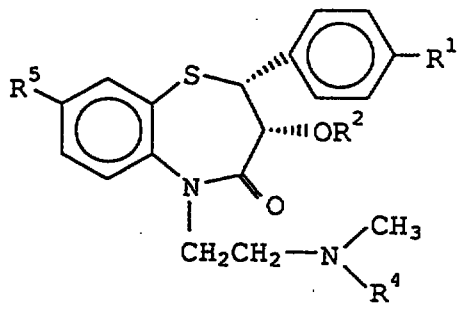
Table 1 Test Compounds

Test Compound					
	R^1	R^2	R^4	R^5	Physical properties
A	CH_3	$COCH_3$	CH_3	CH_3	Maleate m.p.: 195.0 to 197.5 °C
B	CH_3	H	CH_3	CH_3	Hydrochloride m.p.: 138 to 140 °C
C	CH_3	$COCH_3$	H	CH_3	Fumarate m.p.: 167.5 to 170.0 °C
D	CH_3	H	H	CH_3	Hydrochloride m.p.: 128 to 145 °C
E	CH_3	$COCH_3$	CH_3	CH_2OH	Oxalate m.p. 168 to 169 °C
F	OCH_3	$COCH_3$	CH_3	H	Hydrochloride m.p.: 206 to 207 °C

(Method)

Adult dogs (one group consisting of a dog) were intravenously given the test compound under anesthesia and artificial respiration successively at intervals of 60 minutes so that the dose can be 10, 30, 100 and 300 μg/kg body weight, and the blood flow of femoral artery was measured with a time course. The femoral arterial blood flow was measured with an electromagnetic blood flow meter (manufactured by Nihon Koden, MFV-2100, trade name) through a flow probe attached to the femoral artery. An increase in the femoral arterial blood flow was calculated by subtracting the blood flow before the administration of the first dose of test compound as the standard value (the base line) from that 60 minutes after each administration.

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(Results)

The increase in the femoral arterial blood flow after the administration of the test compound is shown in Table 2.

Table 2

Test Compound	Increase in femoral arterial blood flow (ml/min)			
	Dosage (μg/kg)			
	10	30	100	300
A	13	30	34	32
B	22	28	48	74
C	6	19	50	65
D	—	—	11	35
E	—	15	37	36
F	11	21	27	37

Experimental example 2

(Method)

The test compound A was intravenously administered to adult dogs (one group consisting of 4 dogs) in a dosage of 100 μg/kg body weight and the femoral arterial blood flow was measured at 30, 60, 120, 180, 240 and 300 minutes after the administration in the same manner as in Experimental example 1 to determine an increase in the blood flow based on that before the administration of the test compound.

(Results)

The femoral arterial blood flow and the increase in the blood flow after the administration of the test compound A are shown in Table 3.

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Table 3

	Period after administration (min)						
	Before	30	60	120	180	240	300
Blood flow (ml/min)	80.8	136.3	146.3	143.5	141.3	141.5	136.3
Increase in blood flow (ml/min)		55.5	65.5	62.8	60.5	60.8	55.5

Experimental example 3

(Test Compounds)

The compounds A, B, C, E and F listed in Table 1 were used as the test compounds.

(Method)

Adult dogs (one group consisting of 5 dogs) were intravenously given the test compound under anesthesia and artificial respiration successively at intervals of 60 minutes so that the dose can be 10, 30, 100, 300 and 1000 μg/kg body weight, and the blood flow of femoral artery was measured with a time course. The femoral arterial blood flow was measured with an electromagnetic blood flow meter (manufactured by Nihon Koden, MFV-2100, trade name) through a flow probe attached to the femoral artery. An increase in the femoral arterial blood flow was calculated by subtracting the blood flow before the administration of the first dose of test compound as the standard value (the base line) from that of maximum during an interval of 60 minutes after each administration.

(Results)

The increase in the femoral arterial blood flow after the administration of the test compound is shown in Table 4.

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Table 4

Test Compound	Increase in femoral arterial blood flow (ml/min)				
	Dosage (μg/kg)				
	10	30	100	300	1000
A	5.6	40.4	55.2	61.4	
B	10.4	16.4	41.4	70.2	79.2
C	–	6.8	25.6	44.6	49.0
E	–	15.6	55.6	69.2	68.6
F	10.7	21.0	27.3	37.0	

Preparation example

(1) A mixture comprising 2.48 g of (-)-cis-2-(4-methylphenyl)-3-hydroxy-8-trityloxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one, 0.75 g of 2-(dimethylamino)ethyl chloride hydrochloride, 1.70 g of potassium carbonate and 50 ml of acetone was refluxed overnight while stirring. After the mixture was cooled, insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residual was recrystallized from a mixed solution of ethyl acetate and n-hexane to give 2.59 g of (-)-cis-2-(4-methylphenyl)-3-hydroxy-5-[2-(dimethylamino)ethyl]-8-trityloxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one.
m.p.: 110 to 114 °C
$[\alpha]_D^{20}$ -83.7° (c = 0.251, methanol).

(2) A mixture of 2.46 g of the compound obtained in the above (1), 9 ml of acetic anhydride and 25 ml of pyridine was stirred overnight at room temperature. The reaction mixture was poured into water with ice, and extracted with ethyl acetate. The extract was washed, dried, and concentrated under reduced pressure to give 2.72 g of (-)-cis-2-(4-methylphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-8-

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trityloxymethyl-2,3-dihydro-1.5-benzothiazepin-4(5H)-one as an oily material.
IR^{liquid} υ_{max} (cm^{-1}): 1745, 1680.

(3) The compound obtained in the above (2) in an amount of 2.0 g was dissolved in 20 ml of trifluoroacetic acid, followed by stirring at room temperature for 3 hours, and the mixture was concentrated under reduced pressure. To the residue were added 200 ml of saturated aqueous solution of sodium hydrogen carbonate and 100 ml of diethyl ether and the resulting mixture was stirred at room temperature for 30 minutes.

The reaction mixture was extracted with ethyl acetate, and the extract was concentrated under reduced pressure to give (-)-cis-2-(4-methylphenyl)-3-acetoxy-5-[2-(dimethylamino)-ethyl]-8-hydroxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one as a crude product.

The product was treated with oxalic acid, and recrystallized from a mixed solution comprising ethanol and ether to give 966 mg of (-)-cis-2-(4-methylphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-8-hydroxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one oxalate.
m.p.: 168 to 169 °C
$[\alpha]_D^{20}$ -83.1° (c = 0.201, methanol).

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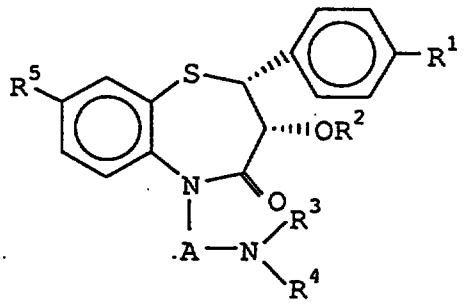
Claims:

1. A peripheral circulation improving agent comprising a (-)-cis-1,5-benzothiazepine compound represented by the following formula:



(I)

wherein R^1 represents a lower alkyl group or a lower alkoxy group; R^2 represents hydrogen atom or a lower alkanoyl group; R^3 represents a lower alkyl group; R^4 represents hydrogen atom or a lower alkyl group; R^5 represent hydrogen atom, a lower alkyl group or a hydroxy lower alkyl group; and A represents a lower alkylene group,

or a pharmaceutically acceptable salt thereof as an active ingredient.

2. The peripheral circulation improving agent according to Claim 1, wherein R^1 is a lower alkyl group, R^2 is a lower alkanoyl group, R^4 is a lower alkyl group, and R^5 is a lower alkyl group.

3. The peripheral circulation improving agent according to Claim 1 or 2, wherein R^1 is a lower alkyl group having 1 to 6 carbon atoms, R^2 is a lower alkanoyl group having 2 to 6 carbon atoms, R^3 is a lower alkyl group having 1 to 6 carbon atoms, R^4 is a lower alkyl group having 1 to 6 carbon atoms, R^5 is a lower alkyl group having 1 to 6 carbon atoms and A is a lower alkylene group having 1 to 6 carbon atoms.

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4. The peripheral circulation improving agent according to Claim 1, wherein R^1 is a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms, R^2 is hydrogen atom or a lower alkanoyl group having 2 to 6 carbon atoms, R^3 is a lower alkyl group having 1 to 6 carbon atoms, R^4 is hydrogen atom or a lower alkyl group having 1 to 6 carbon atoms, R^5 is hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms or a hydroxy lower alkyl group having 1 to 6 carbon atoms and A is a lower alkylene group having 1 to 6 carbon atoms.

5. The peripheral circulation improving agent according to any one of Claims 1 to 4, wherein R^1 is methyl group, R^2 is acetyl group, R^3 is methyl group, R^4 is methyl group, R^5 is methyl group and A is ethylene group.

6. The peripheral circulation improving agent according to any one of Claims 1 to 5 which is adapted to provide a daily dosage level of 0.1 to 300 mg/kg of the (-)-cis-1,5-benzothiazepine compound or a pharmaceutically acceptable salt thereof for oral administration.

7. The peripheral circulation improving agent according to any one of Claims 1 to 5 which is adapted to provide a daily dosage level of 0.001 to 10 mg/kg of the (-)-cis-1,5-benzothiazepine compound or a pharmaceutically acceptable salt thereof for parenteral administration.

8. The use of the peripheral circulation improving agent according to any one of preceding claims, which is a prophylactic and/or curing agent of chronic arterial obstruction.

9. The use of the peripheral circulation improving agent according to any one of preceding claims 1 to 8, which is a prophylactic and/or curing agent of Raynaud's disease or Buerger's disease.

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