



(22) Date de dépôt/Filing Date: 1992/07/03

(41) Mise à la disp. pub./Open to Public Insp.: 1993/01/06

(45) Date de délivrance/Issue Date: 2002/10/22

(30) Priorité/Priority: 1991/07/05 (P 41 22 303.9) DE

(51) Cl.Int.⁵/Int.Cl.⁵ A61K 31/19

(72) Inventeurs/Inventors:

Ulrich, Heinz, DE;
Hettche, Helmut, DE;
Weischer, Carl-Heinrich, DE;
Engel, Jürgen, DE;
Borbe, Harald, DE;
Dimpfel, Wilfried, DE

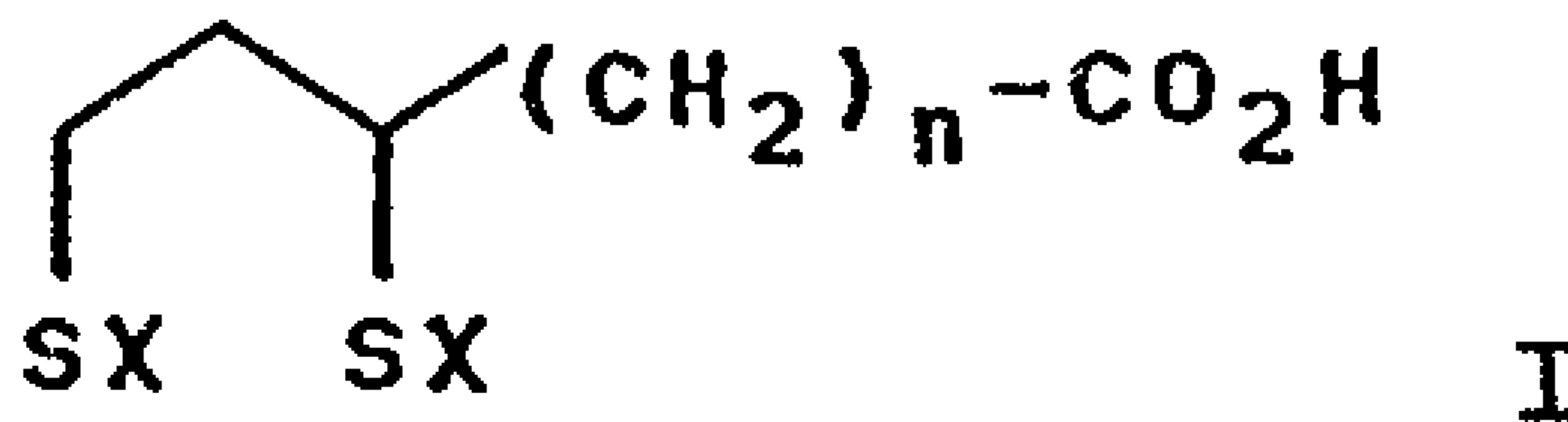
(73) Propriétaire/Owner:

VIATRIS GMBH & CO. KG., DE

(74) Agent: MARKS & CLERK

(54) Titre : EMPLOI D'ACIDES CARBOXYLIQUES SOUFRES POUR COMBATTRE LES TROUBLES EXCITATOIRES D'ORIGINE PHYSIOLOGIQUE ET LES MALADIES QUI S'Y RAPPORTENT, AINSI QUE LES TROUBLES ALLERGIQUES, ET PREPARATION DES MEDICAMENTS CORRESPONDANTS

(54) Title: THE USE OF SULPHUR-CONTAINING CARBOXYLIC ACIDS TO COMBAT PHYSIOLOGICALLY-INDUCED EXCITATORY DISORDERS AND DISEASES RELATED THERETO AS WELL AS ALLERGIC DISEASES AND ALSO THE PREPARATION OF CORRESPONDING MEDICAMENTS



(57) Abrégé/Abstract:

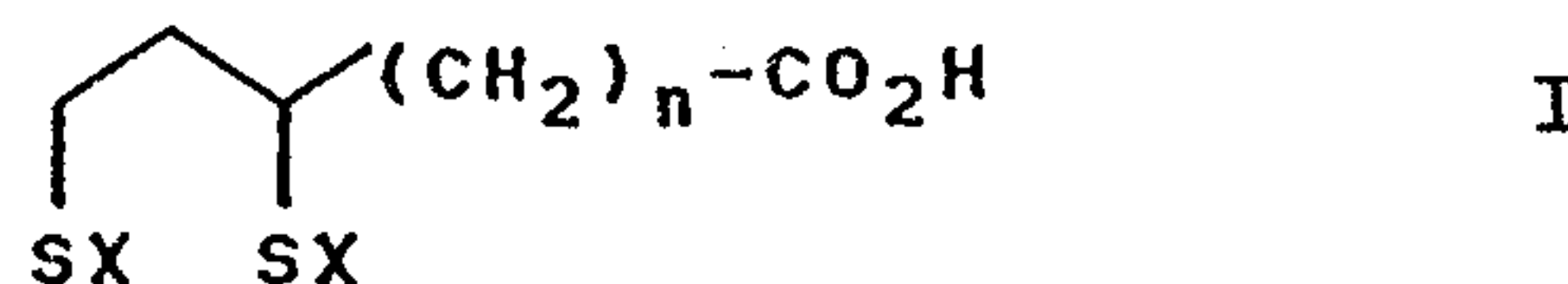
The use of compounds of the formula (see formula I) where X is a hydrogen atom or both X represent a single bond between the two sulphur atoms and n is a number between 1 and 10 or their therapeutically applicable salts for the preparation of a medicament to combat pathophysiologically-induced excitatory disorders and diseases related thereto as well as allergic diseases and the preparation of appropriate medicaments.



2073084

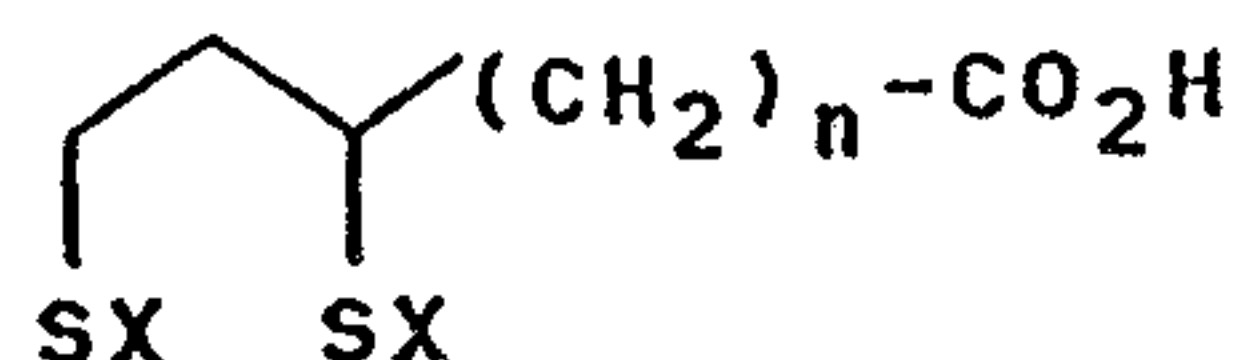
ABSTRACT OF THE DISCLOSURE

The use of compounds of the formula



where X is a hydrogen atom or both X represent a single bond between the two sulphur atoms and n is a number between 1 and 10 or their therapeutically applicable salts for the preparation of a medicament to combat pathophysiologically-induced excitatory disorders and diseases related thereto as well as allergic diseases and the preparation of appropriate medicaments.

The invention relates to the use of compounds of formula



I

5 where X is a hydrogen atom or both X represent a single bond
between the two sulphur atoms and n is a number between 1 and
10, and their therapeutically applicable salts to combat
physiologically-induced excitatory disorders and diseases
related thereto as well as allergic diseases and also the
10 preparation of corresponding medicaments.

The amounts by weight cited in this specification relate in each case to the pure compounds of Formula I and to their enantiomers, that is not to their salts. If salts are used, the appropriate dosages must be used in each case and be
15 appropriately increased to suit the altered molecular weight.

The compounds of Formula I are for example alpha-lipoic acid (racemate and the two optical isomers R(+)- and S(-)-form) as well as dihydrolipoic acid (racemate and the two optical isomers R(+)- and S(-)-form), that is compounds of Formula I where n is the number 4 and X has the meanings given.

Alpha-lipoic acid and the S(-)-form of alpha-lipoic acid are particularly effective in respect of the effects described in the present patent application. This applies in particular to the effect in withdrawal symptoms and drug abuse.

Alpha-lipoic acid is widespread in plants and animals in the form of the racemate (Thioctacid^R); it acts as a coenzyme in many enzymatic reactions, constitutes a growth factor for various bacteria and protozoa and is used in death-head poisoning. The alpha-lipoic acid racemate also has anti-inflammatory, antinociceptive (analgesic) and cytoprotective properties.

Thioctacid is marketed for the following indications:

- fatty liver and fatty cirrhosis,
- chronic liver disease due in particular to alcohol,
- liver damage due to mushroom poisoning,
- diabetic neuropathy,
- alcoholic neuropathy.

Dihydrolipoic acid is 6,8-dimercapto-octanic acid. It is known from animal experiments that dihydrolipoic acid inactivates snake venom. These investigations were for example conducted in rats and mice, using solutions in water or physiological salt solution which contained the snake venom and dihydrolipoic acid.

The compounds of Formula I may also be used in the form of their therapeutically applicable salts. Salts of this kind are prepared in the conventional manner.

Salt-formers that may for example be used are conventional bases or cations which are physiologically acceptable in the salt form. Examples hereof are:

alkaline or alkaline earth metals, ammonium hydroxide, basic amino acids such as arginine and lysine, amines of formula $NR_1R_2R_3$ where the radicals R_1 , R_2 and R_3 are the same or different and represent hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -oxyalkyl such as monoethanolamine and diethanolamine, 1-amino-2-propanol, 3-amino-1-propanol; alkylene diamine with one alkylene chain of 2 to 6 carbon atoms such as ethylene diamine or hexamethylenetetramine, saturated cyclic amino compounds with 4 to 6 ring carbon atoms such as piperidine, piperazine, pyrrolidine, morpholine; N-methylglucamine, creatine, tromethamine.

The compounds of the invention of Formula I have a favourable effect in pathophysiologically caused excitatory disorders, particularly as a consequence of degenerative (preferably neurodegenerative) diseases of the central nervous system and the heart and the changes in excitability associated therewith. The compounds of the invention are in particular also suitable to combat withdrawal symptoms such as occur after the abuse of alcohol, sedatives or drugs. Appropriate medicaments containing the compounds of formula I as active substances have for example an antidegenerative and antiatrophising as well as excitability-stabilizing effect on the central nervous system and the heart as well as an anti-arrhythmic, metabolism-regulating, memory performance increasing, general geriatric and also anti-allergic effect.

In addition, the compounds of Formula I are able, because of their excitability-stabilizing effect to exert a favourable influence on functional disturbances of the central nervous system. Examples that may be cited are withdrawal symptoms after drug abuse and the symptoms of "panic disorder".

The compounds of Formula I also display an effect in damage to the brain and heart, for example in Morbus Alzheimer, Korsakow syndrome, particularly in view of the memory impairment associated with these illnesses, such as also occur in the context of cerebro-organic psychosyndrome.

The compounds of the invention of Formula I display for example in the model to determine the prevention of changes in the EEG of the rat caused by hypoglycaemic or ischaemic insult (as compared to the pre-value) in parenteral application (i.p. = intraperitoneal) at 30 mg/kg (i.p.) of the racemate of alpha-lipoic acid 118 %, in 30 mg/kg i.p. of the (+)-enantiomer 157 % and at 30 mg/kg i.p. of the (-)-enantiomer 85 % change in the performance density of the beta-2-band in the frontal cortex.

The dose range for an effect in the above mentioned experimental model is for example 10 - 100 mg/kg, in particular 15 - 45 mg/kg for the parenteral (intraperitoneal) application.

This investigation was conducted by analogy with the method by Dimpfel et al., Neuropsychobiology 16: 163 - 168, (1986) except that the lead was taken from the hippocampus instead of the thalamus.

(Radioelectroencephalography (Tele-Stereo-EEG) in the rat as a pharmacological model to differentiate the central action of flupirtine from that of opiates, diazepam and phenobarbital).

This test demonstrates effect in the following clinical pictures:

allergic and metabolic-disturbance-related central and peripheral neuropathies with disturbed memory performance as well as nerve conductivity speed for example age-related deterioration in brain performance (minor brain dysfunction). A brief description of the above mentioned test method: 4 bipolar concentric electrodes together with a microplug on a single baseplate were implanted in 4 - 5-month-old male Fischer-344 rats. The plug was used to take up a 4-channel transmitter for telemetric transmission of the field potentials emitted by the frontal cortex, hippocampus, striatum and Formatio Reticularis. The signals were subjected to a Fast Fourier transformation in a Pro Science Computer System in real time and the performance density spectra meaned in each case

over 15 minutes. The subdivision of the spectra in 6 different frequency ranges permits the recordal of pharmaceutical-specific changes in relation to the pre-values within these frequency bands measured in each case before application.

Information on the application protocol on the substances:

The substances were injected intraperitoneally 45 minutes after commencement of measurements (pre-value). Measurements resumed five minutes later, were analysed continuously for at least the next 2 hours and summarized in 15-minute periods. The test substances (for example Thiocetacid) were applied in a dosage of 30 mg/kg.

The experimental series began with the injection of placebo. There followed the first trial of deprenyl. After 4 weeks the chronic application of, for example, R(+)-alpha-lipoic acid began and continued for 7 days with 2 injections/day. Two days after the last injection the effect of deprenyl was measured again. After a 1-week pause for the animals, the effect of R(+)-alpha-lipoic acid was checked again and then once more, 1 week later. After a subsequent wash-out period of a further week and another placebo series, the chronic application of S(-)-alpha-lipoic acid began (total of 4 weeks after completion of the first chronic application). In conclusion 2 days after the last S(-)-alpha-lipoic acid application the effect of deprenyl was recorded once again. During the chronic application of alpha-lipoic acid (racemate) the effect was measured on days 1, 3, 5 and 7.

Statistical comparison of the trials was effected using a multivariant analysis after Ahrens and Läuter (1974) on the basis of changes within the individual frequency bands in all regions of the brain as variables.

The anti-allergic effect is inter alia proven by investigations in PAF (platelet activating factor) acether-oedema in the rat.

The principle of the method is to induce a localized oedema or inflammation in the rat paw using subplantar injection of PAF-acether 2 ug/animal. The investigations are conducted according to the method after SWINGLE and REITER (Agents and actions, 18, 358 - 365, (1986). The animals were given the test substances 0.5 hours before triggering of the oedema. 1 hour thereafter the oedema was determined plethysmographically.

The following results were obtained:

	Oedema inhibition in %	Dose mg/kg intraperitoneally
alpha-lipoic acid	16	50
	14	25
dihydrolipoic acid	63	50
	73	200

Platelet activating factor is one of the partial mediators for the immediate allergic reaction. In the previously mentioned experimental model, oedema inhibition is therefore also proof of an anti-allergic effect.

Indications that may for example be considered for the compounds of Formula I are:

tissue-damaging processes of the central nervous system and the heart as well as the tissue necroses resulting therefrom; ischaemic or hypoxically-induced late organ lesions, in particular of the central nervous system and the heart, such as micro- and macroangiopathies and the hyperexcitability phenomena associated therewith; rhythm disturbances of the heart; damage to the brain or heart, for example Morbus Alzheimer, Korsakow syndrome, in particular in respect of the memory impairment associated with these illnesses also occurring in the context of the cerebro-organic psychosyndrome; allergy-related and

metabolic disorder-related (for example due to diabetes) central and peripheral neuropathies and polyneuropathies (with impaired memory performance and nerve conductivity speed); age-related deterioration of brain performance (minor brain dysfunction). Neuropathophysiological dysfunction in central excitability such as in the clinical picture of panic disorder (Margraf J. and Schneider S.: Panik, published by Springer Verlag 1990) as well as withdrawal symptoms after drug abuse.

The latter indication is for example confirmed by trials in rats treated daily for 2 weeks with higher doses of alcohol or morphine. After withdrawal for 16 hours, the brains of these animals showed hyperexcitability clearly recordable in vitro under controlled conditions, which is totally normalized by the presence of 100 uM of a compound of Formula I. A comprehensive description of these trials is given in Annex A. This Annex A is a constituent part of the specification of this patent application.

The daily doses of the dosage forms of the invention for the above mentioned effects consist for example of 0.1 to 800 mg, preferably 15 to 400 mg and in particular 50 to 300 mg of Compound I (for example alpha-lipoic acid or dihydrolipoic acid or their enantiomers).

In accordance with the invention a daily dose of Compound I (for example alpha-lipoic acid or dihydrolipoic acid or their enantiomers) of 0.1 preferably 10 to 800 mg, for example 25 to 400 mg, in particular 10 to 300 mg is given.

The maximum daily dose should not exceed 800 mg. The daily doses may be used in the form of a single administration of the entire amount or in the form of 1 to 6, in particular 1

2073084

- 7a -

to 4 partial doses per day. In general an administration of
1 to 4 times, in particular 1 to 3 times daily is preferred.
The preferred daily dose is for example 80 to 350 mg for the
5 parenteral form of

application and 800 mg for the oral form. The daily dose for the parenteral form of application is in particular 50 mg and 400 mg for the oral form.

The medicaments are preferably given orally.

The compounds of Formula I (for example alpha-lipoic acid and dihydrolipoic acid or their enantiomers) may also be applied in the form of a solution, for example by the peroral, topical, parenteral, intravenous, intramuscular, subcutaneous, nasal, inhalative, rectal, transdermal route.

Medicaments containing as active substance one or several compounds of Formula I (for example alpha-lipoic acid or dihydrolipoic acid or their enantiomers) may for example be formulated in the form of tablets, capsules, pills or coated tablets, granulates, suppositories, pellets, solutions or emulsions, the active substance being combined with appropriate auxiliary substances and carriers. Solutions contain for example 0.5 to 20 % by weight, preferably 1 to 10 % by weight of the compound of Formula I.

The dosage unit of the medicaments containing one or several compounds of Formula I or a therapeutically applicable salt thereof as active substance may for example contain:

- a) in the case of peroral medicinal forms:
in particular 50 to 400 mg compound/active substance I (for example alpha-lipoic acid or dihydrolipoic acid). The doses may for example be given 1 to 6, preferably 1 to 4, in particular 1 to 3 times daily. A total dose of 800 mg per daily should, however, not be exceeded. The same also applies to the following medicinal forms listed under b) to e).

- b) in the case of parenteral medicinal forms (for example intravenous, intramuscular):
10 to 350 mg, preferably 15 to 350 mg, in particular 20 to 150 mg compound/active substance I. The doses may for example be given 1 to 6, preferably 1 to 4, in particular 1 to 3 times daily.
- c) in the case of medicinal forms for rectal application:
10 to 500 mg, preferably 40 to 400, in particular 50 to 200 mg compound/active substance I. These doses may for example be given 1 to 6, preferably 1 to 4, in particular 1 to 3 times daily.
- d) in the case of medicinal forms for application to the skin and mucous membranes (for example as solutions, lotions, emulsions, ointments and the like):
10 to 500 mg compound/active substance I, preferably 40 to 250 mg, in particular 5 to 200 mg. The doses may for example be given 1 to 6, preferably 1 to 4, in particular 1 to 3 times daily.
- e) In the case of medicinal forms for the inhalation of solutions or aerosols:
0.1 to 300 mg, preferably 0.25 to 150 mg, in particular 0.5 to 80 mg compound/active substance I. These doses may for example be given 1 to 6, preferably 1 to 4, in particular 1 to 3 times daily.
If solutions are used, the compound/active substance I is preferably used in the form of a salt.

It is of course also possible to prepare pharmaceutical formulations which contain the above mentioned dosage units 2 to for example 6 times.

In particular tablets or capsules contain 20 to 600 mg; pellets, powders or granulates 20 to 500 mg; suppositories 20 to 400 mg compound/active substance I.

The medicaments with one or several active substances of Formula I appropriately also contain 0.001 to 1 part by weight of antioxidant (related to 1 part by weight of compound I).

Antioxidants that may for example be considered are: sodium sulphite, sodium hydrogen sulphite, sodium metabisulphite, ascorbic acid, ascorbyl palmitate, ascorbyl myristate, ascorbyl stearate, gallic acid, gallic acid alkyl ester, butylhydroxyanisol, nordihydroguaiacic acid, tocopherols as well as synergists (substances which bind heavy metals through complex formation, for example lecithin, ascorbic acid, phosphoric acid, ethylenediaminetetra-acetic acid, citrates, tartrates). The addition of synergists considerably enhances the antioxygenic effect of antioxidants.

Preservatives that may for example be considered for the medicaments of the invention are sorbic acid, p-hydroxybenzoic acid esters (for example lower alkyl esters), benzoic acid, sodium benzoate, trichloroisobutyl alcohol, phenol, cresol, benzethonium chloride, chlorhexidine and formalin derivatives.

Complex formers that may for example be considered are: chelate formers such as ethylenediaminetetra-acetic acid, nitrilotriacetic acid, diethylenetriaminepentaacetic acid and their salts.

The complex formers may also be those which enclose dihydrolipoic acid in a cavity. Examples of these are urea, thiourea, cyclodextrins, amylose.

Adjustment to a pH range of approx 6 to 9 with physiologically acceptable bases or buffers may optionally be necessary to stabilize the active substance molecule. As neutral or weakly basic a pH value (up to pH 8) is generally preferred.

Examples for pharmaceutical formulations

Example 1:

Tablets containing 50 mg S- or R-alpha-lipoic acid

250 g S-alpha-lipoic acid are evenly ground with 750 g microcrystalline cellulose. After sieving the mixture, 250 g starch (starch 1500/Colorcon), 732.5 g lactose, 15 g magnesium stearate and 2.5 g highly disperse silicon dioxide are mixed in and the mixture pressed into tablets weighing 400.0 mg.

One tablet contains 50 mg S-alpha-lipoic acid.

In the same way it is possible to prepare tablets containing 50 mg R-alpha-lipoic acid by using the same amount of R-alpha-lipoic acid instead of 250 g S-alpha-lipoic acid.

The tablets may optionally be provided with a gastric juice-soluble or gastric juice-permeable film coating using conventional methods.

Example 2:

Ampoules containing 50 mg S- or R-alpha-lipoic acid as tromethamine salt in 2 ml

250 g S-alpha-lipoic acid are dissolved together with 352.3 g tromethamine (2-amino-2-(hydroxymethyl)-1,3-propandiol) in a mixture of 9 litres of water for injection purposes and 200 g 1,2-propylene glycol with stirring. The solution is made up to 10 litres with water for injection purposes and then filtered through a membrane filter of pore size 0.2 μ m with a glass fibre pre-filter. The filtrate is filled under aseptic conditions in 2 ml portions into sterilized 2 ml ampoules.

One ampoule contains 50 mg S-alpha-lipoic acid as tromethamine salt in 2 ml injection solution.

In similar manner it is possible to prepare ampoules with R-alpha-lipoic acid by using the same amount of R-alpha-lipoic acid instead of 250 g S-alpha-lipoic acid.

Example 3:

Ampoules with 250 mg dihydrolipoic acid in 10 ml injection solution

60 g tromethamine and 1 g ethylenediaminetetraacetic acid, disodium salt are dissolved in 1.8 litres water for injection purposes. The solution is gassed with nitrogen for 30 minutes. 2 g sodium disulphite and then 50 g dihydrolipoic acid are dissolved in the mixture with continued nitrogen gassing. The solution is made up to a volume of 2 litres with water for injection purposes gassed with nitrogen. After careful mixing the solution is filtered over a membrane filter of pore size 0.2 um and the filtrate is filled under aseptic conditions and with pre- and post-gassing with nitrogen into ampoules having a filling volume of 10 ml.

One ampoule contains 250 mg dihydrolipoic acid as tromethamine salt in 10 ml solution.

The effect of compounds of Formula I (for example the L-enantiomer of alpha-lipoic acid) on the hippocampus section preparation of ethanol-dependent rats.

5 Results:

Preparations removed from the hippocampus of rats 16 hours after discontinuation of ethanol (5g/kg/day ethanol over a period of 2 weeks) were subjected to decreasing magnesium concentrations in the superfusion medium in order to detect
10 changes in plasticity changes in the excitability of the pyramidal cells. The electrically triggered and spontaneous discharges were monitored in the absence and presence of the S(-)-form of alpha-lipoic acid.

Triggered discharges were found to be totally dampened by the
15 (-)-enantiomer of alpha-lipoic acid.

Material and methods:

Two groups of fully grown, male CD rats (Charles River Wiga) received conventional rat feed ad libitum. The drinking water was sweetened by addition of 1 g glucose/litre. One
20 group received water containing 5 % ethanol. The amounts of water taken up by the animals was determined daily and was an average of 40 ml in both groups. It follows that, during the two-week trial - the ethanol group took up about 5 g/kg ethanol within 24 hours starting from their average weight.

25 The animals received the modified drinking water over a period of 2 weeks. Their body weight was measured daily, no difference being observed between the two groups. 16 hours before measurement of excitability commenced ex vivo, the

animals treated with ethanol also received glucose-containing drinking water to initiate the withdrawal.

5 The animals were exsanguinated under slight anaesthetic, the brain was removed in toto and the isolation of the Formatio hippocampi monitored under a stereomicroscope. The middle portion of the hippocampus was fixed using a cyanacrylate adhesive in cooled phosphate-buffered salt solution (NaCl 124 mM; KCl 5 mM; CaCl₂ mM; MgSO₄ 1.25 mM; NaHCO₃ 26 mM; glucose 10mM) on the table of a Vibratom and sliced into 400 um thick sections. All sections were pre-incubated in a pre-chamber for at least one hour before use in carbon-saturated salt solution. During the experiment the sections were fixed according to the method of Haas et al. (1979) and treated in 15 a special superfusion chamber. The preparation was flushed with 180-240 ml/hour artificial liquor (see above).

Electrical stimulation (200 uA, 100 us) of the Schaffner-collaterals within the CA₂ range and recording of the pyramidal cell section from CA₁ was conducted by means of 20 conventional electrophysiological methods using the Pro Science Laboratory Computer System "LabTEAM" and the software package "NeuroTOOL". For each reaction measurement the mean value of 4 stimulations was determined at 20-second intervals. Measurements were conducted regularly every 10 25 minutes in order to exclude potentiation characteristics. After three stable values had been recorded before the administration of compound I (active substance I) the perfusion was switched over to the artificial liquor with active substance I and maintained for at least 30 minutes. 30 The mean amplitude was determined from the three signals before administration of active substance I and regarded as 100 %. All mean changes after addition of active substance I

relate to this percentage value. At least 6 independent measurements were made under each experimental condition.

5 The amount of Mg^{++} was reduced stepwise in order to activate the transfer controlled by the NDMA receptor. In addition to the earlier measurements, the spontaneous activity of the section preparation was monitored during this experiment. The spontaneous activity in the form of spontaneous population peaks or even discharges was determined by sending
10 the signal through a shielding discriminator adjusted in such a way that the appropriate signals of the individual sections could be recognized.

The S(-)-form of alpha-lipoic acid was tested at a dose of 246 ug/ml.

15 The effect of compounds of Formula I (for example the L-enantiomer of alpha-lipoic acid) on the hippocampus section preparation of morphine-dependent rats.

Results:

20 Preparations removed from the hippocampus of rats 16 hours after withdrawal of morphine (2 mg/kg morphine subcutaneously 2 x daily for 2 weeks) were exposed to decreasing magnesium concentrations in the superfusion medium in order to demonstrate plasticity changes in the excitability of the pyramidal cells. The electrically triggered and spontaneous
25 discharges were observed in the absence and presence of the S(-)-form of alpha-lipoic acid. The (-)-enantiomer of alpha-lipoic acid was able to diminish the spontaneous discharges and reduce the peak amplitudes of the population to normal values which were intensified with lower magnesium

concentrations. This suggests and application/use of alpha-lipoic acid in withdrawal symptoms in drug dependence.

Material and methods

5 Two groups of fully grown, male CD rats (Charles River Wiga) received commercial rat feed ad libitum. During the two weeks of the trial the animals of the first group received 2 mg/kg morphine twice daily. The control group received injections of salt solution. Body weight was recorded daily.
10 16 hours before measurement of excitability commenced ex vivo, injections were discontinued in the animals treated with morphine in order to initiate withdrawal.

The animals were exsanguinated under slight anaesthetic, the brain was removed in toto and the isolation of the Formatio
15 hippocampi monitored under a stereomicroscope. The middle portion of the hippocampus was fixed using a cyanacrylate adhesive in cooled phosphate-buffered salt solution (NaCl 124 mM; KCl 5 mM; CaCl₂ mM; MgSO₄ 1.25 mM; NaHCO₃ 26 mM; glucose 10mM) on the table of a Vibratom and sliced into 400 µm thick
20 sections. All sections were pre-incubated in a pre-chamber for at least one hour before use in carbon-saturated salt solution. During the experiment the sections were fixed according to the method of Haas et al. (1979) and treated in a special superfusion chamber. The preparation was flushed
25 with 180-240 ml/hour artificial liquor (see above).

Electrical stimulation (200 µA, 200 µs) of the Schaffner-collaterals within the CA₂ range and recording of the pyramidal cell section of CA₁ was conducted by means of conventional electrophysiological methods using the Pro
30 Science Laboratory Computer System "LabTEAM" and the software package "NeuroTOOL". For each reaction measurement the mean

value of 4 stimulations was determined at 20-second intervals. Measurements were conducted regularly every 10 minutes in order to exclude potentiation characteristics.

5 After three stable values had been recorded before the administration of compound I (active substance I) the perfusion was switched over to the artificial liquor with active substance I (see above) and maintained for at least 30 minutes.

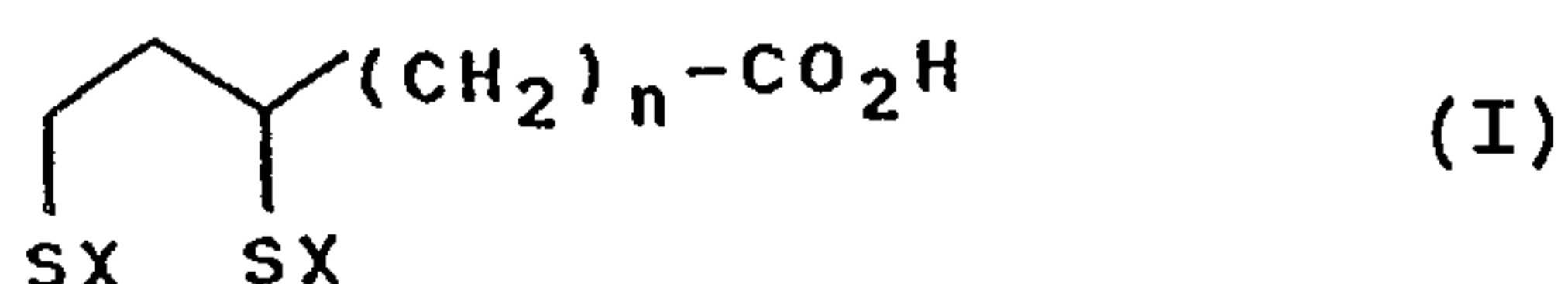
10 The mean amplitude was determined from the three signals before administration of active substance I and regarded as 100 %. All mean changes after addition of active substance I relate to this percentage value. At least 6 independent measurements were made under each experimental condition.

15 The amount of Mg^{++} was reduced stepwise in order to activate the transfer controlled by the NDMA receptor. Apart from the earlier measurements, the spontaneous activity of the section preparation was monitored during this experiment. The spontaneous activity in the form of spontaneous population
20 peaks or even discharges was determined by sending the signal through a shielding discriminator adjusted in such a way that the appropriate signals of the individual sections could be recognized.

25 The S(-)-form of alpha-lipoic acid was tested at a dose of 100 μM .

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical composition for treating physiologically-induced excitatory disorders and diseases related thereto, and allergic diseases, comprising: a pharmaceutically effective amount of a compound of general formula:



wherein n is from one to 10, and X represents H or both X together represent a single bond between the two S, or a therapeutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

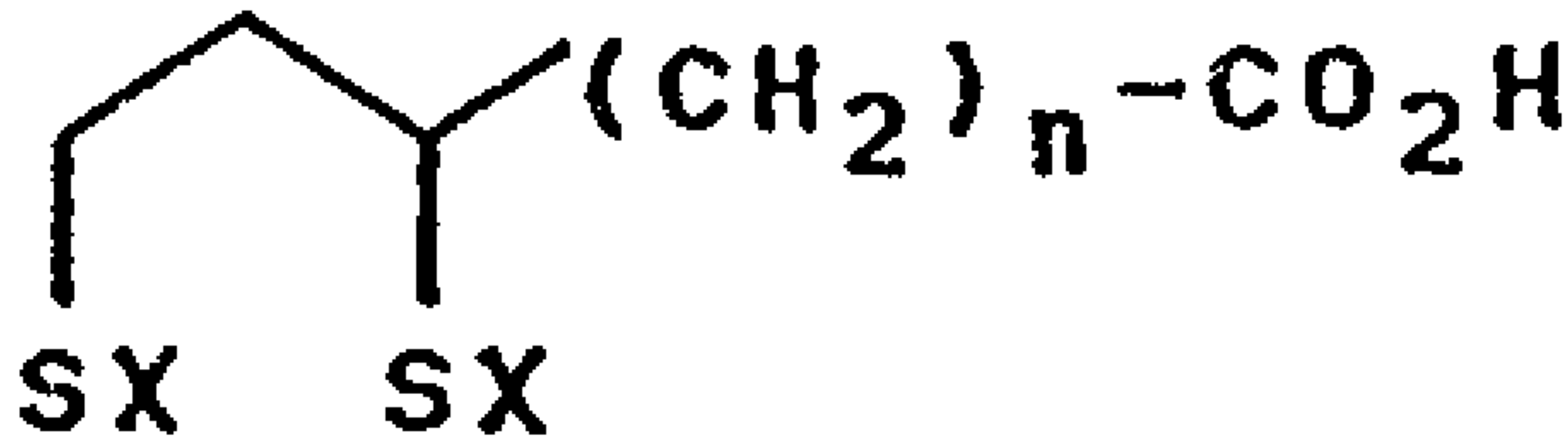
2. The composition of claim 1, comprising a pharmaceutically acceptable antioxidant, complex former or mixture thereof.

3. The composition of claim 1, comprising from 0.1 to 800 mg of compound (I).

4. Use of the composition of claim 1, 2 or 3, for treating physiologically-induced excitatory disorders and diseases related thereto, and allergic diseases.

5. Use of a compound of general formula (I) as defined in claim 1, for treating physiologically-induced excitatory disorders and diseases related thereto, and allergic diseases.

6. Use of a compound of general formula (I) as defined in claim 1, for preparing a pharmaceutical composition.



I