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Copy of the English translation of the specification and claims as originally filed.

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PATENT OF INVENTION

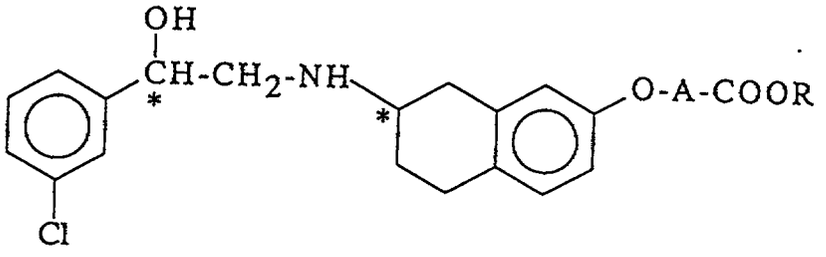
Use of phenylethanolaminotetralins for the preparation of antidepressant and anti-stress medicaments.

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In the name of: SANOFI

The present invention concerns the use of some phenylethanolaminotetralins for the preparation of medicaments suitable for the treatment or prophylaxis of depression and stress.

More particularly a first object of the present invention is the use of at least one phenylethanolaminotetralin of general formula (I)



(I)

in which:

A represents a (C_1–C_4)alkylene radical and

R is hydrogen or a (C_1–C_4)alkyl group,

or one of its pharmaceutically acceptable salts, for the preparation of medicaments suitable for the treatment or prophylaxis of depression and stress.

The compounds of formula (I) are already known in the prior art as intestinal spasmolytics and lypolytics acting through a mechanism of selective stimulation of β–atypical receptors (neither β_1 nor β_2) which are present in the intestine. Their preparation and their characteristics have been described in particular in EP–A–211,721, EP–A–303,545, EP–A–303,546 and EP–A–383,686.

About fifteen years ago, a sedative effect was clearly demonstrated for the conventional β–stimulants *(A. Ksiazek et al J. Pharmacol. Pharm., 26, 287–295, 1974)* and the results of more recent studies also indicate an antidepressant effect for some β_2–stimulant products, such as clenbuterol and salbutamol, which might be related to the central β–adrenergic stimulating activity of said products. In spite of these promising pharmacological results, the cardiovascular side–effects make the conventional β–stimulants very difficult to use in therapy.

It has now been found that the products of formula (I) which possess a stimulating activity on atypical β–receptors, are almost completely inactive on β_1–receptors and have no activity or only a slight activity on β_2–receptors, are therapeutically very interesting as antidepressant agents, as they have an antidepressant activity at least comparable to that of the above–mentioned potent conventional β_2–agonists while being devoid of the unacceptable side–effects (mainly tachycardia) observed with the latter.

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The properties of the compounds of formula (I) have been studied by means of a set of tests in animals conventionally employed in pharmacology and generally considered predictive of antidepressant activity in man (*P. Simon, Therapie, 1973, 28, 209–223*).

More particularly, the compounds of formula (I) have been tested in mice in comparison with clenbuterol and salbutamol in the following four tests:

- Antagonism to the hypothermizing effects of apomorphine
- Antagonism to the hypothermizing effects of reserpine
- Antagonism to the hypothermizing effects of oxotremorine
- Increase in the yohimbine toxicity

Possible behavioural and motor activity modifications following administration of increasing doses of test products have also been observed.

The compounds of formula (I) share common effects with the conventional β–agonist products employed as reference products e.g. clenbuterol and salbutamol: antagonism to the hypothermias induced in mice by reserpine, oxotremorine, or a high dose of apomorphine, and potentiation of yohimbine toxicity. Unlike clenbuterol and salbutamol, the compounds of formula (I) hardly produce any sedation and any decrease of spontaneous motor activity in mice.

These tests have been carried out as follows:

- ***Antagonism to apomorphine–induced hypothermia***

  (*A.J. Puech et al. Psychopharmacology, 75(1), 84–91, 1981*).

  Male CD1 mice (Charles Rives – France) weighing between 22 and 25 g were used. The mice were housed individually in transparent plastic cages. The products to be tested as well as the reference products were suspended in 1% aqueous carboxymethylcellulose solution. The products were administered intraperitoneally with the volume of 10 ml/kg (6 mice per dose). Control animals received the vehicle only.

  Rectal temperature was measured using a probe carrying a thermoelectric couple (connected to a galvanometer) inserted to a constant depth.

  The products to be tested as well as the vehicle were administered 30 minutes after basal rectal temperature was measured and 30 minutes before apomorphine (16 mg/kg) was administered subcutaneously. Rectal temperature was measured again 30 minutes after the administration of apomorphine.

  The results have been expressed as average temperature of each group, by evaluating the significant differences in temperature between treated and

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control mice groups by Student's t test, and used for calculating the M.A.D., i.e. the minimal active dose.

The results are presented in Table I:

TABLE I

COMPOUND	Antagonism to the hypothermia induced by apomorphine (16 mg/kg s.c.) D.M.A. mg/kg i.p.
N-[(2S) 7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (Compound A)	0.1 (0.3 p.o.)
N-[(2R) 7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (Compound B)	0.1
N-[(2S) 7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2S)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (Compound C)	1
N-[(2S)7-(2-ethoxycarbonyl-propan-2-yloxy)-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (Compound D)	0.3
N-[(2R)7-(2-ethoxycarbonyl-propan-2-yloxy)-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy- 2-(3-chlorophenyl)ethanamine hydrochloride (Compound E)	0.3
Clenbuterol	0.03
Salbutamol	1

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- ***Motor activity.***

While clebuterol and salbutamol reduce motor activity in mice, up to 35% of the controls and up to 62% of the controls respectively with a dose of 0.03 mg/kg of clenbuterol and 3 mg/kg of salbutamol, the compounds of formula (I) listed in Table (I) above, at the doses indicated therein, almost do not affect motor activity. Compound A being completely inactive in this respect even at the dose of 10 mg/kg i.p..

- ***Antagonism of the reserpine-induced hypothermia***

The compounds of formula (I) as well as the reference products were administered 4 hours after reserpine (2.5 mg/kg i.p.). Rectal temperature was measured 90 minutes after the administration of the products to be tested.

The results obtained, by way of example, with Compound A are summarized in Table II:

TABLE II

COMPOUND	Dose mg/kg i.p. (groups of 6 to 10 mice per dose)	Rectal temperature °C (± E.S.M.) 1h30 after the administration of the compound . 5h30 after the injection of reserpine (2.5 mg/kg i.p.)	Minimum active dose mg/kg i.p.
Compound A	0	28.9 ± 0.3	0.1 (1 p.o.)
	0.1	30.3 ± 0.4*	
	0.3	30.7 ± 0.3**	
	1	31.4 ± 0.2***	
Clenbuterol	0	32.8 ± 0.3	0.03
	0.03	34.0 ± 0.4*	
	0.1	35.2 ± 0.4***	
	0.3	34.5 ± 0.3***	
Salbutamol	0	29.9 ± 0.6	3
	1	30.5 ± 0.9	
	3	32.6 ± 0.4**	
	10	32.0 ± 0.7*	
* = P < 0.05	** = P < 0.01	*** = P < 0.001	

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– *Antagonism of the oxotremorine–induced hypothermia.*

The substances to be tested were administered 30 minutes before oxotremorine (0.4 mg/kg i.p.). Rectal temperature was measured 30 minutes after the administration of oxotremorine.

The oxotremorine–induced hypothermia was antagonised, at least partially, by the compounds of formula (I) as well as by the reference compounds.

With Compound A, whose activity in this test has been investigated more deeply, it was shown that the antagonism regularly increases with the dose.

– *Increase in yohimbine toxicity.*

Yohimbine administration, at the subcutaneous dose of 30 mg/kg s.c., generally causes the death of one out of ten mice. An increase in the toxicity was evaluated by administering the products to be tested intraperitoneally 30 minutes before yohimbine and calculating the percentage of deaths in the 24 hours following yohimbine subcutaneous injection. The compounds of formula (I) which were subjected to this test showed a clear potentiation of yohimbine toxicity – at doses comparable to the active doses– of the reference compounds. In addition, the compounds of formula (I) are also endowed with a remarkable anti–stress activity.

Several recent studies have shown that stress may have a profound influence on a great number of physiological processes. It is widely known for instance that exposure to stress generating conditions generally brings about reduced immunological functions, intestinal motoricity troubles, etc..

The existence of such a link between stress and some pathological conditions, indicated herein as "stress–induced" conditions, increases the therapeutical interest of the compounds of formula (I) which may therefore be employed in the treatment of depression as well as in the treatment of stress and therefore of stress–induced pathological conditions.

For the evaluation of the anti–stress activity, male CD(BR)SD rats (Charles River – Italy), weighing between 220 and 250 g, were employed and acutely stressed by completely immobilizing them, flat on their chests, on small boards by means of adhesive tape. Three pairs of electrodes were chronically implanted on the animal colon (proximal, distal, and transverse colon) and the wires were exteriorised in the scapular region and connected to an electroencephalograph for recording of myoelectrical activity. The parameter used to evaluate this activity was the number of long–duration spike burst (LSB) per minute.

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Almost immediately upon immobilization, the electromyographic response of the colon, together with the faecal excretion, increases with respect to the unrestrained controls. These effects remain nearly stable during the first hour of stress and begin to decrease during the second.

Administration of a compound of formula (I) just before immobilization protects the animals against stress and reduces both electromyographic response and faecal excretion with respect to the restrained controls. Said protective effect is obtained even when the compound of formula (I) is administered intracranially at very low doses which definitely excludes any peripheral effect on colon. The anti–stress effects elicited by the compounds of formula (I) – a central effect at the CNS level – are similar to those obtained with benzodiazepines and in particular with diazepam.

The results obtained with Compound A, a representative compound of formula (I), are summarized in following Tables III and IV

TABLE III

Effects of Compound A and diazepam on stress–stimulated colon myoelectric activity in rats

COMPOUND	DOSE mg/kg	Colon myoelectric activity (LSB/min) during the first hour of stress		
		Proximal	Transverse	Distal
Unrestrained controls	-	1.75 ± 0.06	1.10 ± 0.15	0.85 ± 0.12
Restrained controls	-	2.41 ± 0.14 **	1.75 ± 0.37 *	1.42 ± 0.25 *
Compound A	0.2 (p.o.)	1.63 ± 0.11 °	1.20 ± 0.15	0.67 ± 0.27 °
	0.5 (p.o.)	1.07 ± 0.14 °°*	1.28 ± 0.25	0.63 ± 0.12 °
	2 (p.o.)	0.76 ± 0.12°°**	1.16 ± 0.22	0.66 ± 0.17 °
	0.003 (i.c.v.)	2.07 ± 0.09	1.25 ± 0.18	0.71 ± 0.15 °
Diazepam	2 (s.c.)	1.64 ± 0.12	0.99 ± 0.08	0.52 ± 0.07 °°

* = P < 0.05 v. unrestrained controls ** = P < 0.01 v. unrestrained controls

° = P < 0.05 v. restrained controls °° = P < 0.01 v. restrained controls

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TABLE IV

Effects of compound A and diazepam on stress–induced faecal excretion in rats.

TABLE IV

COMPOUND	DOSE mg/kg	Faecal excretion during the first hour of stress	
		Faeces - Dry weight (g ± S.E.)	% inhibition over restrained controls
Unrestrained controls	-	0 ± 0	-
Restrained controls	-	1.24 ± 0.05	-
Compound A	0.2 (p.o.)	0.80 ± 0.06 **	35
	2 (p.o.)	0.41 ± 0.07 **	67
Diazepam	2 (s.c.)	0.51 ± 0.07 **	59
** = P < 0.01 v. restrained controls			

Furthemore, the compounds of formula (I) and their pharmaceutically acceptable salts have a very low toxicity which is compatible with their use as medicaments.

The present invention recommends the use of at least one compound of formula (I) in which A and R are as defined above or of a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for the treatment or prophylaxis of depression and stress.

In a particularly preferred aspect, the use of the compounds of formula (I) or of a pharmaceutically salt thereof is recommended for the preparation of a medicament intended for the treatment and prophylaxis of depression.

Another preferred aspect of the invention recommends the use of the compounds of formula (I) or of a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for the treatment or prophylaxis of stress and stress–induced pathological conditions, particularly those associated with intestinal motoricity troubles.

As used herein, the term pharmaceutically acceptable salts includes, on the one hand, the acid addition salts obtained from the free base and from pharmaceutically acceptable mineral or organic acids and, on the other hand, the

salts of the compounds of formula (I) in which R is hydrogen with mineral bases, preferably those with alkali metals such as sodium or potassium, or with pharmaceutically acceptable organic bases.

Among the acids which can be employed for the salification of the free base, there may be cited i.a. hydrochloric acid, hydrobromic acid, acetic acid, formic acid, propionic acid, oxalic acid, fumaric acid, maleic acid, succinic acid, benzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, tartaric acid, aspartic acid, glutamic acid, methanesulfonic acid, p–toluenesulfonic acid, and the like.

The hydrochloride is anyway the preferred acid addition salt according to the present invention.

In the above formula (I), the two asymmetric carbon atoms are labelled with an asterisk. All the compounds of formula (I) may therefore exist in the form of at least four different steric isomers [(R,R), (R,S), (S,S), and (S,R)].

The optically pure stereoisomers, as well as any mixture of two, three, or all four isomers, in any proportion, may be employed for the preparation of antidepressant medicaments according to the present invention. An additional asymmetrical center may be present in the radical A. Analogously, the stereoisomers derived from such chiral center and their mixtures may be employed according to the present invention.

It is however understood that, as it often happens when dealing with pharmaceutically active products possessing one or more chiral centers, the different stereoisomers may have different activity levels. If desired, the person skilled in the art may, on the basis of the indications given in the text of the present application and his own experience in that field, choose from the different stereoisomers or mixtures of isomers of a compound of formula (I), the compound or compounds which are therapeutically most interesting.

As a consequence of the obtained results, the isomers (I) where the carbon atom bound to the hydroxy group has absolute configuration (R), are generally the most interesting and the use of at least one compound of formula (I) where the carbon atom bound to the hydroxy group has absolute configuration (R) for the preparation of an anti–depressant and anti–stress medicament represents a particularly preferred object of the present invention.

A group of compounds of formula (I) preferably used according to the present invention comprises the compounds of formula (I) in which A is a methylene group or an isopropylidene group. A more particularly preferred group

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comprises the compounds of formula (I) in which A is a methylene or isopropylidene group and the carbon atom bound to the hydroxy group has absolute configuration R.

Even more preferred compounds for the use according to the present invention are the compounds of formula (I) in which A is a methylene group and R is a methyl or ethyl group.

For the treatment or prophylaxis of depression and stress the compounds of formula (I) may be administered orally, sublingually, transdermally, rectally, subcutaneously, intramuscularly, or intravenously.

The amount of active principle to be administered will depend, as usually, on the nature and severity of the pathological conditions to be treated as well as on the weight of the patient and the administration route.

In human beings the daily dose typically varies between 0.01 and 30 mg/kg of body weight, and preferably between 0.01 and 10 mg/kg of body weight.

Said daily dose is generally subdivided in 2, 3, or 4 administrations. Preferably, for the treatment and prophylaxis of depression and stress, the active principles (the compounds of formula (I) and their pharmaceutically acceptable salts) are formulated in unit dosage forms containing 0.1 to 400 mg and preferably from 0.5 to 100 mg of active principle in combination with a pharmaceutical carrier.

Unit dosage forms suitable for oral administration include tablets, capsules, powders, granules, and solutions or suspensions for oral use.

When a solid composition is prepared in the form of tablets, the main active principle is mixed with a pharmaceutical vehicle such as gelatine, starch, lactose, magnesium stearate, talc, gum arabic, and the like. The tablets may be coated with sucrose or other appropriate materials or they may be treated so that their activity is extended or delayed and they continuously release a predetermined amount of active principle.

A preparation in the form of capsules is obtained by mixing the active principle with a diluent and filling the obtained mixture in soft or hard capsules.

A preparation in the form of a syrup or elixir for the administration in drops, may contain the active principle jointly with a sweetening agent, preferably acaloric, methylparaben and propylparaben as antiseptics, as well as a flavoring agent and an appropriate dye.

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Water–dispersible powders or granules may contain the active principle in admixture with dispersing agents, wetting agents or suspending agents such as polyvinylpyrrolidone, and with sweetening or flavouring agents as well.

For rectal administration, suppositories can be employed which are prepared with binders at rectal temperature, such as cocoa butter or polyethyleneglycols.

For sublingual administration microtablets or microcapsules can be prepared which, placed under the tongue, will rapidly dissolve. These compositions will generally contain the active principle in admixture with wetting and/or dispersing agents and optionally with absorption enhancers.

For transdermal administration, the use of polymeric diffusion matrices for the continuous and preferably delayed release of the active principle is recommended as well as the use of the active principle as a microemulsion with excipients adapted for contact with the skin.

For parenteral administration, aqueous suspensions, isotonic saline solutions, or sterile injectable solutions are used, which contain pharmacologically compatible dispersing and/or wetting agents, for example propyleneglycol or butyleneglycol.

The active principle of formula (I) may also be formulated in the form of microcapsules, possibly with one or more carriers or additives.

The active principle of formula (I) may be administered as the free base or a pharmaceutically acceptable salt thereof, as such or complexed with a cyclodextrine for instance, or even in admixture with or associated to other active principles.

It is thus another object of the present invention to provide a pharmaceutical composition intended in particular for the treatment or prophylaxis of depression and stress containing, as the active principle, at least one compound of formula (I) above or a pharmaceutically acceptable salt thereof.

By way of example, suitable pharmaceutical compositions may be prepared as follows:

- Tablets comprising N–[(2S)7–ethoxycarbonylmethoxy–1,2,3,4–tetrahydro–naphth–2–yl]–(2R)–2–hydroxy–2–(3–chlorophenyl)ethanamine hydrochloride (Compound A) having the following composition

Compound A	5 mg
Microcrystalline cellulose	40 mg

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Dried corn starch	40 mg
Lactose	100 mg
Magnesium stearate	5 mg

are prepared by grinding the active ingredient to a particular size of 0.4 mm, passing it through a sieve with 0.4 mm openings, mixing the ground material with the other ingredients and compressing the mixture to obtain tablets.

Analogously, tablets containing 10 mg of active ingredient can be obtained.

- By operating essentially as described above but using N–[(2S)7–(2–ethoxycarbonyl–propan–2–yloxy)–1,2,3,4–tetrahydronaphth–2–yl]–(2R)–2–hydroxy–2–(3–chlorophenyl)ethanamine hydrochloride (Compound D) as the active principle, tablets with the following composition are prepared

Compound D	50.0 mg
Dried corn starch	100.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg

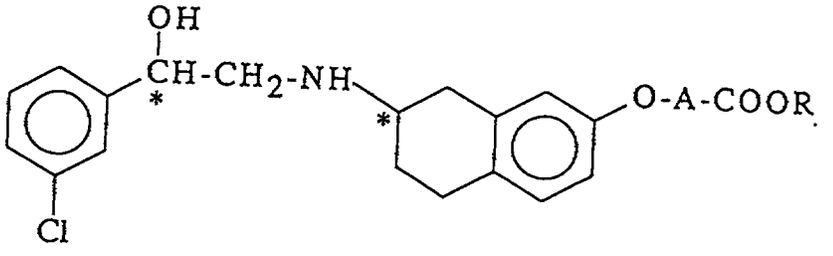
- 10,000 capsules containg 20 mg of active principle are prepared starting from the following ingredients: Compound A (200 g), microcrystalline cellulose (990 g), amorphous silica gel (10 g). The above ingredients are well mixed together and then filled into hard gelatin capsules.
- An aqueous sterile solution suitable for parenteral administration, in ampoule form comprising compound A and having the following composition:

Compound A	5 mg
Sodium chloride	1 mg
Distilled water q.s.p.	2 ml

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CLAIMS

1. Use of at least one compound of general formula (I)



(I)

in which A represents a (C_1–C_4)alkylene group and R is a hydrogen atom or a (C_1–C_4)alkyl group, or of a pharmaceutically acceptable salt thereof for the preparation of a medicament suitable for the treatment or prophylaxis of depression and stress.

2. Use according to claim 1, in which A represents a methylene or isopropylidene group.

3. Use according to one of claims 1 or 2, characterized in that the carbon atom bound to the hydroxy group in formula (I) has absolute configuration (R).

4. Use according to any one of claims 1 to 3, characterized in that R is the methyl group or the ethyl group.

5. Use according to claim 4, characterized in that the compound of formula (I) is selected from N–[(2S)7–ethoxycarbonylmethoxy–1,2,3,4–tetrahydronaphth–2–yl]–(2R)–2–hydroxy–2–(3–chlorophenyl)ethanamine and the pharmaceutically acceptable salts thereof.

6. Pharmaceutical composition suitable for the treatment or prophylaxis of depression and stress containing, as the active principle, at least one compound of formula (I) in which A and R are as defined in claim 1 or a pharmaceutically acceptable salt thereof.

* C L M S *