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Copy of the specification and claims as originally filed.

BREVET D'INVENTION

Utilisation de phényléthanolaminotétralines pour la préparation de médicaments antidépressifs et anti-stress.

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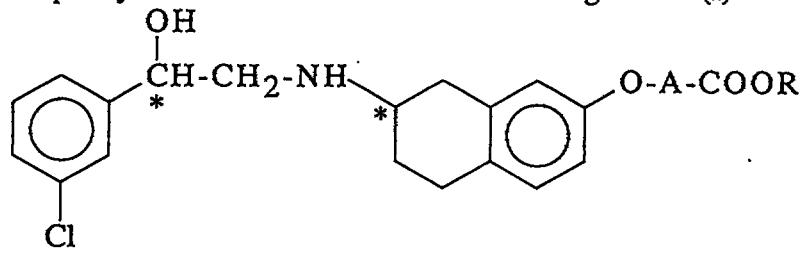
La présente invention concerne l'utilisation de certaines phényléthanolaminotétralines dans la préparation de médicaments destinés au traitement ou à la prophylaxie de la dépression et du stress.

Plus particulièrement, un premier objet de la présente invention est l'utilisation d'au moins une phényléthanolaminotétraline de formule générale (I)



(I)

dans laquelle :

A représente un groupe (C_1-C_4)alkylène, et

R répresente un atome d'hydrogène ou un groupe (C_1-C_4) alkyle,

ou un de ses sels pharmaceutiquement acceptables, pour la préparation de médicaments destinés au traitement ou à la prophylaxie de la dépression et du stress.

Les composés de formule (I) sont déjà connus dans l'art antérieur en tant qu'agents lypolytiques et spasmolytiques intestinaux agissant par un mécanisme de stimulation séléctive de récepteurs β atypiques (ni β_1, ni β_2) présents dans l'intestin. Leur préparation et leurs caractéristiques ont été décrites en particulier dans EP-A-211721, EP-A-303545, EP-A-303546 et EP-A-383686.

Il y a une quinzaine d'années, un effet sédatif a été mis clairement en évidence pour les β-stimulants classiques (*A. Ksiazek et al., J. Pharmacol. Pharm., 1974, 26, 287-295*), et des travaux plus récents ont montré aussi un effet antidépresseur pour certains produits β_2-stimulants, par exemple clenbutérol et salbutamol, effet qui pourrait être lié à l'activité stimulante β-adrénergique de ces produits exercée au niveau central. Malgré ces résultats pharmacologiques prometteurs, les effets secondaires dans le domaine cardiovasculaire rendent l'usage clinique des β-stimulants conventionnels extrêmement difficile.

On vient de trouver à présent que les produits de formule (I), qui exercent une activité stimulante sur les récepteurs β atypiques, n'ont presque aucune activité sur les récepteurs β_1 et aucune, ou dans certains cas une activitée modérée, sur les récepteurs β_2, sont thérapeutiquement très interessants en tant qu'agents antidépresseurs ayant une activité au moins comparable à celle des puissants β_2-agonistes classiques mentionnés ci-dessus et étant dépourvus des effets secondaires inacceptables (notamment tachycardie) observés avec ces derniers.

Les proprietés des composés de formule (I) ont été étudiées à l'aide d'une batterie de tests habituellement utilisés en pharmacologie et généralement considérés en tant que prévisionnels chez l'animal d'une activité antidépressive chez l'homme (*P. Simon, Thérapie, 1973, 28, 209-223*).

Plus particulièrement, les composés de formule (I) ont été essayés chez la souris en comparaison avec le clenbutérol et le salbutamol dans les quatre tests suivants :

- Antagonisme aux effets hypothermisants de l'apomorphine
- Antagonisme aux effets hypothermisants de la réserpine
- Antagonisme aux effets hypothermisants de l'oxotrémorine
- Accroissement de la toxicité à la yohimbine

On a observé aussi les modifications éventuelles du comportement et de l'activité motrice chez des souris après traitement avec des doses croissantes des produits à tester.

Les composés de formule (I) possèdent des effets communs aux produits β-agonistes classiques utilisés comme produits de référence tels que le clenbutérol et le salbutamol: antagonisme aux hypothermies exercées chez la souris par la réserpine, l'oxotrémorine et l'apomorphine à forte dose, et une potentialisation de la toxicité de la yohimbine. Contrairement au clenbutérol et au salbutamol, les composés de formule (I) ne produisent presqu'aucune sédation et aucune diminution de l'activité motrice spontanée chez les souris.

Ces tests ont été conduits de la façon suivante :

- ***Antagonisme à l'hypothermie induite par l'apomorphine***

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

On a utilisé des souris mâles CD1 (Charles Rives, France) d'un poids compris entre 22 et 25 g. Les souris sont placées isolément dans des boites en matière plastique transparente. Les produits à tester ainsi que les produits de comparaison ont été mis en suspension dans une solution aqueuse à 1% de carboxyméthylcellulose. Les produits ont été administrés par voie intrapéritoneale sous le volume de 10 ml/kg (6 souris par dose). Les animaux de contrôle ont reçu seulement le véhicule.

La température rectale a été mesurée à l'aide d'une sonde porteuse d'un couple thermoélectrique (relié à un galvanomètre) enfoncée à une profondeur constante.

Les produits à tester ainsi que le véhicule ont été administrés 30 minutes après la mesure de la température rectale de base et 30 minutes avant l'apomorphine (16 mg/kg sous-cutanée). La température rectale a été mesurée à nouveau 30 minutes après l'administration d'apomorphine.

Les résultats ont été exprimés comme température moyenne de chaque groupe, en évaluant les significations des variations de température entre les groupes de souris traitées et ceux du contrôle à l'aide du test t de Student, et utilisés pour calculer la D.M.A., c'est à dire la dose minimum active.

Les résultats sont présentés dans le TABLEAU I :

TABLEAU I

COMPOSE	Antagonisme à l'hypothermie induite par l'apomorphine 16 mg/kg s.c. D.M.A. mg/kg i.p.
Chlorhydrate de N-[(2S)7-éthoxycarbonyl-méthoxy-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé A)	0,1 (0,3 p.o.)
Chlorhydrate de N-[(2R)7-éthoxycarbonyl-méthoxy-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé B)	0,1
Chlorhydrate de N-[(2S)7-éthoxycarbonyl-méthoxy-1,2,3,4-tétrahydronapht-2-yl]-(2S)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé C)	1
Chlorhydrate de N-[(2S)7-(2-éthoxycarbonyl-propan-2-yloxy)-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé D)	0,3
Chlorhydrate de N-[(2R)7-(2-éthoxycarbonyl-propan-2-yloxy)-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé E)	0,3
Clenbutérol	0,03
Salbutamol	1

- ***Activité motrice.***

Alors que, chez la souris, le clenbutérol et le salbutamol diminuent l'activité motrice qui, à la dose de 0,03 mg/kg de clenbutérol et de 3 mg/kg de salbutamol, n'est plus, respectivement, que de 35 et 62% de celle des témoins, aux doses indiquées ci-dessus les composés (I) énumerés dans le tableau (I) n'ont provoqué presqu'aucune variation

de la motricité, le Composé A étant complètement inactif même à la dose de 10 mg/kg i.p.

- ***Antagonisme de l'hypothermie induite par la réserpine.***

Les composés de formule (I) ainsi que les produits de référence ont été administrés 4 heures après la réserpine (2,5 mg/kg, i.p.). La température rectale a été mesurée 90 minutes après l'administration des produits à tester.

Les résultats qui ont été obtenus, à titre d'exemple, avec le Composé A, sont résumés dans le TABLEAU II :

TABLEAU II

COMPOSE	Dose mg/kg i.p. (groupes de 6 à 10 souris par dose)	Température rectale °C (± E.S.M.) 1h30 après administration du composé; 5h30 après injection de réserpine (2,5 mg/kg i.p.)	Dose minimum active mg/kg i.p.
Composé 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***	
Clenbutérol	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			

- ***Antagonisme de l'hypothermie induite par l'oxotrémorine.***

Les substances à tester ont été administrées 30 minutes avant l'oxotrémorine (0,4 mg/kg, i.p.). La température rectale a été mesurée 30 minutes après l'administration d'oxotrémorine.

L'hypothermie induite par l'administration d'oxotrémorine est antagonisée, au moins partiellement, par les composés de formule (I) ainsi que par les composés de référence.

Avec le Composé A, dont l'activité dans ce test, a été étudiée plus à fond, on a verifié que l'antagonisme progresse régulièrement avec la dose.

- *Accroissement de la toxicité à la yohimbine.*

L'administration de yohimbine, à la dose de 30 mg/kg sous-cutanée, provoque en moyenne la mort de 1 souris sur 10. Un accroissement de la toxicité est évalué en administrant les produits à tester par voie intra-péritonéale 30 minutes avant la yohimbine et en comptabilisant le pourcentage de mortalité 24 heures après l'injection sous-cutanée de yohimbine. Les composés de formule (I) qui ont été soumis à ce test ont montré une potentialisation nette de la toxicité de la yohimbine à des doses comparables aux doses actives des composés de référence.

En plus, on a maintenant trouvé que les composés de formule (I) exercent une activité anti-stress remarquable.

De nombreuses études récentes ont montrés que le stress peut avoir une influence profonde dans un grand nombre de processus physiologiques. Il est bien connu, par exemple, que l'exposition à des situations créant un stress s'accompagne en général d'une diminution des fonctions immunologiques, des troubles de la motricité intestinale, etc.

L'existence d'un tel lien entre le stress et certains états pathologiques, qu'on indique comme "induits par le stress", augmente l'intérêt thérapeutique des composés de formule (I) qui peuvent donc être utilisés dans le traitement de la dépression ainsi que du stress et donc des états pathologiques induits par le stress.

Pour l'évaluation de l'activité anti-stress on a utilisé des rats mâles CD(BR)SD Charles River (Italie) ayant un poids compris entre 220-250 g et on a provoqué chez eux une situation de stress aigu en les immobilisant complètement, à plat ventre, sur des plaques avec du ruban adhésif. Trois couples d'électrodes ont été implantés de façon permanente sur le côlon (proximal, distal et transverse) des animaux et les fils des électrodes ont été sortis par la région scapulaire et reliés à un électroencéphalographe pour l'enregistrement de l'activité myoélectrique. Comme paramètre de cette activité, on a utilisé le nombre de salves de potentiel (spike-bursts) de longue durée par minute (LSB/min).

Presque immédiatement après l'immobilisation on note une augmentation de la réponse électromyographique du côlon ainsi qu'une augmentation de l'excrétion fécale par rapport aux animaux contrôles non contraints. Ces effets restent plus au moins stables pendant la première heure de stress et diminuent pendant la seconde.

En administrant aux animaux un composé de formule (I) juste avant leur immobilisation, on les protège contre le stress et on remarque ainsi, par rapport aux contrôles contraints, une diminution tant de la réponse électromyographique que de l'excrétion fécale. On obtient cette protection même quand le composé de formule (I) est administré par voie intracranienne à des doses très faibles, ce qui exclut l'existence

d'effets périphériques au niveau du côlon. L'effet anti-stress qu'on obtient avec les composés de formule (I) - un effet central au niveau du SNC - peut être rapproché de celui provoqué par les benzodiazépines, en particulier par le diazepam.

Les résultats obtenus avec le Composé A, composé représentatif de formule (I), sont resumés dans les Tableaux III et IV qui suivent.

TABLEAU III

Effets du Composé A et du diazepam sur l'activité myoélectrique du côlon stimulée par le stress chez le rat.

COMPOSE	DOSE mg/kg	Activité myoélectrique du côlon (LSB/min) pendant la première heure de stress		
		Proximal	Transverse	Distal
Contrôles non contraints	-	1,75 ± 0,06	1,10 ± 0,15	0,85 ± 0,12
Contrôles contraints	-	2,41 ± 0,14 **	1,75 ± 0,37 *	1,42 ± 0,25 *
Composé 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. contrôles pas contraints ** = P < 0,01 v. contrôles pas contraints
° = P < 0,05 v. contrôles contraints °° = P < 0,01 v. contrôles contraints

TABLEAU IV

Effets du Composé A et du diazepam sur l'excrétion fécale induite par le stress chez le rat.

COMPOSE	DOSE mg/kg	Excrétion fécale pendant la première heure de stress	
		poids sec des selles (g ± S.E.)	% inhibition par rapport aux contrôles contraints
Contrôles non contraints	-	0 ± 0	-
Contrôles contraints	-	1,24 ± 0,05	-
Composé 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. contrôles contraints

En outre, les composés de formule (I) et leurs sels pharmaceutiquement acceptables possèdent une toxicité très faible, compatible avec l'utilisation de ces produits en tant que médicaments.

Selon la présente invention on préconise donc l'utilisation d'au moins un composé de formule (I) dans laquelle A et R sont tels que définis ci-dessus ou un de ses sels pharmaceutiquement acceptables pour la préparation d'un médicament destiné au traitement ou à la prophylaxie de la dépression et du stress.

Suivant un aspect particulièrement préféré, on préconise l'utilisation des composés de formule (I) ou de leurs sels pharmaceutiquement acceptables pour la préparation d'un médicament destiné au traitement et à la prophylaxie de la dépression.

Selon un autre aspect préféré de l'invention, on préconise l'utilisation des composés de formule (I) ou de ses sels pharmaceutiquement acceptables pour la préparation d'un médicament destiné au traitement ou à la prophylaxie du stress et des états pathologiques induits par le stress, en particulier ceux associés aux troubles de la motricité intestinale.

Par sels pharmaceutiquement acceptables, on entend ici, d'une part les sels d'addition d'acides obtenus à partir de la base libre et d'acides minéraux ou organiques pharmaceutiquement acceptables et d'autre part les sels des composés de formule (I) dans laquelle R est l'hydrogène avec des bases minérales de préférence celles avec des métaux alcalins tels que le sodium ou le potassium, ou avec des bases organiques pharmaceutiquement acceptables.

Parmi les acides utilisables pour salifier la base libre, on peut notamment mentionner les acides chlorhydrique, bromohydrique, acétique, formique, propionique, oxalique, fumarique, maléique, succinique, benzoïque, cinnamique, mandélique, citrique, malique, tartrique, aspartique, glutamique, méthanesulfonique, p-toluènesulfonique, etc.

Le chlorhydrate est de toute façon le sel d'addition acide préféré selon la présente l'invention.

Dans la formule (I) ci-dessus, les deux atomes de carbone asymétriques sont marqués par un astérisque. Tous les composés de formule (I) peuvent donc exister sous forme d'au moins quatre isomères stériques différents [(R,R), (R,S), (S,S) et (S,R)].

Les stéréoisomères optiquement purs, ainsi que les mélanges de deux, trois, ou des quatre isomères, dans une proportion quelconque, peuvent être utilisés pour la préparation de médicaments antidépresseurs selon la présente invention. Un autre centre d'asymétrie pourrait être présent dans le radical A. De même, les stéréoisomères provenant de la présence de ce centre chiral et leurs mélanges peuvent être utilisés selon la présente invention.

Il est de toute façon sous-entendu que, comme il arrive souvent lorsque il s'agit de produits pharmaceutiquement actifs ayant un ou plusieurs centres chiraux, les différents stéréoisomères peuvent avoir des niveaux d'activité différents. S'il le désire, l'homme de métier pourra, sur la base des indications données dans le texte de la présente demande et selon son expérience dans le domaine, choisir parmi les differents stéreoisomères ou mélanges d'isomères d'un composé de formule (I), le ou les plus intéressants du point de vue thérapeutique.

Des résultats obtenus ,il ressort que les isomères (I) où l'atome de carbone lié au groupe hydroxy a la configuration absolue (R) sont en général les plus intéressants, et l'utilisation d'au moins un composé de formule (I). où l'atome de carbone lié au groupe hydroxy a la configuration absolue (R), pour la préparation d'un médicament antidépressif et anti-stress représente donc un objet particulièrement préféré de la présente invention.

Un groupe de composés de formule (I) utilisés de préférénce selon la présente invention comprend les composés de formule (I) dans laquelle A est groupe méthylène ou un groupe isopropylidène. Un groupe plus particulièrement préféré comprend les composés de formule (I) dans laquelle A est un groupe méthylène ou isopropylidène et l'atome de carbone lié au groupe hydroxy a la configuration absolue R.

Les composés encore plus préférés pour l'utilisation selon la présente invention sont les composés de formule (I) dans laquelle A est un groupe méthylène et R est un groupe méthyle ou éthyle.

Pour le traitement ou la prophylaxie de la dépression et du stress, les composés de formule (I) peuvent être administrés par voie orale, sublinguale, transdermique, rectale, sous-cutanée, intramusculaire ou intraveineuse.

La quantité de principe actif à administrer dépend, comme il en est d'habitude, de la nature et de la sévérité des affections à traiter, ainsi que du poids des malades et de la voie d'administration.

La dose par jour chez l'homme varie généralement entre 0,01 et 30 mg par kg de poids du corps, et de préférence entre 0,01 et 10 mg par kg de poids du corps.

Cette dose est normalement subdivisée pendant la journée en 2,3, ou 4 administrations. De préférence, pour le traitement ou la prophylaxie de la dépression ainsi que du stress, les principes actifs (les composés de formule (I) et leurs sels pharmaceutiquement acceptables) sont formulés en unités de dosage contenant de 0,1 à 400 mg, et préférablement de 0,5 à 100 mg de principe actif en combinaison avec un support pharmaceutique.

Des formes unitaires de dosage appropriées pour l'administration orale comprennent les comprimés, les gélules, les poudres, les granules et les solutions ou suspensions orales.

Lorsqu'on prépare une composition solide sous forme de comprimés, on mélange le principe actif principal avec un véhicule pharmaceutique tel que la gélatine, l'amidon, le lactose, le stéarate de magnésium, le talc, la gomme arabique ou analogues. On peut enrober les comprimés de saccharose ou d'autres matières appropriées ou encore on peut les traiter de telle sorte qu'ils aient une activité prolongée ou retardée et qu'ils libèrent d'une façon continue une quantité prédéterminée de principe actif.

On peut obtenir une préparation en gélules en mélangeant le principe actif avec un diluant et en versant le mélange obtenu dans des gélules molles ou dures.

Une préparation sous forme de sirop ou d'élixir ou pour l'administration sous forme de gouttes peut contenir le principe actif conjointement à un édulcorant, acalorique de préférence, du méthylparaben et du propylparaben comme antiseptiques, ainsi qu'un agent donnant du goût et un colorant approprié.

Les poudres ou les granules dispersibles dans l'eau peuvent contenir l'ingrédient actif en mélange avec des agents de dispersion ou des agents mouillants, ou des agents de mise en suspension, comme la polyvinylpyrrolidone, de même qu'avec des édulcorants ou des correcteurs du goût.

Pour une administration rectale, on recourt à des suppositoires qui sont préparés avec des liants à la température rectale, par exemple du beurre de cacao ou des polyéthylèneglycols.

Pour une administration sublinguale on peut préparer des microcomprimés ou microgélules qui se dissolvent rapidement lorsqu'ils sont mis sous la langue. Ces compositions contiennent, en général, le principe actif en mélange avec des agents mouillants et/ou des agents de dispersion et éventuellement des agents qui augmentent l'absorption.

Pour une administration transdermique on préconise l'utilisation des matrices de diffusion polymériques pour la libération continue et préférablement retardée du principe actif, ainsi que l'utilisation du principe actif sous forme de microémulsion avec des excipients appropriés au contact avec la peau.

Pour une administration parentérale, on utilise des suspensions aqueuses, des solutions salines isotoniques ou des solutions stériles et injectables qui contiennent des agents de dispersion et/ou des agents mouillants pharmacologiquement compatibles, par exemple le propylèneglycol ou le butylèneglycol.

Le principe actif principal de formule (I) peut être formulé également sous forme de microcapsules, éventuellement avec un ou plusieurs supports ou additifs.

Le principe actif de formule (I) peut être administré sous forme de base libre ou de sel pharmaceutiquement acceptable tel quel ou sous forme de complexe avec, par exemple, une cyclodextrine ou bien en association ou en co-administration avec d'autres principes actifs.

Un autre objet de la présente invention est donc une composition pharmaceutique destinée notamment au traitement ou à la prophylaxie de la dépression et du stress renfermant, en tant que principe actif, au moins un composé de formule (I) ci-dessus ou un de ses sels pharmaceutiquement acceptables.

A titre d'exemple des compositions pharmaceutiques appropriées peuvent être préparés comme décrit ci-dessus.

- On prépare des comprimés à base du chlorhydrate de N-[(2S)7-éthoxycarbonyl-méthoxy-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé A), ayant la composition suivante :

Composé A	5 mg
Cellulose microcristalline	40 mg
Amidon de mais séché	40 mg
Lactose	100 mg
Stéarate de magnésium	5 mg

en broyant l'ingrédient actif jusqu'à une dimension particulière de 0,4 mm, en le faisant passer à travers un tamis de 0,4 mm d'ouverture de maille, en mélangeant la matière broyée avec les autres constituants et en comprimant pour former les comprimés. De la même façon, on prépare des comprimés contenant 10 mg d'ingrédient actif.

- On opère substantiellement de la même façon mais en utilisant en tant que principe actif le chlorhydrate de N-[(2S)7-(2-éthoxycarbonyl-propan-2-yloxy)-1,2,3,4-tétrahydronapht-2-yl]-(2R)-2-hydroxy-2-(3-chlorophényl)éthanamine (Composé D), et on obtient des comprimés ayant la composition suivante :

Composé D	50,0 mg
Amidon de maïs séché	100,0 mg
Lactose	95,0 mg
Talc	4,5 mg
Stéarate de magnésium	0,5 mg

- 10.000 gélules avec une teneur en substance active de 20 mg sont préparées à partir des constituants suivants: 200 g de Composé A, 990 g de cellulose microcristalline, 10

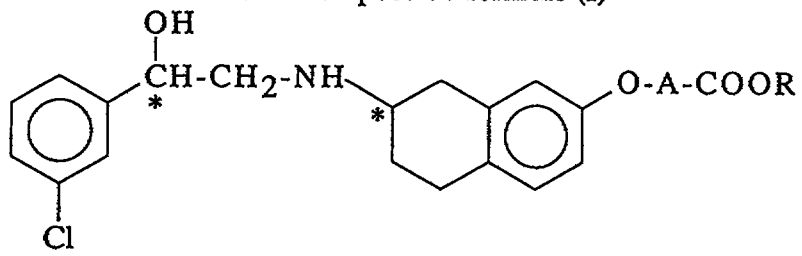
g de gel de silice amorphe. Les constituants ci-dessus sont bien mélangés et introduits dans des gélules de gélatine dure.

- On prépare une solution aqueuse stérile appropriée pour une utilisation parentérale en ampoules à base du Composé A ayant la composition suivante :

Composé A	5 mg
Chlorure de sodium	1 mg
Eau distillée q.s.p.	2 ml

REVENDICATIONS

1. Utilisation d'au moins un composé de formule (I)



(I)

dans laquelle A répresente un groupe (C_1-C_4)alkylène et R répresente un groupe (C_1-C_4)alkyle ou un atome d'hydrogène ou un de ses sels pharmaceutiquement acceptables pour la préparation d'un médicament destiné au traitement ou à la prophylaxie de la dépression et du stress.

2. Utilisation selon la revendication 1, dans laquelle A représente un groupe méthylène ou isopropylidène.

3. Utilisation selon l'une des revendications 1 ou 2, caractérisée en ce que l'atome de carbone lié au groupe hydroxy dans la formule (I) a la configuration absolue R.

4. Utilisation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que R est le groupe méthyle ou le groupe éthyle.

5. Utilisation selon la revendication 4, caractérisée en ce que le composé de formule (I) est choisi entre le N-[(2S) 7-éthoxycarbonylméthoxy-1,2,3,4-tétrahydronapht-2--yl]-(2R)-2-hydroxy-2-(3-chlorophényl)-éthanamine, et ses sels pharmaceutiquement acceptables.

6. Composition pharmaceutique destinée au traitement ou à la prophylaxie de la dépression et du stress renfermant, en tant que principe actif, au moins un composé de formule (I) dans laquelle A et R sont tels que définis dans la revendication 1, ou un de ses sels pharmaceutiquement acceptables.

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BREVET D'INVENTION

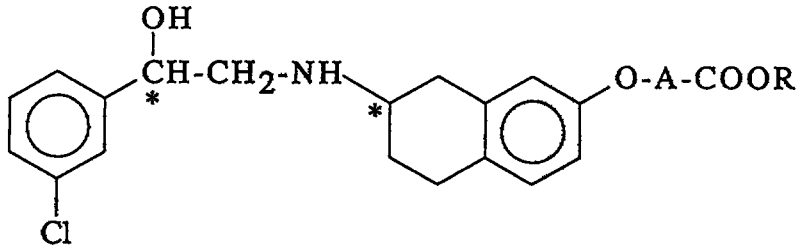
Utilisation de phényléthanolaminotétralines pour la préparation de médicaments antidépressifs et anti-stress.

Inventeurs : Peter-Eugène KEANE — Alberto BIANCHETTI
Jacques SIMIAND — Tiziano CROCI

Au nom de : SANOFI

ABREGE

L'invention concerne l'utilisation de phényléthanolaminotétralines de formule I ci-après pour la préparation de médicaments destinés au traitement ou à la prophylaxie de la dépression et du stress



(I)

dans laquelle A répresente un groupe (C_1-C_4)alkylène et R répresente un groupe (C_1-C_4)alkyle ou un atome d'hydrogène.

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EUROPEAN PATENT APPLICATION

N° 91403263.6

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

REPLACED SHEETS		SG
☑ Description	: paged 1	to paged 11
☑ Claim(s)	: paged 12	to paged –
☐ Drawing(s)	: paged	to paged .....
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PATENT OF INVENTION

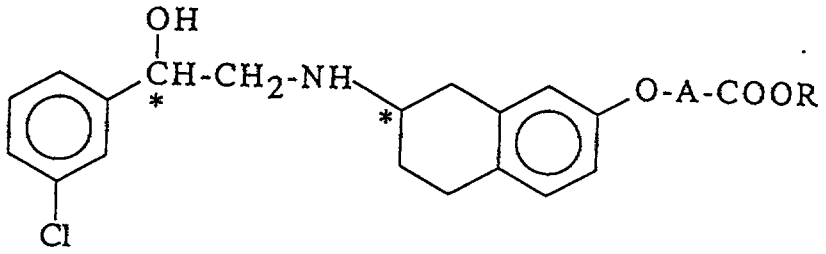
Use of phenylethanolaminotetralins for the preparation of antidepressant and anti-stress medicaments.

Inventors: Peter-Eugène KEANE, Alberto BIANCHETTI, Jacques SIMIAND, Tiziano CROCI

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

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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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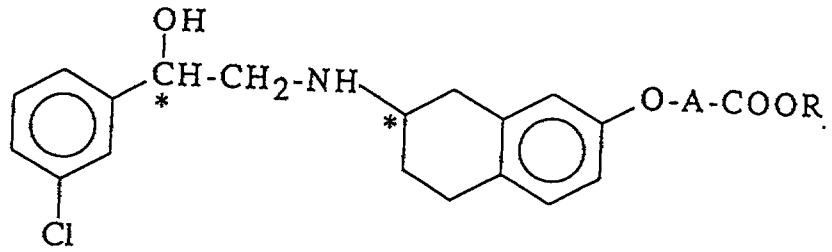
CLAIMS

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 *

PATENT OF INVENTION

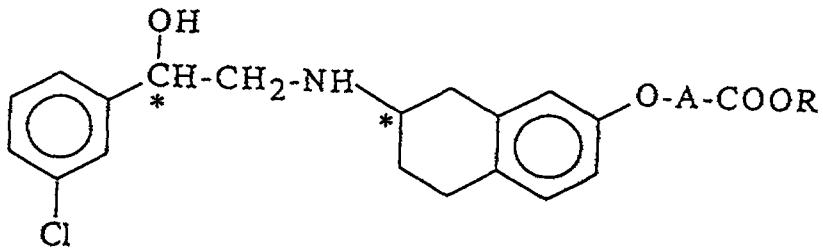
Use of phenylethanolaminotetralins for the preparation of antidepressant and anti-stress medicaments.

Inventors: Peter-Eugène KEANE, Alberto BIANCHETTI, Jacques SIMIAND, Tiziano CROCI

In the name of: SANOFI

ABSTRACT OF THE DISCLOSURE

The invention relates to the use of phenylethanolaminotetralins of formula I hereinafter for the preparation of medicaments suitable for the treatment or prophylaxis of depression and stress



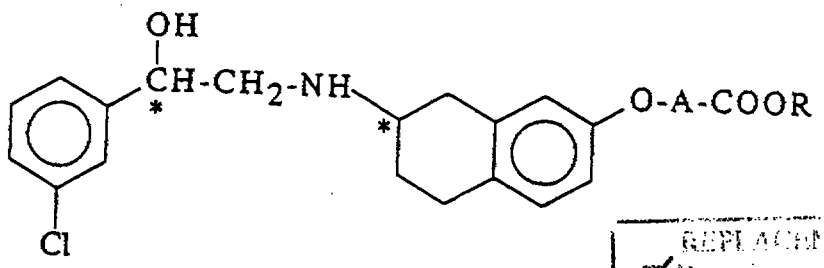
(I)

in which A represents a (C_1-C_4)alkylene group and R represents a (C_1-C_4)alkyl group or a hydrogen atom.

USE OF PHENYLETHANOLAMINOTETRALINS FOR THE PREPARATION OF ANTIDEPRESSANT AND ANTI-STRESS MEDICAMENTS

The present invention concerns the use of some phenylethanolaminotetralins in the preparation of medicaments intended 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)



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in which:

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or one of its pharmaceutically acceptable salts, for the preparation of medicaments intended 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 (non β_1 non 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 more recent works also indicated an antidepressant effect for some β_2–stimulating products, for example clenbuterol and salbutamol, said effect likely to be related to the β–adrenergic stimulating activity of these products which is exerted at the central level. In spite of these promising pharmacological results, the side–effects in the cardiovascular field of the conventional β–stimulants make their use in therapy extremely difficult.

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

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activity on β_2-receptors, are therapeutically very interesting as antidepressant agents, as they have an activity at least comparable to that of the above-mentioned potent conventional β_2-agonists and in the meantime are devoid of the unacceptable side-effects (mainly tachycardia) observed with these last compounds.

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, Thérapie, 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 of apomorphine-induced hypothermia
- antagonism of reserpine-induced hypothermia
- Antagonism of oxotremorine-induced hypothermia
- Increase of yohimbine toxicity

Possible behavioural and motor activity modifications in mice following administration of increasing doses of the products to be tested have also been noted.

The compounds of formula (I) share some common effects with the conventional β-agonist products employed as reference products e.g. clenbuterol and salbutamol: antagonism to the hypothermia induced in mice by reserpine, oxotremorine, and a high dose of apomorphine, and potentiation of yohimbine toxicity. Unlike clenbuterol and salbutamol, the compounds of formula (I) hardly produce any sedation and no decrease of spontaneous motor activity in mice.

These tests have been conducted as follows:

- ***Antagonism of apomorphine-induced hypothermia***

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

  Male CD1 mice (Charles River - France) weighing 22-25 g were used. The mice were placed individually in boxes made from a transparent plastic material. The products to be tested as well as the reference products were suspended in 1% aqueous solution of carboxymethylcellulose and administered intraperitoneally (10 ml/kg; 6 mice per dose). The control animals only received the vehicle.

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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 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 of the hypothermia induced by apomorphine 16 mg/kg s.c. M.A.D. 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

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N-[(2S)-7-(2-ethoxycarbonylpropan-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-ethoxycarbonylpropan-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

- ***Motor activity***

  While clenbuterol and salbutamol reduce motor activity in mice, up to 35% of that of the controls with 0.03 mg/kg of clenbuterol and up to 62% of that of the controls with 3 mg/kg of salbutamol, the compounds of formula (I) listed in Table (I), at the doses indicated therein, hardly provoked any difference in motor activity, Compound A being completely inactive 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 administration of the products to be tested.

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

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TABLE II

COMPOUND	Dose mg/kg i.p. (groups of 6 to 10 mice per dose)	Rectal temperature °C (± M.S.D.) 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

- ***Antagonism of the oxotremorine-induced hypothermia***

  The substances to be tested were administered 30 minutes before the administration of 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 of yohimbine toxicity***

  Yohimbine administration (30 mg/kg s.c.) generally causes the death of one out of ten mice. Increase of the toxicity was evaluated by administering the products to be tested intraperitoneally 30 minutes before yohimbine and calculating the mortality rate in the 24 hours following yohimbine s.c. injection. The compounds of formula (I) which

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were submitted to this test showed a clear potentiation of yohimbine toxicity at doses comparable to the active doses of the reference compounds.

In addition it was discovered that the compounds of formula (I) are also endowed with a remarkable anti-stress activity.

Several recent studies have shown that stress may have a great influence on a number of physiological processes. It is widely known for instance that exposure to stress generating conditions generally brings about reduced immunological functions, intestinal motility disorders, 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 and 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 220-250 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 permanently implanted on the animal colon (proximal, distal, and transverse colon) and the electrode 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 bursts (LBS) per minute.

Almost immediately upon immobilization, the electromyographic response of the colon as well as the faecal excretion increase with respect to the unrestrained control animals. These effects remain nearly stable during the first hour of stress and decrease during the second.

Administration of a compound of formula (I) just before immobilization protects the animals against the stress and reduces both electromyographic response and faecal excretion with respect to the restrained controls. Said protection is also obtained when the compound of formula (I) is administered intracranially at very low doses which definitely excludes any peripheral effect on colon. The anti-stress effect obtained with the compounds of formula (I) - a central effect at the CNS level - may be related to the effect caused by the benzodiazepines and in particular by diazepam.

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The results obtained with Compound A, a representative compound of formula (I), are summarized in the 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 myoelectrographic 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

TABLE IV

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

COMPOUND	DOSE mg/kg	Faecal excretion during the first hour of stress	
		Faeces – Dry weight (g + S.D.)	% 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

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

According to the present invention the use of at least one compound of formula (I) in which A and R are as defined above or one of its pharmaceutically acceptable salts is recommended for the preparation of a medicament intended for the treatment or prophylaxis of depression and stress.

According to a particularly preferred aspect, the use of the compounds of formula (I) or of their pharmaceutically acceptable salts is recommended for the preparation of a medicament intended for the treatment and prophylaxis of depression.

According to another preferred aspect of the invention, the use of the compounds of formula (I) or of their pharmaceutically acceptable salts is recommended for the preparation of a medicament intended for the treatment or prophylaxis of stress and stress-induced pathological conditions, particularly those associated with intestinal motility disorders.

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 marked by 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)].

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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 asymmetry centre may be present in the radical A. Analogously, the stereoisomers derived from the presence of such additional chiral centre 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 according to his experience in this field, choose from the different stereoisomers or mixtures of isomers of a compound of formula (I) which are therapeutically most interesting.

It is apparent from the obtained results that the isomers (I) where the carbon atom linked to the hydroxy group has absolute configuration (R) are generally more interesting and the use of at least one compound of formula (I) where the carbon atom linked to the hydroxy group has absolute configuration (R) for the preparation of an antidepressant and antistress medicament thus represents a particularly preferred object of the present invention.

A preferably used group of compounds of formula (I) according to the present invention comprises the compounds of formula (I) in which A is a methylene or isopropylidene group. A more particularly preferred group comprises the compounds of formula (I) in which A is a methylene or isopropylidene group and the carbon atom linked to the hydroxy group has absolute configuration (R).

Even more preferred compounds to be used 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 usual, 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.

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In human beings the daily dosage 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 dosage is generally subdivided in 2, 3, or 4 administrations. Preferably, for the treatment or 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 from 0.1 to 400 mg and preferably from 0.5 to 100 mg of active principle in admixture with a pharmaceutical carrier.

Unit dosage forms that are suitable for oral administration include tablets, capsules, powders, granules, and solutions or suspensions to be taken orally.

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

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

A preparation in the form of a syrup or elixir or for the administration in drops, may contain the active principle jointly with a sweetener, preferably calorie-free, methylparaben and propylparaben as antiseptics, as well as a flavouring agent and an appropriate color.

The water-dispersible powders or granules may contain the active ingredient in admixture with dispersants, wetting agents or suspending agents such as polyvinylpyrrolidone, and with sweeteners or taste correctors as well.

For rectal administration, suppositories can be employed which are prepared with binders melting at the 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 agents and/or dispersants and optionally with absorption enhancers.

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

For parenteral administration, aqueous suspensions, isotonic saline solutions, or sterile and injectable solutions are used, which contain pharmacologically compatible dispersants 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 a free base or a pharmaceutically acceptable salt, as such or in the form of a complex with a cyclodextrine for example, or else in association or co-administration with active principles.

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

- Tablets containing N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (Compound A) having the following composition:

Compound A	5 mg
Microcrystalline cellulose	40 mg
Dried corn starch	40 mg
Lactose	100 mg
Magnesium stearate	5 mg

  are prepared by grinding the active ingredient to a particle size of 0.4 mm, passing it through a sieve with 0.4 mm openings, mixing the ground material with the other constituents and compressing the mixture to obtain tablets. Analogously, tablets containing 10 mg of active principle are prepared.

- By operating essentially as described above but using N-[(2S)-7-(2-ethoxycarbonylpropan-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 obtained:

Compound D	50.0 mg
Dried corn starch	100.0 mg

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Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg

- 10,000 capsules containing 20 mg each of active substance are prepared from the following constituents: Compound A (200 g), microcrystalline cellulose (990 g), amorphous silica gel (10 g). The above constituents are mixed together and then filled into hard gelatin capsules.
- An aqueous sterile solution suitable for parenteral use in vial form based on Compound A having the following composition is prepared:

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

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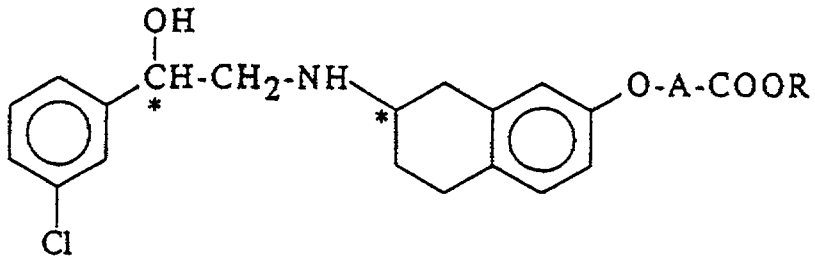
CLAIMS

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



(I)

in which A represents a (C_1–C_4)alkylene group and R represents a (C_1–C_4)alkyl group or a hydrogen atom, or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended 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, characterised in that the carbon atom linked to the hydroxy group in formula (I) has absolute configuration (R).

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

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

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