

AUSTRALIA
Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the persons identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[54] Invention Title: NEW BENZOSPIROALKENE DERIVATIVES, THEIR PROCESS OF PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM

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BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
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Basic Applicant(s): ADIR ET COMPAGNIE

Drawing number recommended to accompany the abstract

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Louis C. Gebhardt
Registered Patent Attorney

DATED this 18th day of July 1994.

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NOTICE OF ENTITLEMENT

(To be filed before acceptance)

We, **ADIR ET COMPAGNIE**, of 1, rue Carle Hébert, 92415 Courbevoie Cedex, France,
being the applicant in respect of Application No. 67549/94 state the following:-

The Person nominated for the grant of the patent has entitlement from the actual inventors.

The actual inventors are the employees of the Nominated Person and the invention was
made in the course of their normal duties.

The person nominated for the grant of the patent is the applicant of the basic application
listed on the patent request form.

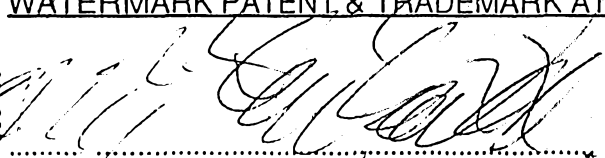
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The basic application listed on the request form is the first application made in a
Convention country in respect of the invention.

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By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

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Louis C. Gebhardt
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9 September 1996

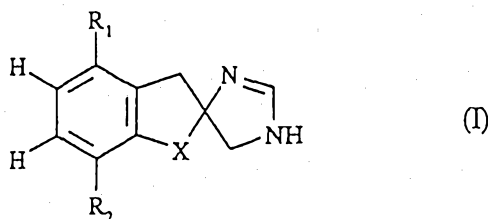


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NEW BENZOSPIROALKENE DERIVATIVES, THEIR PROCESS OF PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM
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- (57) Claim

1. A compound of formula (I):



wherein:

- X represents -CH₂-, -(CH₂)₂-, -CH=CH-, -O-CH₂-, -S-CH₂-, -SO-CH₂- or -SO₂-CH₂-,
- R₁ represents a hydrogen or halogen atom or a linear or branched (C₁-C₆) alkoxy group,
- R₂ represents a linear or branched (C₁-C₆) alkoxy or linear or branched (C₁-C₆) alkylthio group,

its isomers and its addition salts with a pharmaceutically acceptable acid.

6. A method of treating a subject including administering to the subject at least one active compound as claimed in any one of claims 1 - 3 and wherein the treatment is that of one or more of hypotension, hypersomnia, vigilance and memory disorders or symptoms appearing in degenerative diseases.

AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title:

NEW BENZOSPIROALKENE DERIVATIVES, THEIR PROCESS OF
PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH
CONTAIN THEM

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

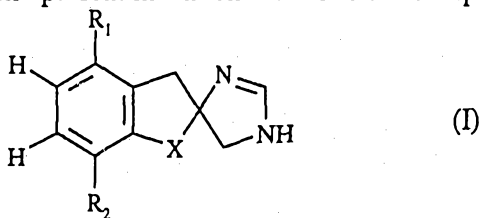
The present invention relates to new benzospiroalkenes, to their process of preparation and to the pharmaceutical compositions which contain them, as well as to their use as α_1 -adrenergic agonists.

The adrenergic nervous system plays a significant role at a number of levels, for example arterial, venous, cardiac, renal and at the level of the peripheral and central autonomous nervous system. Consequently, products capable of interacting with adrenergic receptors can induce a large number of physiological responses such as vasoconstriction, vasodilation, increase or reduction in the heart rate, and variation in the force of contraction of the cardiac muscle and metabolic activities. Various adrenergic compounds have been used in the past for modifying these or other physiological responses.

In the central nervous system, adrenergic stimulation is particularly useful for compensating for the decline in neurotransmission induced in the locus ceruleus by age, depression or degenerative diseases.

The compounds described in the present invention, in addition to the fact that they are novel, have an α_1 -adrenergic agonist profile. This property makes them useful, as was shown by P. Timmermans et al. in "Comprehensive Medicinal Chemistry" (Vol. III, p. 134-185, 1990 - edited by C. Hansh, Pergamon, Oxford 1990) and J. Nozulak et al. (J. Med. Chem., 35, 480-489, 1992), as sympathomimetics, in the treatment of hypotension, hypersomnia and vigilance and memory disorders, as well as as vasoconstrictors and for curing the symptoms which appear in degenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntingdon's chorea. The therapeutic usefulness of the products of the invention is based on their selectivity for adrenergic receptor subtypes and their selective adjustment of adrenergic functions in various tissues and organs.

More specifically, the present invention relates to the compounds of formula I:



wherein:

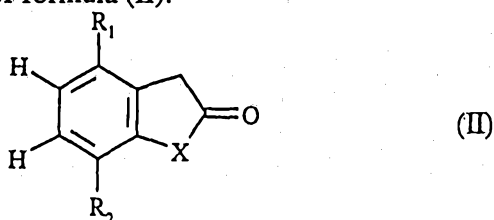
- X represents $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{SO}-\text{CH}_2-$ or $-\text{SO}_2-\text{CH}_2-$,
- R₁ represents a hydrogen or halogen atom or a linear or branched (C₁-C₆)alkoxy group,
- R₂ represents a linear or branched (C₁-C₆)alkoxy or linear or branched (C₁ - ζ)alkylthio group,

to their isomers and to their addition salts with a pharmaceutically acceptable acid.

Mention may be made, among pharmaceutically acceptable acids, without implied limitation, of hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, lactic, malonic, succinic, fumaric, tartaric, maleic, citric and methanesulfonic acids and the like.

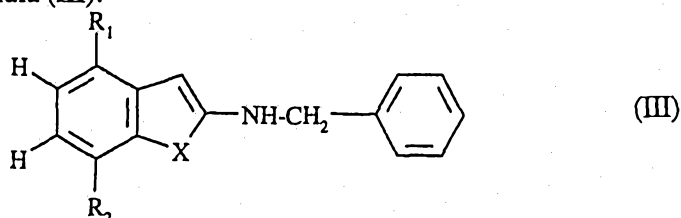
- 5 Mention may be made, among possible isomers of the compounds of formula (I), of enantiomers, diastereoisomers, epimers and tautomers.

The invention also covers the process for the preparation of the compounds of formula (I), wherein a compound of formula (II):



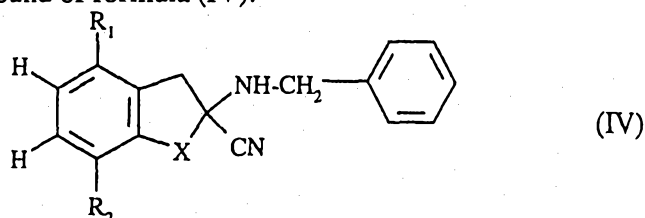
10 in which X, R₁ and R₂ have the same meaning as in the formula (I) is used as starting material and is reacted:

- either with benzylamine in the presence of para-toluenesulfonic acid to lead to the compound of formula (III):

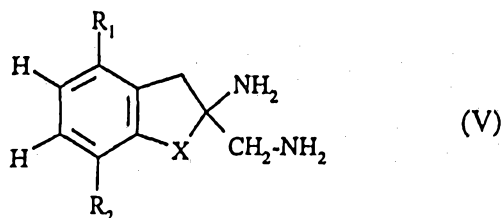


15 in which X, R₁ and R₂ have the same meaning as in the formula (I) which is reacted, under an inert atmosphere, with trimethylsilyl cyanide in the presence of zinc iodide,

to lead to the compound of formula (IV):

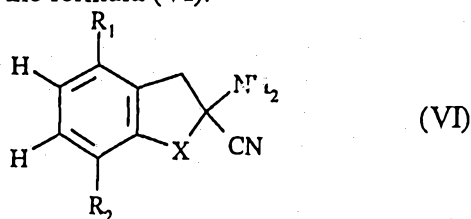


- 20 in which X, R₁ and R₂ have the same meaning as in the formula (I), which is reduced using lithium aluminum hydride and then by catalytic hydrogenation to lead to the compound of formula (V):



in which X, R₁ and R₂ have the same meaning as in the formula (I),

- or with potassium cyanide in the presence of ammonium chloride in an inert medium or with sodium cyanide in an acidic medium, or else with trimethylsilyl cyanide in the presence of zinc iodide and then with a saturated alcoholic ammonia solution, to lead to the compound of the formula (VI):



in which X, R₁ and R₂ have the same meaning as in the formula (I),

which is reduced using lithium aluminum hydride to lead to the compound of formula (V) described above,

which compound of formula (V)

is reacted with formamidine in an alcoholic medium or an alkyl formate, to lead to the compound of formula (I),

which is purified, if appropriate, according to a conventional purification technique, the isomers of which are separated, if desired, according to a conventional purification technique,

and which are optionally converted to their addition salts with a pharmaceutically acceptable acid.

Another subject of the present invention is the pharmaceutical compositions containing, as active principle, at least one compound of general formula (I) or one of its addition salts with a pharmacologically acceptable acid, alone or in combination with one or more inert and nontoxic excipients or vehicles.

Mention may more particularly be made, among pharmaceutical compositions according to the invention, of those which are suitable for oral, parenteral or nasal administration, simple or sugar-coated tablets, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels and the like.

The dose varies according to the age and weight of the patient, the nature and the severity of the complaint, and the administration route.

The latter can be oral, nasal, rectal or parenteral. The unit dose will generally range between 0.1 and 1000 mg for a treatment taken 1 to 3 times per 24 hours.

5 The following examples illustrate the invention. The starting materials used are known products or products prepared according to known procedures.

The product described in Preparation A leads to a starting material which is useful in the preparation of a compound of the invention.

Preparation A : 5-Methylthio-8-methoxy-3,4-dihydronaphthalen-2(1H)-one

10 **Stage A** : Spiro[(1,3-dioxolane)-2,2'-(8'-methoxy-1',2',3',4'-tetrahydronaphthalene)]

15 A solution containing 69 mmol of 8-methoxy-3,4-dihydronaphthalen-2(1H)-one, 75 mmol of ethylene glycol and 100 mg of p-toluenesulfonic acid in 500 ml of toluene is brought to reflux with azeotropic distillation of the water/toluene mixture for 3 hours. After cooling and evaporation under vacuum, the residue is taken up in 100 ml of ethyl ether. After washing with water and evaporation, the expected product is obtained in the form of an oil by distillation of the residue under vacuum.

20 **Boiling point**: 122-125C (p = 1.33 Pa)

Stage B : Spiro[(1,3-dioxolane)-2,2'-(5'-iodo-8'-methoxy-1',2',3',4'-tetrahydronaphthalene)]

25 A solution of 108 mmol of iodine in 1 liter of acetic acid and a solution of 56 mmol of mercuric diacetate in 1 liter of acetic acid are added dropwise and simultaneously, at a temperature not exceeding 55C, to a solution, heated to 50C, containing 35 mmol of the compound obtaining in the preceding stage in 200 ml of acetic acid. The whole mixture is stirred for 30 minutes at this temperature and then for 2 hours at 20C. The acetic acid is evaporated under vacuum and the residue taken up in a 10% potassium iodide solution. After filtration, the residue is taken up in an ammonia solution and extracted with dichloromethane. The organic phase is dried, evaporated and leads to the expected product in the solid form.

Melting point 88-90C

Stage C : Spiro[(1,3-dioxolane)-2,2'-(5'-methylthio-8'-methoxy-1',2',3',4'-tetrahydronaphthalene)]

18 mmol of the compound obtained in the preceeding stage, in 90 ml of dimethyl sulfoxide (DMSO), and then 286 mmol of cuprous oxide are added to a suspension containing 184 mmol of freshly prepared lithium methanethiolate in 180 ml of DMSO. The mixture is stirred for 5 hours at 80C under a nitrogen atmosphere. After cooling, the precipitate is filtered, the filtrate is concentrated and the residue thus obtained is taken up in dichloromethane. The organic phase is washed with water, dried and evaporated. The expected product is then obtained after purification of the residue by chromatography on a silica column, dichloromethane being used as eluent.

Melting point: 42-44C

Stage D : 5-Methylthio-8-methoxy-3,4-dihydronaphthalen-2(1H)-one

A solution containing 20 mmol of the compound obtained in the preceeding stage in 50 ml of a 30% aqueous acetic acid solution is heated for 3 hours at 90C. After cooling, the mixture is poured onto ice-cold water. The expected product is obtained by filtering the precipitate and washing with water.

Melting point: 88-90C

Example 1 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-dimethoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

Stage A : 2-Benzylamino-5,8-dimethoxy-3,4-dihydronaphthalene

A mixture containing 82 mmol of 5,8-dimethoxy-3,4-dihydronaphthalen-2(1H)-one, 82 mmol of benzylamine and 0.20 g of p-toluenesulfonic acid is brought to reflux with azeotropic distillation of the water/toluene mixture. After heating for 2 hours, the mixture is cooled, filtered and the solvent evaporated under vacuum and leads to the expected product in the form of an oil.

Stage B : 2-Benzylamino-2-cyano-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

80 mmol of trimethylsilyl cyanide and 1 g of zinc iodide are added successively to a solution, maintained under nitrogen, containing 80 mmol of the compound obtained in the preceeding stage in 400 ml of dichloromethane. The mixture is stirred at 20C overnight and

then washed with water. After drying the organic phase and evaporation, the expected product is obtained in the form of an oil.

Stage C : 2-Benzylamino-2-aminomethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

70 mmol of the compound obtained in the preceeding stage in 100 ml of anhydrous tetrahydrofuran (THF) are added dropwise, at a temperature not exceeding 20C, to a suspension containing 140 mmol of lithium aluminum hydride in 350 ml of anhydrous THF. After stirring for 2 hours, the mixture is cooled to 0C and then hydrolyzed by successive addition of 6 ml of water, 6 ml of 2N sodium hydroxide solution and 12 ml of water. The resulting suspension is filtered and the filtrate concentrated. The oily residue thus obtained is dissolved in 200 ml of ethyl acetate. This solution is washed with water and extracted with a 1N hydrochloric acid solution. The aqueous phase is basified with 35% sodium hydroxide solution and extracted with ethyl acetate. After drying and evaporation, the expected product is obtained in the form of an oil.

Stage D : 2-Amino-2-aminomethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

A suspension containing 30 mmol of the compound obtained in the preceeding stage, 125 mmol of ammonium formate and 6 g of 10% palladium-on-charcoal in 250 ml of methanol is heated at reflux with stirring for 90 minutes. After cooling, filtration of the catalyst and evaporation of the solvent, the expected product is obtained in the form of an oil.

Stage E : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-dimethoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

A mixture containing 26 mmol of the compound obtained in the preceeding stage and 27 mmol of formamidine acetate in 150 ml of ethanol is stirred at 20C under nitrogen for 10 hours. After evaporation of the solvent, the residue is taken up in 100 ml of 1N hydrochloric acid. This organic phase is washed with ethyl acetate and basified with 35% sodium hydroxide solution. After extraction with ethyl acetate, the organic phases are washed with a saturated sodium chloride solution, concentrated and lead to a solid residue. This residue is dissolved in 80 ml of ethanol treated with one equivalent of fumaric acid dissolved in 50 ml of ethanol. After evaporation of the solvent, the expected product crystallizes from ethanol.

Melting point: 185-188C

<u>Elemental microanalysis</u> :	C %	H %	N %
calculated	59.66	6.12	7.73
found	59.41	6.07	7.74

Examples 2, 3 and 4 were obtained according to the process described in Example 1 by using the corresponding starting materials.

Example 2 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5'-ethoxy-8'-methoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

5 **Melting point:** 174-178C

Elemental microanalysis :	C %	H %	N %
calculated	58.06	6.03	6.45
found	58.07	6.10	6.50

Example 3 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-diethoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

Melting point: 196-198C

Elemental microanalysis :	C %	H %	N %
calculated	61.53	6.71	7.17
found	61.40	6.97	7.06

Example 4 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(4',7'-dimethoxyindane)] 1/2 fumarate

Melting point: 224-228C

Elemental microanalysis:	C %	H %	N %
calculated	62.06	6.25	9.65
found	61.50	6.24	9.43

20 **Example 5 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5'-methoxy-1',2',3',4'-tetrahydronaphthalene)]**

Stage A : 2-Amino-2-cyano-5-methoxy-1,2,3,4-tetrahydronaphthalene

112 mmol of potassium cyanide and 116 mmol of ammonium chloride are added successively to a solution, maintained under nitrogen and with stirring, containing 110 mmol

of 5-methoxy-3,4-dihydronaphthalen-2(1H)-one in 90 ml of ethanol and 50 ml of water. The whole mixture is stirred for 20 hours at 20C and then concentrated under vacuum. The residue is taken up in 200 ml of ethyl acetate. This phase is then washed with water and extracted with 1N hydrochloric acid. The acid phase is basified with 35% sodium hydroxide solution and extracted with methyl acetate. The combined organic phases are dried and evaporated under vacuum and lead to the expected product in the solid form.

Melting point: 97C

Stage B : 2-Amino-2-aminomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene

A solution containing 70 mmol of the compound described in the preceeding stage in 80 ml of THF is added dropwise, at a temperature not exceeding 20C, to a suspension containing 162 mmol of lithium aluminum hydride in 200 ml of anhydrous THF. After stirring for 1 hour, the mixture, cooled to 0C, is hydrolyzed by successive addition of 5.5 ml of water, 5.5 ml of 2N sodium hydroxide solution and 96 ml of water. The resulting suspension is filtered and the filtrate evaporated. The oily residue is then dissolved in 250 ml of ethyl acetate. This phase is washed with water and extracted with 1N hydrochloric acid. The aqueous phases are then basified with 35% sodium hydroxide solution and extracted with ethyl acetate. After drying and evaporation of the organic phases, the expected product is obtained in the form of an oil.

Stage C : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5'-methoxy-1',2',3',4'-tetrahydronaphthalene)]

The expected product is obtained, according to the process described in Stage E of Example 1, from the compound described in the preceeding stage.

Melting point: 188-190C

<u>Elemental microanalysis:</u>	C %	H %	N %
calculated	61.44	6.07	8.43
found	61.23	6.02	8.34

Example 6 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5'-methylthio-8'-methoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

Stage A : 2-Amino-2-cyano-5-methylthio-8-methoxy-1,2,3,4-tetrahydronaphthalene

1 ml of concentrated hydrochloric acid is added dropwise with stirring to a mixture containing 9 mmol of the compound described in Preparation A and 29 mmol of sodium cyanide in 50 ml of water and 40 ml of ethyl ether. After stirring for 1 hour at 20C, the organic phase is separated by settling, washed with water, dried and evaporated. The oil obtained is then treated with a methanolic ammonia solution (3.5M), with stirring, in a closed environment, for 6 hours at 20C. After evaporation of the solvent, the oil is taken up in ethyl ether and extracted with 1N hydrochloric acid. The aqueous phases are basified with 35% sodium hydroxide solution and then extracted with ethyl ether. The expected product is then obtained in the solid form after drying and evaporation of the organic phase.

Melting point: 128-130C

Stage B : 2-Amino-2-aminomethyl-5-methylthio-8-methoxy-1,2,3,4-tetrahydro-naphthalene

The expected product is obtained according to the process described in Stage B of Example 5 by using the compound described in the preceding stage.

Stage C : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5'-methylthio-8'-methoxy-1',2',3',4'-tetrahydronaphthalene)] fumarate

The expected product is obtained according to the process described in Stage C of Example 5 by using the compound described in the preceding stage.

Melting point: 188-190C

<u>Elemental microanalysis:</u>	C %	H %	N %	S %
calculated	57.13	5.86	7.40	8.47
found	57.05	6.01	7.50	8.53

Example 7 : Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-dimethoxy-1',2',3',4'-tetrahydro-naphthalene)] fumarate, isomer α

The expected product is obtained by resolution of the compound described in Example 1 using [+] -dibenzoyl-D-tartaric acid and by successive recrystallizations from ethanol. The enantiomeric purity is monitored by Diacelog chiral column chromatography, using an isopropanol/n-heptane/diethylamine (20/80/0.1) mixture as eluent. The salt is then shared between 1N sodium hydroxide solution and dichloromethane. The aqueous phase is extracted with dichloromethane. After drying and evaporation of the organic phases, the residue is taken up in an ethanolic solution containing one equivalent of fumaric acid and the whole mixture is

brought to reflux. The expected product is obtained after cooling and filtration in the form of a white solid.

Melting point: 187-188C

<u>Elemental microanalysis:</u>	C %	H %	N %
5 calculated	59.66	6.12	7.73
found	59.59	6.08	7.65

Example 8: Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-dimethoxy-1',2',3',4'-tetrahydro naphthalene)] fumarate, isomer β

The expected product is obtained according to the process described in Example 7 by resolution of the compound described in Example 1 using [-]-dibenzoyl-L-tartaric acid.

Melting point: 187-188C

<u>Elemental microanalysis:</u>	C %	H %	N %
10 calculated	59.66	6.12	7.73
found	59.36	6.09	7.74

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

Example 9 : In vitro study on the femoral arteries and saphenous veins of dogs

The technique used is based on that described by Fowler et al. (J. Pharmacol. Exp. Ther., 229, 712-718, 1984). Male or female mongrel dogs weighing approximately 15-25 kg were used as organ sources. The animals are anesthetized with pentobarbital (30 mg/kg, intravenously). Incisions are made in the legs and the vessels are withdrawn. They are placed in Krebs-Ringer liquid (NaCl 118mM, NaHCO₃ 25 mM, Glucose 10 mM, KCl 4.7 mM, CaCl₂ 1.25 mM, MgSO₄ 1.19 mM, KH₂PO₄ 1.14 mM) at room temperature and while bubbling with carbogen (95% O₂, 5% CO₂). These vessels are then carefully freed from their fat, then cut into rings with a width of 2 mm and mounted under a base tension of 4 g (femoral arteries) or 1 g (saphenous veins) in vessels thermostatically controlled at 37C containing Krebs-Ringer liquid through which carbogen is constantly bubbling. A lower hook constitutes the set point whereas the upper hook is connected to an isometric force sensor. The tension variations are digitized, stored on disk and processed by a computer system. After mounting, the organs are left at rest for 90 minutes, rinsings being carried out every 30 min. After readjusting the base tension, a contraction is caused by a single dose of KCl (100 mM). After

stabilisation, washing and returning to the base line, a contraction is provoqued by a single dose of phenylephrine (submaximal concentration) in order to regularize the following contractions. After washing and returning to the base line, a concentration/effect curve is produced by addition of cumulative doses of agonist (the spacing between the doses is a half-log). This experiment makes it possible to calculate the 50% effective concentration (EC₅₀) in the following way: the tension values are first converted to percentages with respect to the maximum effect caused by 100 mM of KCl. This EC₅₀ is determined by non-linear regression by the Simplex method (M.S. Caceci, Byte, 340-362, 1984), calculated according to the model of the law of mass action of L. Michaelis and M.L. Menten (Biochem. Zeitschrift, 49, 333-369, 1913).

$E = (E_{max} * C^n) / (EC_{50}^n + C^n)$ where E=effect, E_{max}=maximum effect, C=concentration, EC=EC₅₀ and n=Hill number.

The products of the invention contract the arteries and veins of dogs. The maximum of these contractions approaches that obtained with KCl. The results obtained are presented in the table below:

Example	ARTERY		VEIN	
	EC ₅₀ (μM)	Max (% KCl)	EC ₅₀ (μM)	Max (% KCl)
1	0,16	72	0,2	100
5	1,5	93	6,4	100
6	0,08	85	0,8	98
7	0,03	95	0,12	109

Example 10 : In vivo study on AMYELOUS RATS

Male Sprague-Dawley rats (300-400 g) are anesthatized with ether. A cannula is inserted in the trachea, the spinal cord is destroyed using a steel rod and the animal is immediately placed under artificial respiration. The vagus nerves are sectioned. The carotid arteries are ligatured and a catheter is placed in one and is used to record the arterial pressure. Three other catheters are placed in the jugular veins and the vein of the penis and are used for injections. The temperature of the animals is maintained at 36C. The animal is pretreated with an injection of tertatolol (100 g/kg). The animal is also pretreated 10 minutes afterwards with prazosin (100 g/kg) or yohimbine (1 mg/kg) when it is wished to determine the 1 or 2-adrenergic properties of the product. Ten minutes later, increasing cumulative doses of product are injected every 20 seconds. The arterial pressure variations are detected using a

P23XL Statham pressure cell and are recorded. The pressure values are expressed in mmHg. This experiment makes it possible to calculate the concentration which increases the pressure by 20mmHg (C_{20}) by non-linear regression according to the model of the Michaelis and Menten mass action law as described above. The maximum effect obtained is then converted to a percentage with respect to the maximum effect caused by phenylephrine. The 1 or 2 -adrenergic components of the product are estimated using the ratio of the C_{20} values obtained in the presence of prazosin or of yohimbine to the values obtained in the absence of these antagonists. In amyelous rats, the products of the invention induce hypertensions which are inhibited more by prazosin than by yohimbine. The results are collected in the table below:

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Example	C_{20} ($\mu\text{g/kg}$)	Ratio C_{20} treated / C_{20} control	
		Prazosin	Yohimbine
1	0,009	97	11
2	0,06	22	5
3	0,6	24	8

Example 11 : Pharmaceutical composition

Formula for the preparation of 1000 tablets containing a dose of 10 mg

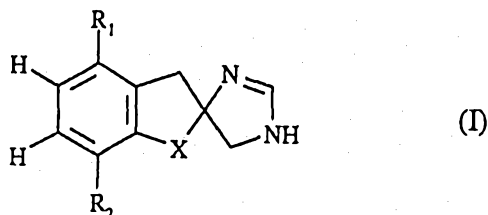
15

Compound of Example	10 g
Hydroxypropyl cellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

CLAIMS

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):

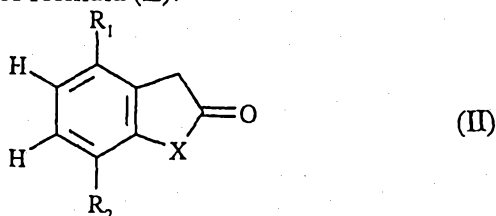


wherein:

- X represents -CH₂-, -(CH₂)₂-, -CH=CH-, -O-CH₂-, -S-CH₂-, -SO-CH₂- or -SO₂-CH₂-,
- R₁ represents a hydrogen or halogen atom or a linear or branched (C₁-C₆) alkoxy group,
- R₂ represents a linear or branched (C₁-C₆) alkoxy or linear or branched (C₁-C₆) alkylthio group,

its isomers and its addition salts with a pharmaceutically acceptable acid.

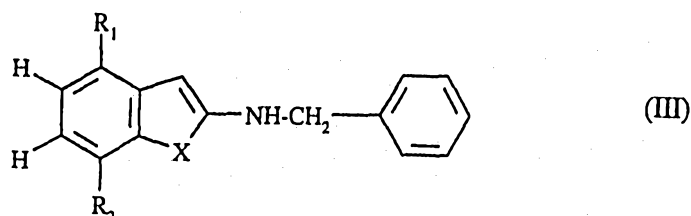
2. The compound of formula (I) as claimed in claim 1 such that X represents -(CH₂)₂-, its isomers and its addition salts with a pharmaceutically acceptable acid.
3. The compound of formula (I) as claimed in claim 1 which is spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',8'-dimethoxy-1',2',3',4'-tetrahydronaphthalene)], its isomers and its addition salts with a pharmaceutically acceptable acid.
4. A process for the preparation of the compound of formula (I) as claimed in claim 1, wherein a compound of formula (II):



in which X, R₁ and R₂ have the same meaning as in the formula (I)

is used as starting material and is reacted:

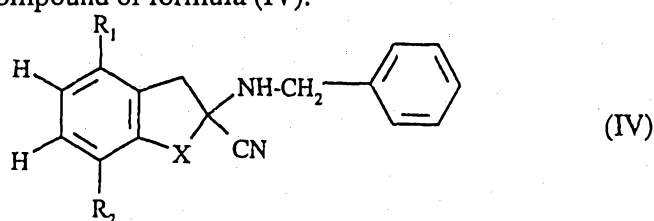
- either with benzylamine in the presence of para-toluenesulfonic acid to lead to the compound of formula (III):



in which X, R₁ and R₂ have the same meaning as in the formula (I)

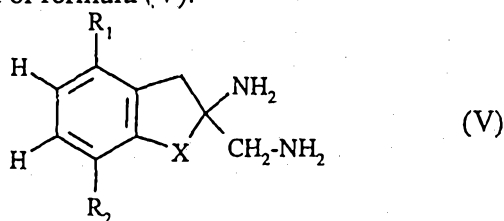
which is reacted, under an inert atmosphere, with trimethylsilyl cyanide in the presence of zinc iodide,

5 to lead to the compound of formula (IV):



in which X, R₁ and R₂ have the same meaning as in the formula (I),

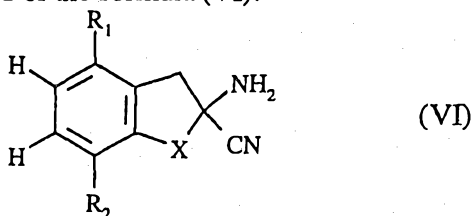
which is reduced using lithium aluminum hydride and then by catalytic hydrogenation to lead to the compound of formula (V):



in which X, R₁ and R₂ have the same meaning as in the formula (I),

- or with potassium cyanide in the presence of ammonium chloride in an inert medium or ^{and then with a saturated alcoholic ammonia solution} with sodium cyanide in an acidic medium, or else with trimethylsilyl cyanide in the presence of zinc iodide and then with a saturated alcoholic ammonia solution,

15 to lead to the compound of the formula (VI):



in which X, R₁ and R₂ have the same meaning as in the formula (I),

which is reduced using lithium aluminum hydride to lead to the compound of formula (V) described above,



which compound of formula (V)
is reacted with formamidine in an alcoholic medium or an alkyl formate,
to lead to the compound of formula (I),
which is purified, if appropriate, according to a conventional purification
technique, the isomers of which are separated, if desired, according to a
conventional purification technique,
and which are optionally converted to their addition salts with a
pharmaceutically acceptable acid.

5. A pharmaceutical composition containing, as active principle, at least one
compound as claimed in any one of claims 1 - 3, in combination with one
or more pharmaceutically acceptable, nontoxic and inert excipients or
vehicles.
6. A method of treating a subject including administering to the subject at
least one active compound as claimed in any one of claims 1 - 3 and
wherein the treatment is that of one or more of hypotension, hypersomnia,
vigilance and memory disorders or symptoms appearing in degenerative
diseases.

DATED this 9th day of September, 1996

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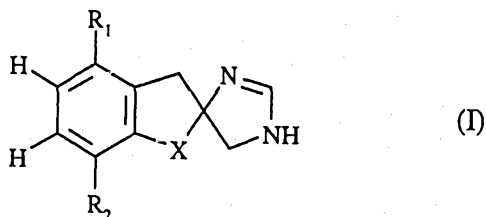


ABSTRACT

NEW BENZOSPIROALKENE DERIVATIVES, THEIR PROCESS OF PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM

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Compounds of formula (I) :



10 wherein:

- X represents -CH₂-, -(CH₂)₂-, -CH=CH-, -O-CH₂-, -S-CH₂-, -SO-CH₂- or -SO₂-CH₂-,
- R₁ represents a hydrogen or halogen atom or a linear or branched (C₁-C₆)alkoxy group,
- R₂ represents a linear or branched (C₁-C₆)alkoxy or linear or branched (C₁-C₆)alkylthio group,

15 their isomers and their addition salts with a pharmaceutically acceptable acid.

Medicaments.