649864

Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, ADIR ET COMPAGNIE, of 1 rue Carle Hebert, F-92415, Courbevoie Cedex, France, being the applicant in respect of Application No. 20950/92 state the following:-

The Person nominated for the grant of the patent has entitlement from the actual inventors by virtue of a contract of employment with the inventors.

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

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

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

16 March 1994

Louis C. Gebhardt
Registered Patent Attorney

AUSTRALIA

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person 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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[70] Nominated Person: ADIR ET COMPAGNIE

Address: 1 RUE CARLE HEBERT, F-92415 COURBEVOIE CEDEX, FRANCE

[54] Invention Title: NEW ARYLETHYLAMINE COMPOUNDS, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITONS CONTAINING THEM

[72] Name(s) of actual inventor(s): DANIEL LESIEUR, SAID YOUS, PATRICK DEPREUX, JEAN ANDRIEUX, GERARD ADAM, DANIEL HENRI CAIGNARD AND BEATRICE GUARDIOLA

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BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
9110261	FRANCE	FR	13TH AUGUST 1991

Drawing number recommended to accompany the abstract .....

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....

DATED this 11th day of August 1992.

Louis C. Gebhardt

Registered Patent Attorney

AU9220950

(12) PATENT ABRIDGMENT (11) Document No. AU-B-20950/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 649864

(54) Title
NEW ARYLETHYLAMINE COMPOUNDS, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
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C07D 261/20 C07D 307/81 C07D 333/58 A61K 031/415
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(21) Application No. : 20950/92 (22) Application Date : 12.08.92

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ADIR ET COMPAGNIE

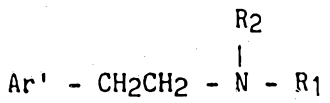
(72) Inventor(s)
DANIEL LESIEUR; SAID YOUS; PATRICK DEPREUX; JEAN ANDRIEUX; GERARD ADAM; DANIEL HENRI CAIGNARD; BEATRICE GUARDIOLA

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
AU 87154/91 C07D 209/14

(57) Claim

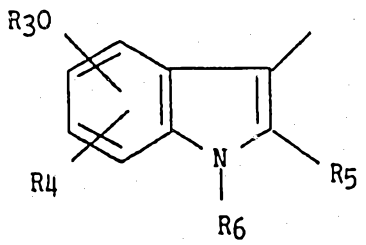
1. Compounds of the general formula (I):



(I)

in which:

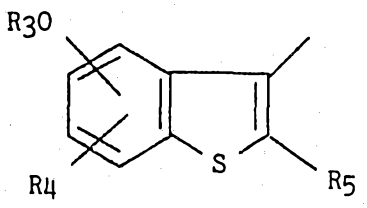
- Ar' represents:
  - an indol-3-yl nucleus of formula (II):



(II)

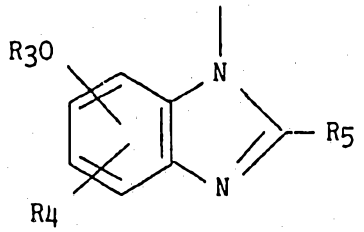
  - a benzo[b]thiophen-3-yl nucleus of formula (III):

.../2



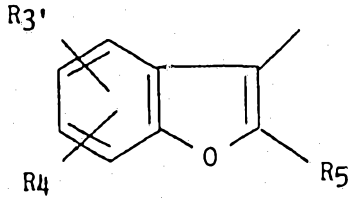
(III)

- a benzimidazol-1-yl nucleus of formula (IV):



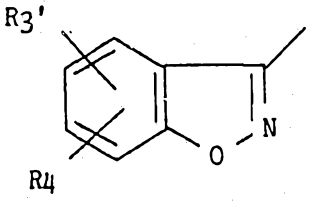
(IV)

- a benzo[b]furan-3-yl nucleus of formula (V):



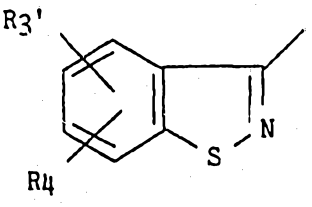
(V)

- a 1,2-benzisoxazol-3-yl nucleus of formula (VI):



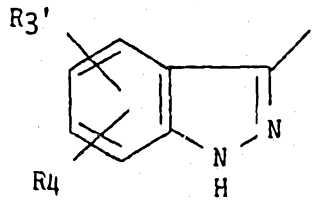
(VI)

- a 1,2-benzisothiazol-3-yl nucleus of formula (VII):



(VII)

- an indazol-3-yl nucleus of formula (VIII):



(VIII)

R_1 represents:

- a group $-\overset{\overset{O}{\|}}{C}-R_7$ in which R_7 represents an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)alkyl radical, or a trifluoromethyl group,
and, when Ar' represents a group selected from those of formulae (IV), (VI), (VII) and (VIII), R_7 may also represents a linear or branched alkyl radical having from 1 to 6 carbon atoms that is unsubstituted or substituted by 1 or 2 halogen radicals,

- a group $-\overset{\overset{O}{\|}}{C}-NHR_8$ or $-\overset{\overset{S}{\|}}{C}-NHR_8$ in which R_8 represents a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)-alkyl radical, an optionally substituted aryl radical, or an optionally substituted arylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms, or

- a group $-\overset{\overset{O}{\|}}{C}-(CH_2)n-E_1$ in which

n represents an integer from 1 to 3 and E_1 represents a radical selected from:
- morpholino, and
- piperazine that is unsubstituted or substituted by a radical $-(CH_2)_{n'}-E_2$ wherein n' represents an integer from 1 to 4 and E_2 represents a phenyl or naphthyl radical

each of which is unsubstituted or substituted by from 1 to 3 radicals selected from: halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

-R_2 represents a hydrogen atom or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;
-R_3 represents a hydrogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted aryl radical, an optionally substituted arylalkyl or diarylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms, or a cycloalkyl or cycloalkylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms;

-R_3' represents a hydrogen atom or a group -O-R_3 wherein R_3 is as defined above;

-R_4 represents a hydrogen atom, a halogen atom, a hydroxy radical, a linear or branched alkoxy radical having from 1 to 6 carbon atoms, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-R_5 represents a hydrogen atom, a halogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted phenyl radical, or an optionally substituted phenylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms; and

-R_6 represents a hydrogen atom, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-the isomers, epimers and diastereoisomers thereof,

-and the addition salts thereof with a pharmaceutically acceptable acid or base,

-with the provisos that:

. Ar' may not represent a 7-methoxybenzo[b]furan-yl group when R_1 represents a

...15

cyclopropylcarbonyl radical;

R_1 may not represent a trifluoroacetyl radical when Ar' represents an indole radical wherein $R_2 = R_3 = R_4 = R_5 = R_6 = H$;

. and R_1 may not represent an anilinothiocarbonyl radical that is unsubstituted or substituted at the 4-position of the phenyl by an alkoxy radical, when Ar represents an indol-3-yl nucleus and R_3 represents a methyl or benzyl radical;

and wherein

-the term "substituted" associated with the expressions "aryl", "arylalkyl", "diarylalkyl", "phenyl" and "phenylalkyl" indicates that the aromatic nucleus or nuclei may be substituted by one or more radicals selected from: linear or branched lower alkyl having from 1 to 6 carbon atoms, linear or branched lower alkoxy having from 1 to 6 carbon atoms, hydroxy, halogen, nitro, and trifluoromethyl;

-the term "substituted" associated with the expressions "cycloalkyl" and "cycloalkyl-(C_1-C_4)alkyl" indicates that the cyclic system may be substituted by one or more radicals selected from: halogen, linear or branched lower alkyl having from 1 to 6 carbon atoms, and linear or branched lower alkoxy having from 1 to 6 carbon atoms;

-the term "cycloalkyl" designates a saturated or unsaturated cyclic system having from 3 to 8 carbon atoms; and

-the expression "aryl group" is understood as meaning a pyridyl, phenyl, naphthyl, thienyl, furyl or pyrimidyl group.

23. A method of treatment of disorders of the melatoninergic system comprising the administration, to a patient suffering said disorder, of an effective amount of a pharmaceutical composition as claimed in claim 22.

24. A method of treatment of stress, of sleep disorders, of anxiety, of seasonal depression, of insomnia and fatigue due to jet lag, of schizophrenia, of panic attacks, of melancholia, of regulation of the appetite, of insomnia, of psychotic disorders, of epilepsy, of Parkinson's disease, of senile dementia, of disorders associated with normal or

pathological ageing, of migraine, of memory loss, of Alzheimer's disease, as well as of disorders of cerebral circulation, of certain cancers, of psoriasis, of acne, and of seborrhoea, or as ovulation inhibitors, or in veterinary medicine in disorders of the fur comprising the administration, to a patient suffering said disorder, of an effective amount of a pharmaceutical composition as claimed in claim 22.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

649864

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: NEW ARYLETHYLAMINE COMPOUNDS, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS CONTAINING 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 arylethylamine compounds, to processes for the preparation thereof, and to pharmaceutical compositions containing them.

A certain number of arylethylamine compounds having an indole nucleus are described as being agonists or antagonists of melatonin, both in patents GB 219 2001 and WO 89/01472, and in the publications J. Med. Chem. (1979) 22 (1) pp. 63-69 and Chemical Abstract (1968) 70 (1) no. 3722 T.

The same applies to a number of compounds having a benzo[b]thiophene nucleus: J. Med. Chem. (1970) 13 pp. 1205-1208, J. Heterocyclic Chem. (1978) 15 pp. 1351-1359, (1983) 20 pp. 1697-1703.

Benzo[b]furan analogues of melatonin have likewise been synthesised: Annalen (1963) 662 pp. 147-159 and patent FR 1343073, but no pharmacological activity of the melatoninomimetic type appears to have been found.

The same applies in the benzimidazole series, where demethoxylated analogues of melatonin have been prepared without such activity appearing to have been found: Khimiko Farmatsevticheskii Zhurnal (1968) 9 pp. 21-23.

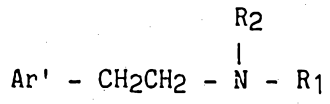
The Applicant has now found new compounds having an affinity for the melatonin receptors that is very considerably superior to that of the products described in the literature and to that of melatonin itself.

Those compounds possess numerous valuable pharmacological activities on account of their agonistic or antagonistic nature towards melatonin.

In addition to their beneficial action on disturbances in the circadian rhythm and sleep disorders and on seasonal disorders, they have valuable pharmacological properties on

the central nervous system, especially anxiolytic, anti-psychotic and analgesic properties, and on ovulation, cerebral circulation and immunomodulation.

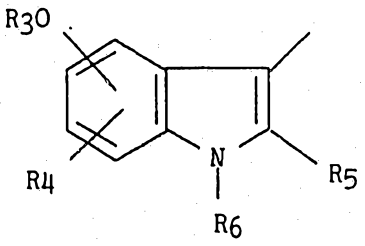
More specifically, the present invention relates to the compounds of the general formula (I):



(I)

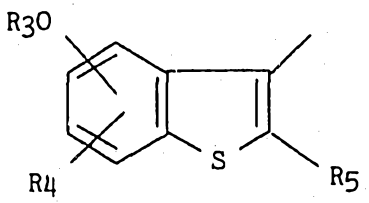
in which:

- Ar' represents:
  - an indol-3-yl nucleus of formula (II):



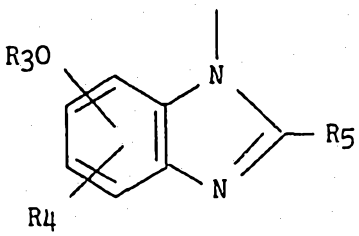
(II)

  - a benzo[b]thiophen-3-yl nucleus of formula (III):



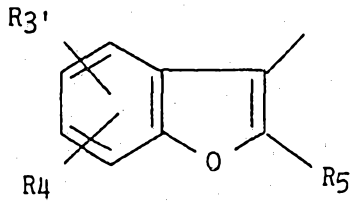
(III)

  - a benzimidazol-1-yl nucleus of formula (IV):



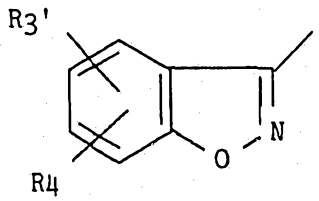
(IV)

- a benzo[b]furan-3-yl nucleus of formula (V):



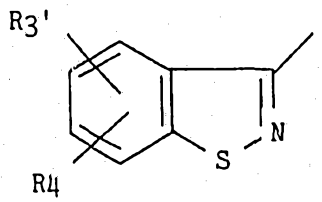
(V)

- a 1,2-benzisoxazol-3-yl nucleus of formula (VI):



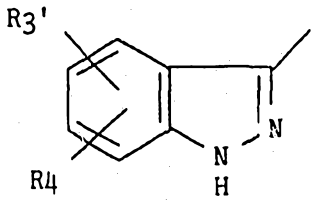
(VI)

- a 1,2-benzisothiazol-3-yl nucleus of formula (VII):



(VII)

- an indazol-3-yl nucleus of formula (VIII):



(VIII)

- R_1 represents:

- a group $-\overset{\overset{O}{\|}}{C}-R_7$ in which R_7 represents an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)alkyl radical, or a trifluoromethyl group,

and, when Ar' represents a group selected from those of formulae (IV), (VI), (VII) and (VIII), R_7 may also represents a linear or branched alkyl radical having from 1 to 6 carbon atoms that is unsubstituted or substituted by 1 or 2 halogen radicals,

- group $-\overset{\overset{O}{\|}}{C}-NHR_8$ or $-\overset{\overset{S}{\|}}{C}-NHR_8$ in which R_8 represents a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)-alkyl radical, an optionally substituted aryl radical, or an optionally substituted arylalkyl radical the alkyl chain of which contains from 1 to 3 carbon atoms, or

- a group $-\overset{\overset{O}{\|}}{C}-(CH_2)n-E_1$ in which

n represents an integer from 1 to 3 and E_1 represents a radical selected from:

- morpholino and
- piperazine that is unsubstituted or substituted by a radical $-(CH_2)_{n'}-E_2$ wherein n' represents an integer from 1 to 4 and E_2 represents a phenyl or naphthyl radical each of which is unsubstituted or substituted by from 1 to 3 radicals selected from: halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

$-R_2$ represents a hydrogen atom or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-R_3 represents a hydrogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted aryl radical, an optionally substituted arylalkyl or diarylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms, or a cycloalkyl or cycloalkylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms;

-R_3' represents a hydrogen atom or a group -O-R_3 wherein R_3 is as defined above;

-R_4 represents a hydrogen atom, a halogen atom, a hydroxy radical, a linear or branched alkoxy radical having from 1 to 6 carbon atoms, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-R_5 represents a hydrogen atom, a halogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted phenyl radical, or an optionally substituted phenylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms; and

-R_6 represents a hydrogen atom, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-the isomers, epimers and diastereoisomers thereof,

-and the addition salts thereof with a pharmaceutically acceptable acid or base,

-with the provisos that:

- Ar' may not represent a 7-methoxybenzo[b]furan-3-yl group when R_1 represents a cyclopropylcarbonyl radical;
- R_1 may not represent a trifluoroacetyl radical when Ar' represents an indole radical wherein $R_2 = R_3 = R_4 = R_5 = R_6 = H$;

. and R_1 may not represent an anilinothiocarbonyl radical that is unsubstituted or substituted at the 4-position of the phenyl by an alkoxy radical, when Ar represents an indol-3-yl nucleus and R_3 represents a methyl or benzyl radical;

and wherein

-the term "substituted" associated with the expressions "aryl", "arylalkyl", "diarylalkyl", "phenyl" and "phenylalkyl" indicates that the aromatic nucleus or nuclei may be substituted by one or more radicals selected from: linear or branched lower alkyl having from 1 to 6 carbon atoms, linear or branched lower alkoxy having from 1 to 6 carbon atoms, hydroxy, halogen, nitro, and trifluoromethyl;

-the term "substituted" associated with the expressions "cycloalkyl" and "cycloalkyl-(C_1-C_4)alkyl" indicates that the cyclic system may be substituted by one or more radicals selected from: halogen, linear or branched lower alkyl having from 1 to 6 carbon atoms, and linear or branched lower alkoxy having from 1 to 6 carbon atoms;

-the term "cycloalkyl" designates a saturated or unsaturated cyclic system having from 3 to 8 carbon atoms; and

-the expression "aryl group" is understood as meaning a pyridyl, phenyl, naphthyl, thienyl, furyl or pyrimidyl group.

The present invention relates also to a process for the preparation of the compounds of formula (I), characterised in that there is used as starting material an amine of the general formula (IX):

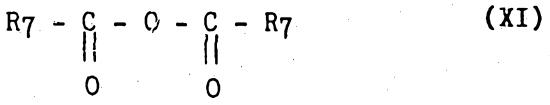
$$Ar'\text{-}CH_2CH_2\text{-}NHR_2 \qquad (IX),$$

in which Ar' and R_2 have the same meaning as in formula (I), which is treated:

- with an acid chloride of formula (X):

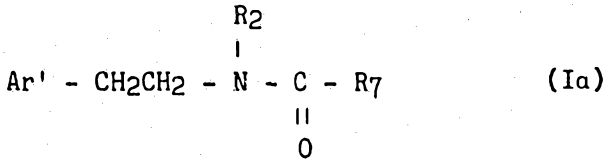
(X)

or with the corresponding acid anhydride of formula (XI):



(XI)

in which formulae R_7 has the same meaning as in formula (I), to obtain the compounds of formula (Iα):



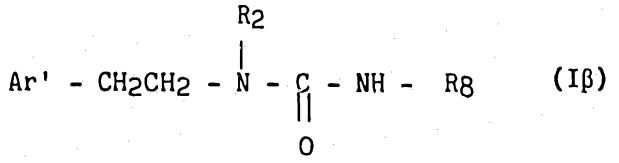
(Iα)

in which Ar', R_2 and R_7 have the same meaning as in formula (I),

- or with an isocyanate of formula (XII):

(XII),

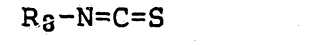
in which R_8 has the same meaning as in formula (I), to obtain the compounds of formula (Iβ):



(Iβ)

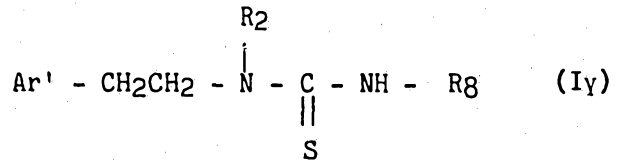
in which Ar', R_2 and R_8 have the same meaning as in formula (I),

- or with an isothiocyanate of formula (XIII):



(XIII),

in which R_8 has the same meaning as in formula (I), to obtain the compounds of formula (Iγ):



(Iγ)

in which Ar', R_2 and R_8 have the same meaning as in formula (I),

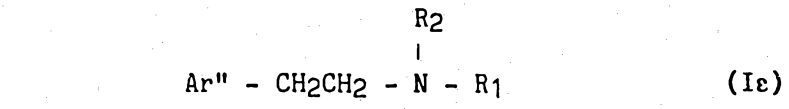
it being understood that the compounds of formulae (Iα), (Iβ) and (Iγ) form part of the invention and together constitute the compounds of formula (I),

it being possible for the compounds of formula (I) to be:

- purified by one or more purification methods selected from crystallisation, chromatography over a silica column, extraction, filtration, and passage over carbon and/or resin,
- separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers,

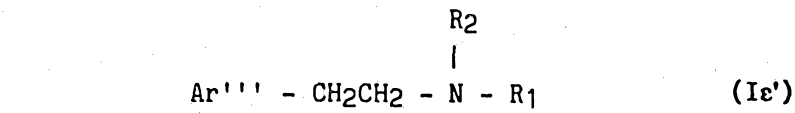
- and/or converted into salts by means of a pharmaceutically acceptable acid or base.

The invention also includes a process for obtaining the compounds of formula (Iε):



(Iε)

in which R_1 and R_2 are as defined in formula (I) and Ar" represents a group Ar' as defined in formula (I) that is substituted by a group $-O-R_3$" wherein R_3" represents a group selected from optionally substituted aryl, optionally substituted arylalkyl or diarylalkyl, and cycloalkyl or cycloalkylalkyl (the terms "aryl", "arylalkyl", "diarylalkyl", "cycloalkyl", "cycloalkylalkyl" and "substituted" being as defined in formula (I)),characterised in that a compound of formula (Iε'):



(Iε')

in which R_1 and R_2 are as defined above and Ar"' represents a group Ar' as defined in formula (I) that is substituted by a group $-O-R_3$"' wherein R_3"' represents a hydrogen atom, is reacted with a compound of formula (XIV):

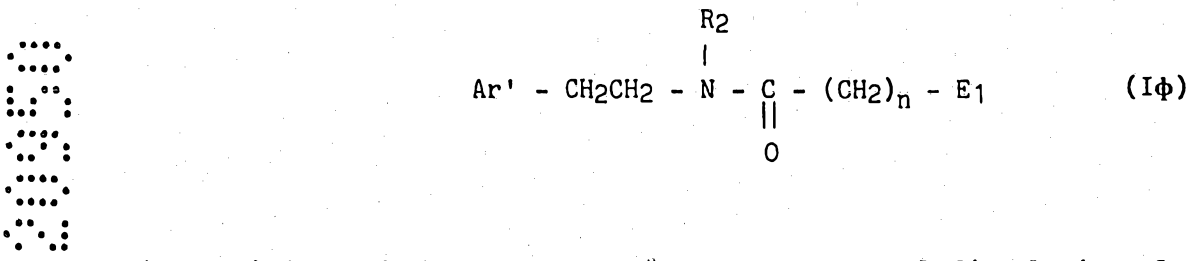
R"-Hal (XIV),

in which Hal represents a halogen atom and R" represents a group selected from optionally substituted aryl, optionally substituted arylalkyl or diarylalkyl, and cycloalkyl or cycloalkylalkyl (the terms "aryl", "arylalkyl", "diarylalkyl", "cycloalkyl", "cycloalkylalkyl" and "substituted" being as defined in formula (I)),

it being possible for the compounds of formula (Iε) to be:

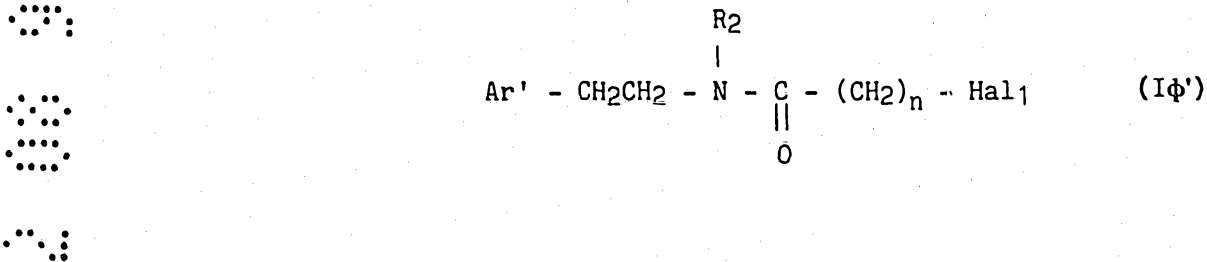
- purified by one or more purification methods selected from crystallisation, chromatography over a silica column, extraction, filtration, and passage over carbon and/or resin,
- separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers,
- and/or converted into salts by means of a pharmaceutically acceptable acid or base.

The invention also includes a process for the preparation of the compounds of formula (IΦ):



$$Ar' - CH_2CH_2 - N(R_2) - C(=O) - (CH_2)_n - E_1 \qquad (I\Phi)$$

in which Ar', R_2, E_1 and n are as defined in formula (I), characterised in that a compound of formula (IΦ'):



$$Ar' - CH_2CH_2 - N(R_2) - C(=O) - (CH_2)_n - Hal_1 \qquad (I\Phi')$$

in which Ar', R_2 and n are as defined in formula (I) and Hal_1 represents a halogen atom, is reacted with a morpholine group or with a piperazine group that is unsubstituted or substituted by a radical $-(CH_2)_{n'}-E_2$ wherein n' and E_2 are as defined in formula (I),

it being possible for the compounds of formula (IΦ) to be:

- purified by one or more purification methods selected from crystallisation, chromatography over

a silica column, extraction, filtration, and passage over carbon and/or resin,

- separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers,
- and/or converted into salts by means of a pharmaceutically acceptable acid or base.

The amines of formula (IX) are either commercially available or readily accessible to the person skilled in the art.

The compounds of formula (I) have valuable pharmacological properties.

The pharmacological study of those compounds has in fact shown that they have low toxicity and a very high selective affinity for the melatonin receptors (which is far superior to that of melatonin itself and to that of its analogues described in the literature).

Among their important activities on the central nervous system, the compounds of the invention have sedative, anxiolytic, anti-psychotic and analgesic properties as well as properties affecting microcirculation, as a result of which they can be used in the treatment of stress, of sleep disorders, of anxiety, of seasonal depression, of insomnia and fatigue due to jet lag, of schizophrenia, of panic attacks, of melancholia, of regulation of the appetite, of insomnia, of psychotic disorders, of epilepsy, of Parkinson's disease, of senile dementia, of disorders associated with normal or pathological ageing, of migraine, of memory loss, of Alzheimer's disease and of disorders of cerebral circulation.

The compounds of the invention also have ovulation-inhibiting and immunomodulatory properties, which enable them to be used in the treatment of certain cancers.

When administered externally, they may be used in the treatment of psoriasis, of acne and of seborrhoea, and they protect the skin.

They may also be used in veterinary medicine for their properties on the fur.

The present invention relates also to pharmaceutical compositions containing the products of formula (I) on their own or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or vehicles.

Of the pharmaceutical compositions according to the invention there may be mentioned, by way of non-limiting examples, those which are suitable for oral, parenteral, nasal, per- or transcutaneous, rectal, perlingual, ocular or respiratory administration, and especially tablets, dragées, sublingual tablets, sachets, paquets, gelatin capsules, glossettes, lozenges, suppositories, creams, ointments, dermic gels, and injectable and drinkable ampoules.

The dosage varies according to the age and weight of the patient, the mode of administration and the nature of the therapeutic indication or of any associated treatments, and ranges from 0.1 mg to 1 g per 24 hours.

The following Examples illustrate the invention but do not limit it in any way.

EXAMPLE 1: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-CYCLOPROPYL-CARBOXAMIDE

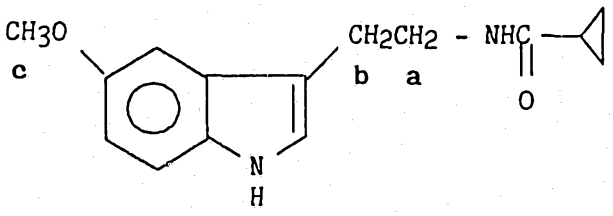
3 g of 5-methoxytryptamine are added to a solution of 2.2 g of potassium carbonate in 40 cm^3 of water. 80 cm^3 of chloroform are added, and then 1.7 g of cyclopropanecarboxylic acid chloride are added with very vigorous stirring. After stirring at room temperature for 30 minutes, the organic phase is separated off, washed with water and then dried.

The resulting residue is crystallised in toluene, yielding 3.3 g (80.5%) of N-[2-(5-methoxyindol-3-yl)ethyl]-cyclopropylcarboxamide.

Melting point: 101-102°C

Infra-red (KBr disc):
- 3390 cm^{-1} ν NH indole
- 3250-3300 cm^{-1} ν NH amide
- 2900-3050 cm^{-1} ν CH alkyl
- 1630 cm^{-1} ν CO amide

^1H-NMR 80 MHz ($CDCl_3$)



0.7-1 ppm	(5H)	cyclopropyl
2.8-3 ppm	(2H)	CH_2 **b**
3.4-3.7 ppm	(2H)	CH_2 **a**
3.8 ppm	(H)	OCH_3
6.7-7.3 ppm	(4H)	indole
8.1 ppm	(1H)	NH (indole)

EXAMPLE 2: N-[2-(6-FLUORO-5-METHOXYINDOL-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 5-methoxy-6-fluorotryptamine (J. Heterocyclic Chem. (1976) 13 pp. 1253-1256), N-[2-(5-methoxy-6-fluoroindol-3-yl)ethyl]-cyclopropylcarboxamide is obtained. Melting point (dichloromethane-ether) : 125-126° C

EXAMPLE 3: N-[2-(6-CHLORO-5-METHOXYINDOL-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 5-methoxy-6-chlorotryptamine (Synthesis (1983) pp. 935-936), N-[2-(5-methoxy-6-chloroindol-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

EXAMPLE 4: N-[2-(5-METHOXY-2,6-DIMETHYLINDOL-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 5-methoxy-2,6-dimethyltryptamine (Journal of Medicinal Chemistry (1973) 16 pp. 757-765), N-[2-(5-methoxy-2,6-dimethylindol-3-yl)ethyl]-cyclopropyl-carboxamide is obtained.

EXAMPLE 5: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]thiophene (Journal of Medicinal Chemistry (1970) 13 pp. 1205-1208), N-[2-(5-methoxybenzo[b]thiophen-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

Melting point : 124-126° C

Infra-red (KBr disc): 3270 cm^{-1} ν NH amide
1640 cm^{-1} ν CO amide

EXAMPLE 6: N-[2-(6-CHLORO-5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

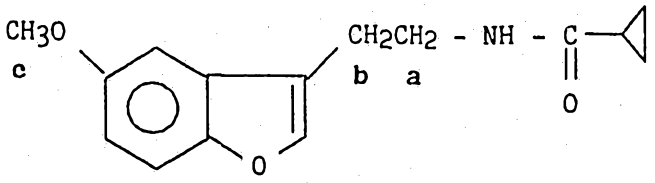
Following the procedure of Example 1 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxy-6-chlorobenzo[b]thiophene (J. Heterocyclic Chem. (1983) 20 pp. 1671-1703), N-[2-(5-methoxy-6-chlorobenzo[b]thiophen-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

EXAMPLE 7: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]furan (Annalen (1963) 662 pp. 147-159 or Aust. J. Chem. (1975) 28 pp. 1097-1111), N-[2-(5-methoxybenzo[b]furan-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

Infra-red (KBr disc): 3290 cm^{-1} ν NH amide
1680 cm^{-1} ν C=O amide

^{1}H-NMR 80 MHz ($CDCl_3$)



0.7-1 ppm	(5H)	cyclopropyl
2.9 ppm	(2H)	CH_2 b
3.5-3.7 ppm	(2H)	CH_2 a
3.9 ppm	(3H)	OCH_3
6.8-7.3 ppm	(4H)	benzo[b]furan

EXAMPLE 8: N-[2-(2-METHYL-5-METHOXYBENZO[b]FURAN-3-YL)-ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 2-methyl-3-β-aminoethyl-5-methoxybenzo[b]furan (Patent FR 1343073), N-[2-(2-methyl-5-methoxybenzo[b]furan-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

Infra-red (KBr disc): 3320 cm^{-1} ν NH amide
1650 cm^{-1} ν CO amide

EXAMPLE 9: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 1-β-aminoethyl-6-methoxybenzimidazole (J. Chem. Soc. (1957) pp. 1671-1674), N-[2-(6-methoxybenzimidazol-1-yl)ethyl]-cyclopropylcarboxamide is obtained.

Melting point (Ethyl acetate) : 86-88° C

Infra-red (KBr disc): 3300 cm^{-1} ν NH amide
1660 cm^{-1} ν CO amide

EXAMPLE 10: N-[2-(2-BENZYL-6-METHOXYBENZIMIDAZOL-1-YL)-ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 1-β-aminoethyl-2-benzyl-6-methoxybenzimidazole (Patent FR 2182915), N-[2-(2-benzyl-6-methoxybenzimidazol-1-yl)ethyl]-cyclopropylcarboxamide is obtained.

EXAMPLE 11: N-[2-(5-METHOXY-1,2-BENZISOXAZOL-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxy-1,2-benzisoxazole (Chem. Pharm. Bull. (1976) 24 (4) pp. 632-643), N-[2-(5-methoxy-1,2-benzisoxazol-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

EXAMPLE 12: N-[2-(5-METHOXY-1,2-INDAZOL-3-YL)ETHYL]-CYCLOPROPYLCARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxyindazole (J.A.C.S. (1957) 79 pp. 5245-5247), N-[2-(5-methoxy-1,2-indazol-3-yl)ethyl]-cyclopropylcarboxamide is obtained.

EXAMPLE 13: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-TRIFLUORO-ACETAMIDE

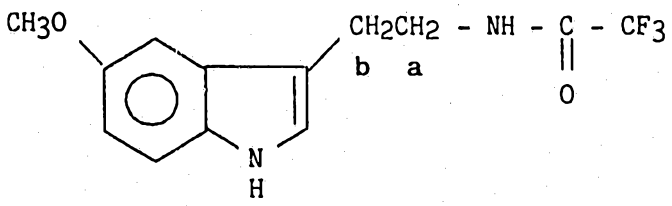
1.14 g of trifluoroacetic acid are added dropwise to a suspension, at -5°C, of 1.90 g of 5-methoxytryptamine in 6 cm^3 of pyridine. The mixture is stirred at room temperature for 30 minutes and then the reaction medium is poured onto ice-water. The resulting precipitate is isolated by filtration, washed with water, dried and then recrystallised in toluene.

1.14 g (40%) of N-[2-(5-methoxyindol-3-yl)ethyl]-trifluoroacetamide are obtained.

Melting point: 135-136°C

Infra-red (KBr disc): 3400 cm^{-1} ν NH indole
3300 cm^{-1} ν NH amide
1700 cm^{-1} ν C=O

^{1}H-NMR 80 MHz ($CDCl_3$)



3 ppm	(2H)	CH_2	b
3.6 ppm	(2H)	CH_2	a
3.8 ppm	(3H)	OCH_3	
6.8-7.3 ppm		aromatic protons	

EXAMPLE 14: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-TRIFLUOROACETAMIDE

Following the procedure of Example 13 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]thiophene, N-[2-(5-methoxybenzo[b]thiophen-3-yl)ethyl]-trifluoroacetamide is obtained.

Infra-red (KBr disc): 3280 cm^{-1} ν NH amide
1690 cm^{-1} ν C=O

EXAMPLE 15: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-TRIFLUOROACETAMIDE

Following the procedure of Example 13 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]furan, N-[2-(5-methoxybenzo[b]furan-3-yl)ethyl]-trifluoroacetamide is obtained.

Infra-red (KBr disc): 3290 cm^{-1} ν NH amide
1700 cm^{-1} ν C=O amide

EXAMPLE 16: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-TRIFLUOROACETAMIDE

Following the procedure of Example 13 but replacing 5-methoxytryptamine with 1-β-aminoethyl-6-methoxybenzimidazole, N-[2-(6-methoxybenzimidazol-1-yl)ethyl]-trifluoroacetamide is obtained.

Infra-red (KBr disc): 3300 cm^{-1} ν NH amide
1690 cm^{-1} ν C=O amide

EXAMPLE 17: N-[2-(5-METHOXY-1,2-BENZISOXAZOL-3-YL)ETHYL]-TRIFLUOROACETAMIDE

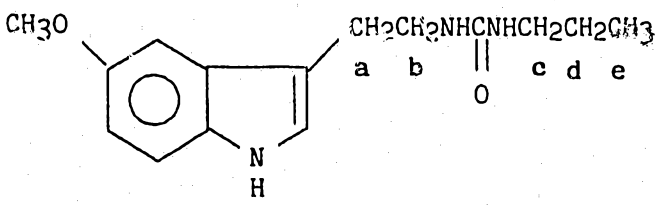
Following the procedure of Example 13 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxy-1,2-benzisoxazole, N-[2-(5-methoxy-1,2-benzisoxazol-3-yl)ethyl]-trifluoroacetamide is obtained.

EXAMPLE 18: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-PROPYLUREA

0.851 g of propyl isocyanate is added to a suspension of 1.902 g of 5-methoxytryptamine in 4 cm^3 of pyridine at +5°C. The mixture is stirred at room temperature for 2 hours and then the reaction medium is poured onto ice-water. The mixture is acidified slightly with a 1N hydrochloric acid solution. The resulting precipitate is isolated by filtration, washed with

water, dried and then recrystallised in toluene, yielding 2.34 g (85%) of N-[2-(5-methoxyindol-3-yl)ethyl]-N'-propylurea.

Melting point: 79-80°C
^{1}H-NMR 90 MHz ($CDCl_3$)



0.9 ppm	(3H)	CH_3	e
1.4 ppm	(2H)	CH_2	d
2.9 ppm	(4H)	CH_2 a CH_2	c
3.4 ppm	(2H)	CH_2	b
3.9 ppm	(3H)	OCH_3	
6.6-7.3 ppm		aromatic protons	

EXAMPLE 19: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-N'-PROPYLUREA

Following the procedure of Example 18 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]thiophene, N-[2-(5-methoxybenzo[b]thiophen-3-yl)ethyl]-N'-propylurea is obtained.

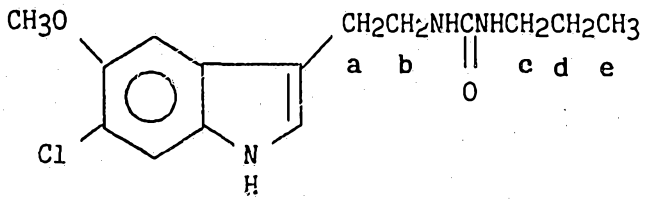
Infra-red (KBr disc): 3300 cm^{-1} ν NH
1620 cm^{-1} ν C=O

EXAMPLE 20: N-[2-(6-CHLORO-5-METHOXYINDOL-3-YL)ETHYL]-N'-PROPYLUREA

Following the procedure of Example 18 but replacing 5-methoxytryptamine with 5-methoxy-6-chlorotryptamine, N-[2-(5-methoxy-6-chloroindol-3-yl)ethyl]-N'-propylurea is obtained.

Infra-red (KBr disc): 3250 cm^{-1} ν NH
1620 cm^{-1} ν C=O

^{1}H-NMR 80 MHz ($CDCl_3$)



0.9-1 ppm	(3H)	CH_3	e
1.5 ppm	(2H)	CH_2	d
2.8-3 ppm	(4H)	CH_2 b	CH_2 c
3.4 ppm	(2H)	CH_2	a
3.90 ppm	(3H)	OCH_3	

EXAMPLE 21: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-PROPYLUREA

Following the procedure of Example 18 but replacing 5-methoxytryptamine with 3-β-aminoethyl-5-methoxybenzo[b]furan, N-[2-(5-methoxybenzo[b]furan-3-yl)ethyl]-N'-propylurea is obtained.

Infra-red (KBr disc): 3290 cm^{-1} ν NH
1620 cm^{-1} ν C=O

EXAMPLE 22: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-PROPYL-THIOUREA

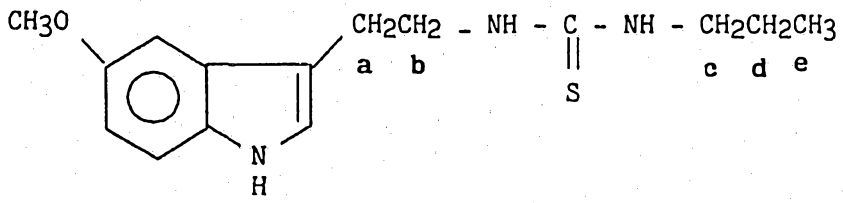
1.11 g of propyl isothiocyanate are added to a suspension of 2.27 g of 5-methoxytryptamine in 5 cm^3 of pyridine.

The reaction medium is stirred at 80° for one hour and then, after cooling, is poured onto a mixture of water and ice and acidified slightly with a 1N hydrochloric acid solution.

The resulting precipitate is isolated by filtration, washed with water, dried and then recrystallised in toluene.

In this manner, 2.18 g (75%) of N-[2-(5-methoxyindol-3-yl)ethyl]-N'-propylthiourea are obtained.

^{1}H-NMR 80 MHz ($CDCl_3$)



0.85 ppm	(3H)	CH_3	e
1.45 ppm	(2H)	CH_2	d
2.95 ppm	(4H)	CH_2 c CH_2	a
3.4 ppm	(2H)	CH_2	b
3.85 ppm	(3H)	OCH_3	
5,50 ppm	(2H)	HNCNH (S)	disappears in D_2O

6.7-7.3 ppm aromatic protons

EXAMPLE 23: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-CYCLOBUTYL-CARBOXAMIDE

Following the procedure of Example 1 but replacing cyclopropanecarboxylic acid chloride with cyclobutanecarboxylic acid chloride, the title compound is obtained.

Melting point: 111-112°C
Crystallization solvent: chloroform-acetone

EXAMPLES 24 TO 25:

Following the procedure of Example 1 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chloride or, where applicable, its corresponding acid

anhydride, the compounds of the following Examples are obtained:

EXAMPLE 24: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-CYCLOHEXYL-CARBOXAMIDE

EXAMPLE 25: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-3-CYCLOPENTYLPROPIONAMIDE

EXAMPLE 26: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-MORPHOLINO-ACETAMIDE

Step I: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-BROMOACETAMIDE

Following the procedure of Example 1 but replacing cyclopropanecarboxylic acid chloride with bromoacetic acid chloride, N-[2-(5-methoxyindol-3-yl)ethyl]-bromoacetamide is obtained.

Step II: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-MORPHOLINO-ACETAMIDE

0.01 mol of morpholine is dissolved in 50 cm^3 of acetone, with magnetic stirring. 0.012 mol of triethylamine and 0.01 mol of N-[2-(5-methoxyindol-3-yl)ethyl]-2-bromoacetamide are added. The mixture is refluxed for one hour with magnetic stirring. The resulting precipitate is suction filtered and the filtrate is evaporated.

The residue is taken up in alkaline water, and the precipitate is suction filtered, washed, dried and recrystallised in a toluene-cyclohexane mixture, yielding the title compound.

EXAMPLES 27 AND 28:

Following the procedure of Example 26 but replacing morpholine in step II with 1-benzylpiperazine and then with 1-(2,3,4-

trimethoxybenzyl)piperazine, the compounds of the following Examples are obtained in succession:

EXAMPLE 27: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-2-(4-BENZYL-PIPERAZIN-1-YL)ACETAMIDE

EXAMPLE 28: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-2-(4-(2,3,4-TRIMETHOXYBENZYL)PIPERAZIN-1-YL)ACETAMIDE

EXAMPLE 29: N-[2-(5-HYDROXYINDOL-3-YL)ETHYL]-CYCLOPROPYL-CARBOXAMIDE

Following the procedure of Example 1 but replacing 5-methoxytryptamine with 5-hydroxytryptamine, the title compound is obtained.

EXAMPLE 30: N-{2-[5-(CYCLOHEXEN-3-YLOXY)INDOL-3-YL]-ETHYL}-CYCLOPROPYLCARBOXAMIDE

1.98×10^{-2} mol of potassium carbonate, 1.33×10^{-2} mol of N-[2-(5-hydroxyindol-3-yl)ethyl]cyclopropylcarboxamide dissolved in 20 cm^3 of anhydrous acetone, and 2.1×10^{-2} mol of 3-bromocyclohexene are introduced into a 50 cm^3 flask with a ground neck. The mixture is heated under reflux for 22 hours. The reaction medium is filtered and the filtrate is evaporated under reduced pressure. Recrystallisation of the evaporation residue in ethyl acetate yields purified N-{2-[5-(cyclohexen-3-yloxy)indol-3-yl]ethyl}-cyclopropylcarboxamide.

EXAMPLE 31: N-[2-(5-BENZYLOXYINDOL-3-YL)ETHYL]-CYCLO-PROPYLCARBOXAMIDE

0.23 g of sodium is introduced in small portions, with magnetic stirring, into a 150 cm^3 flask containing 50 cm^3 of absolute ethanol.

0.01 mol of N-[2-(5-hydroxyindol-3-yl)ethyl]-cyclopropyl-carboxamide is then added, stirring is continued for 30 minutes, and then the mixture is evaporated to dryness.

The resulting sodium compound is dissolved in 30 cm^3 of anhydrous dimethylformamide. 0.011 mol of benzyl bromide is added, with magnetic stirring, by means of a dropping funnel.

The mixture is heated at 90°C for 4 hours. The reaction medium is allowed to cool and is then poured onto ice. The resulting precipitate is suction filtered and washed with a 1N sodium hydroxide solution and then with water. The mixture is dried and recrystallised, yielding purified N-[2-(5-benzyloxyindol-3-yl)ethyl]-cyclopropylcarboxamide.

EXAMPLES 32 TO 37:

Following the procedure of Example 18 but replacing propyl isocyanate with the appropriate isocyanates or isothiocyanate, the compounds of the following Examples are obtained:

EXAMPLE 32: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-BENZYL-UREA

EXAMPLE 33: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-CYCLO-PROPYLUREA

EXAMPLE 34: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-CYCLO-BUTYLUREA

EXAMPLE 35: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-BUTYLUREA

EXAMPLE 36: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-PROPYL-THIOUREA

EXAMPLE 37: N-[2-(5-METHOXYINDOL-3-YL)ETHYL]-N'-CYCLO-HEXYLTHIOUREA

EXAMPLES 38 AND 39:

Following the procedure of Example 5 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chloride or acid anhydride, the compounds of the following Examples are obtained:

EXAMPLE 38: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-CYCLOBUTYLCARBOXAMIDE

EXAMPLE 39: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-CYCLOOCTYLCARBOXAMIDE

EXAMPLES 40 AND 41:

Following the procedure of Example 19 but replacing propyl isocyanate with the appropriate isocyanate or isothiocyanate, the compounds of the following Examples are obtained:

EXAMPLE 40: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-N'-CYCLOPROPYLUREA

EXAMPLE 41: N-[2-(5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-N'-CYCLOHEXYLTHIOUREA

EXAMPLES 42 AND 43:

Following the procedure of Example 6 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chloride, the compounds of the following Examples are obtained:

EXAMPLE 42: N-[2-(6-CHLORO-5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-CYCLOBUTYLCARBOXAMIDE

EXAMPLE 43: N-[2-(6-CHLORO-5-METHOXYBENZO[b]THIOPHEN-3-YL)ETHYL]-3-CYCLOPENTYLPROPIONAMIDE

EXAMPLES 44 TO 46:

Following the procedure of Example 7 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chlorides, the compounds of the following examples are obtained:

EXAMPLE 44: N-[2-(BENZO[b]FURAN-3-YL)ETHYL]-CYCLOBUTYL-CARBOXAMIDE

EXAMPLE 45: N-[2-(BENZO[b]FURAN-3-YL)ETHYL]-CYCLOHEXYL-CARBOXAMIDE

EXAMPLE 46: N-[2-(BENZO[b]FURAN-3-YL)ETHYL]-TRIFLUORO-ACETAMIDE

EXAMPLES 47 TO 51:

Following the procedure of Example 21 but replacing propyl isocyanate with the appropriate isocyanate or isothiocyanate, the compounds of the following Examples are obtained:

EXAMPLE 47: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-METHYLUREA

EXAMPLE 48: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-ETHYLUREA

EXAMPLE 49: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-HEXYLUREA

EXAMPLE 50: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-BENZYLUREA

EXAMPLE 51: N-[2-(5-METHOXYBENZO[b]FURAN-3-YL)ETHYL]-N'-PROPYLTHIOUREA

EXAMPLES 52 TO 54:

Following the procedure of Example 11 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chloride, the compounds of the following Examples are obtained:

EXAMPLE 52: N-[2-(5-METHOXY-1,2-BENZISOXAZOL-3-YL)ETHYL]-ACETAMIDE

EXAMPLE 53: N-[2-(5-METHOXY-1,2-BENZISOXAZOL-3-YL)ETHYL]-BUTYRAMIDE

EXAMPLE 54: N-[2-(5-METHOXY-1,2-BENZISOXAZOL-3-YL)ETHYL]-3-CHLOROPROPIONAMIDE

EXAMPLES 55 AND 56:

Following the procedure of Example 12 but replacing cyclopropanecarboxylic acid chloride with the appropriate acid chloride, the compounds of the following Examples are obtained:

EXAMPLE 55: N-[2-(5-METHOXY-1,2-INDAZOL-3-YL)ETHYL]-ACETAMIDE

EXAMPLE 56: N-[2-(5-METHOXY-1,2-INDAZOL-3-YL)ETHYL]-PROPIONAMIDE

EXAMPLES 57 TO 60:

Following the procedure of Example 9 but replacing cyclopropanecarboxylic acid chloride with the corresponding acid chloride, the compounds of the following Examples are obtained:

EXAMPLE 57: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-

ACETAMIDE

Melting point: 173-175°C

EXAMPLE 58: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-BUTYRAMIDE

EXAMPLE 59: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-PENTANAMIDE

EXAMPLE 60: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-2-BROMOACETAMIDE

EXAMPLES 61 TO 65:

Following the procedure of Example 16 but replacing propyl isocyanate with the appropriate isocyanates or isothiocyanates, the compounds of the following Examples are obtained:

EXAMPLE 61: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-N'-PROPYLUREA

EXAMPLE 62: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-N'-BENZYLUREA

EXAMPLE 63: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-N'-PROPYLTHIOUREA

EXAMPLE 64: N-[2-(6-METHOXYBENZIMIDAZOL-1-YL)ETHYL]-N'-CYCLOHEXYLTHIOUREA

EXAMPLE 65 : N-[2-(6-FLUORO-5-METHOXYINDOL-3-YL)ETHYL]-N'-PROPYLUREA

Melting point (dichloromethane-ether) : 109-110° C

EXAMPLE A: DETERMINATION OF BINDING TO MELATONIN RECEPTORS

The binding of the compounds of the invention to melatonin receptors was carried out according to conventional methods on receptors of the pars tuberalis of sheep (Journal of Neuroendocrinology, Vol. 1, No. 1, pp. 1-4 (1989)).

The compounds of the invention bind in an extremely specific manner to the melatonin receptors with an affinity, for those exhibiting the most affinity, that is more than 100 times greater than that of melatonin itself. The compounds of the invention which were tested have a dissociation constant (Kd) of the order of 10^{-13} mol.l^{-1}, as compared with 6.3×10^{-11} mol.l^{-1} for melatonin itself.

EXAMPLE B: FOUR-PLATE TEST

The products of the invention are administered by the oesophageal route to groups of ten mice. One group receives gum syrup.

30 minutes after the administration of the products to be studied, the animals are placed in containers the floors of which comprise four metal plates. Each time the animal passes from one plate to another, it receives a slight electric shock (0.35 mA). The number of passages is recorded for a period of one minute. After administration, the compounds of the invention increase significantly the number of passages, which indicates the anxiolytic activity of the compounds of the invention.

EXAMPLE C: ACTIVITY OF THE PRODUCTS OF THE INVENTION ON ISCHAEMIC MICROCIRCULATION

The experimental study was carried out on the cremaster muscles of male rats (Sprague-Dawley) following ligature of the common iliac artery.

The muscles were placed in a transparent chamber and perfused with a solution of bicarbonate buffer equilibrated with a

gaseous CO_2/N_2 mixture 5/95%. The velocity of the red corpuscles and the diameter of the first- or second-order arterioles irrigating the cremaster were measured, and the arterial blood flow was calculated. Identical information was obtained for four types of vessels.
The same type of measurement was carried out simultaneously:

- on the cremaster perfused normally,
- on the cremaster after ligature, that is to say the ischaematised cremaster, 2, 7, 14 and 21 days following ligature.

Two groups of animals were studied:

- a control group without treatment,
- a group treated p.o. with a product of the invention, at a dose of 0.1 mg.kg^{-1} per day.

No difference was noted in either the velocity of the corpuscles or the diameter of the vessels in the normally irrigated cremaster muscles in the treated animals as compared with the controls.

On the other hand, at the level of the ischaematised cremaster muscle, the mean diameter of the arterioles was improved in the treated animals as compared with the controls. The velocity of the red corpuscles was normalised by treatment for 21 days.

In fact, in the treated animals, the velocity of the red corpuscles and the blood flow measured 7 days after ligature show no significant difference as compared with the values obtained in the non-ischaematised cremaster. These results are obtained without modification of the arterial pressure.

These results indicate that chronic treatment with one of the compounds of the invention improves microcirculation and blood irrigation of the ischaemic regions.

EXAMPLE D: STIMULATION OF IMMUNE RESPONSES

Red corpuscles of sheep were administered to groups of six mice. Those groups of mice were then treated subcutaneously with the compounds of the invention for a period of six days, and a control group was treated with a placebo. The mice are then left for four weeks and then received a repeat injection of red corpuscles of sheep without receiving further administrations of the product of the invention. The immune response was evaluated 3 days after the repeat injection. It is statistically increased in the group treated with the compounds of the invention.

EXAMPLE E: INHIBITION OF OVULATION

Adult female rats with regular four-day cycles are used. Vaginal smears were taken daily, and rats were selected after they had exhibited at least two consecutive four-day cycles.

Each cycle is composed of two days of dioestrus, one day of pro-oestrus and one day of oestrus.

On the afternoon of the day of pro-oestrus, luteinizing hormone is released into the blood by the hypophysis.

This hormone induces ovulation, which is indicated by the presence of eggs at the oviduct on the day of oestrus.

The compounds of the invention are administered orally at mid-day on the day of oestrus. The treated rats and the controls are sacrificed on the day of oestrus. The oviducts are examined. A significant percentage reduction in the number of eggs in the oviducts of rats treated with the compounds of the invention is noted.

EXAMPLE F: PHARMACEUTICAL COMPOSITION

Tablets containing 5 mg of N-[2-(5-METHOXY-INDOL-3-YL)ETHYL]-N'-PROPYLUREA

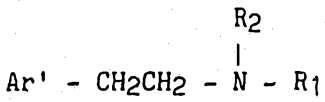
Preparation formulation for 1000 tablets:

N-[2-(5-methoxyindol-3-yl)ethyl]-N'-propylurea	5 g
wheat starch	20 g
corn starch	20 g
lactose	30 g
magnesium stearate	2 g
silica	1 g
hydroxypropylcellulose	2 g

CLAIMS

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

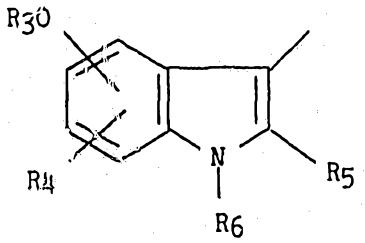
1. Compounds of the general formula (I):



(I)

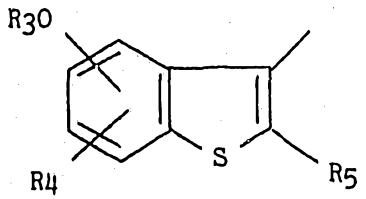
in which:

- Ar' represents:
  - an indol-3-yl nucleus of formula (II):



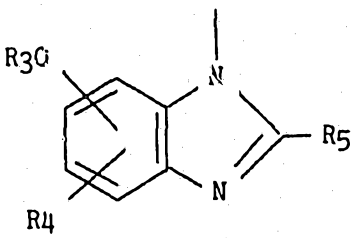
(II)

  - a benzo[b]thiophen-3-yl nucleus of formula (III):



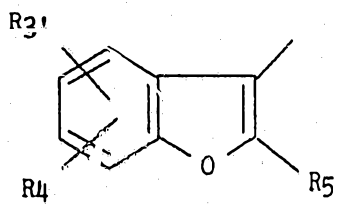
(III)

  - a benzimidazol-1-yl nucleus of formula (IV):



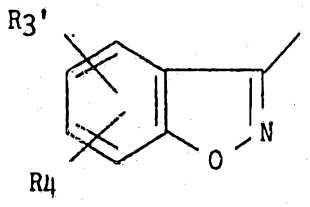
(IV)

  - a benzo[b]furan-3-yl nucleus of formula (V):



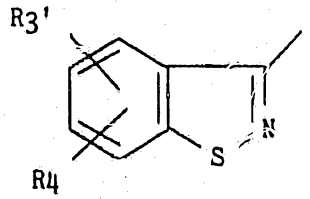
(V)

- a 1,2-benzisoxazol-3-yl nucleus of formula (VI):



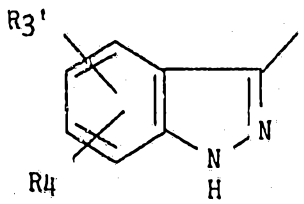
(VI)

- a 1,2-benzisothiazol-3-yl nucleus of formula (VII):



(VII)

- an indazol-3-yl nucleus of formula (VIII):



(VIII)

- R_1 represents:

  - a group $-\overset{\overset{O}{\|}}{C}-R_7$ in which R_7 represents an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)alkyl radical, or a trifluoromethyl group,
  and, when Ar' represents a group selected from those of formulae (IV), (VI), (VII) and (VIII), R_7 may also represents a linear or branched alkyl radical having from 1 to 6 carbon atoms that is unsubstituted or substituted by 1 or 2 halogen radicals,

  - a group $-\overset{\overset{O}{\|}}{C}-NHR_8$ or $-\overset{\overset{S}{\|}}{C}-NHR_8$ in which R_8 represents a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted cycloalkyl radical, an optionally substituted cycloalkyl-(C_1-C_4)-alkyl radical, an optionally substituted aryl radical, or an optionally substituted arylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms, or

  - a group $-\overset{\overset{O}{\|}}{C}-(CH_2)n-E_1$ in which

  n represents an integer from 1 to 3 and E_1 represents a radical selected from:
  - morpholino, and
  - piperazine that is unsubstituted or substituted by a radical $-(CH_2)_{n'}-E_2$ wherein n' represents an integer from 1 to 4 and E_2 represents a phenyl or naphthyl radical each of which is unsubstituted or substituted by from 1 to 3 radicals selected from: halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

$-R_2$ represents a hydrogen atom or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-R_3 represents a hydrogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted aryl radical, an optionally substituted arylalkyl or diarylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms, or a cycloalkyl or cycloalkylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms;

-R_3' represents a hydrogen atom or a group -O-R_3 wherein R_3 is as defined above;

-R_4 represents a hydrogen atom, a halogen atom, a hydroxy radical, a linear or branched alkoxy radical having from 1 to 6 carbon atoms, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-R_5 represents a hydrogen atom, a halogen atom, a linear or branched lower alkyl radical having from 1 to 6 carbon atoms, an optionally substituted phenyl radical, or an optionally substituted phenylalkyl radical in which the alkyl chain contains from 1 to 3 carbon atoms; and

-R_6 represents a hydrogen atom, or a linear or branched lower alkyl radical having from 1 to 6 carbon atoms;

-the isomers, epimers and diastereoisomers thereof,

-and the addition salts thereof with a pharmaceutically acceptable acid or base,

-with the provisos that:

- Ar' may not represent a 7-methoxybenzo[b]furan-3-yl group when R_1 represents a cyclopropylcarbonyl radical;
- R_1 may not represent a trifluoroacetyl radical when Ar' represents an indole radical wherein $R_2 = R_3 = R_4 = R_5 = R_6 = H$;

. and R_1 may not represent an anilinothiocarbonyl radical that is unsubstituted or substituted at the 4-position of the phenyl by an alkoxy radical, when Ar represents an indol-3-yl nucleus and R_3 represents a methyl or benzyl radical;

and wherein

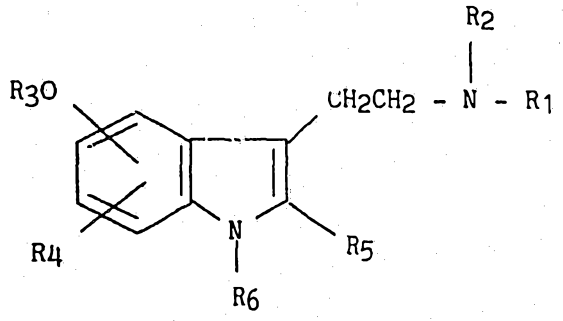
-the term "substituted" associated with the expressions "aryl", "arylalkyl", "diarylalkyl", "phenyl" and "phenylalkyl" indicates that the aromatic nucleus or nuclei may be substituted by one or more radicals selected from: linear or branched lower alkyl having from 1 to 6 carbon atoms, linear or branched lower alkoxy having from 1 to 6 carbon atoms, hydroxy, halogen, nitro, and trifluoromethyl;

-the term "substituted" associated with the expressions "cycloalkyl" and "cycloalkyl-(C_1-C_4)alkyl" indicates that the cyclic system may be substituted by one or more radicals selected from: halogen, linear or branched lower alkyl having from 1 to 6 carbon atoms, and linear or branched lower alkoxy having from 1 to 6 carbon atoms;

-the term "cycloalkyl" designates a saturated or unsaturated cyclic system having from 3 to 8 carbon atoms; and

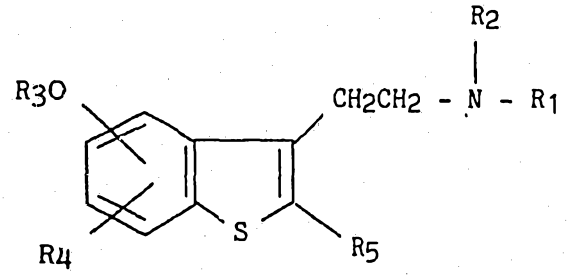
-the expression "aryl group" is understood as meaning a pyridyl, phenyl, naphthyl, thienyl, furyl or pyrimidyl group.

2. Compounds according to claim 1 in which Ar' represents an indol-3-yl nucleus, which correspond to the indoles of formula:



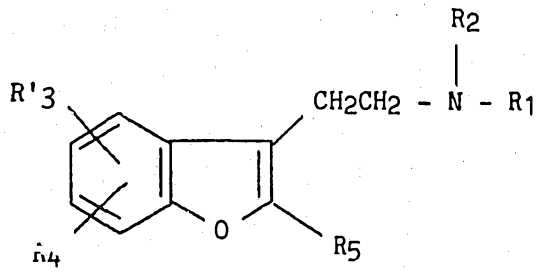
in which R_1, R_2, R_3, R_4, R_5 and R_6 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compounds according to claim 1 in which Ar' represents a benzo[b]thiophen-3-yl nucleus, which correspond to the benzo[b]thiophenes of formula:



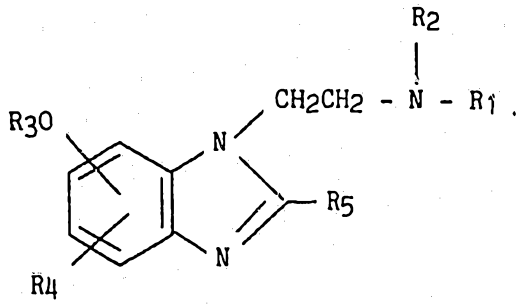
in which R_1, R_2, R_3, R_4 and R_5 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compounds according to claim 1 in which Ar' represents a benzo[b]furan-3-yl nucleus, which correspond to the benzo[b]furans of formula:



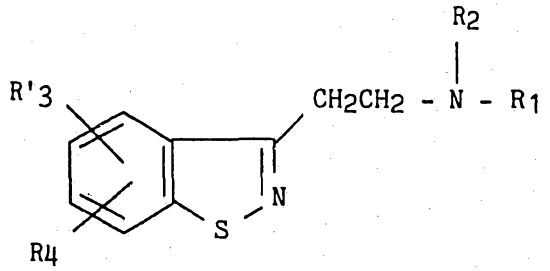
in which R_1, R_2, R'_3, R_4 and R_5 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

5. Compounds according to claim 1 in which Ar' represents a benzimidazol-1-yl nucleus, which correspond to the benzimidazoles of formula:



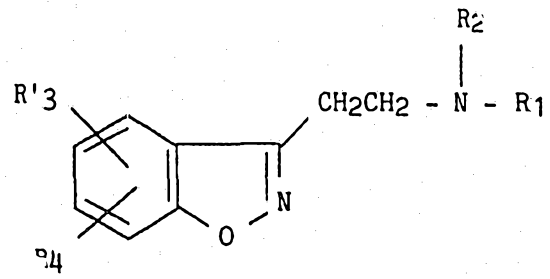
in which R_1, R_2, R_3, R_4 and R_5 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

6. Compounds according to claim 1 in which Ar' represents a 1,2-benzisothiazol-3-yl nucleus, which correspond to the 1,2-benzisothiazoles of the general formula:



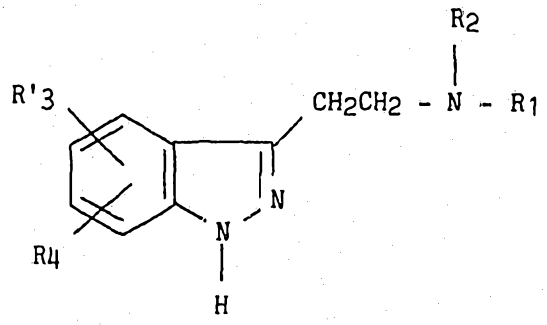
in which R_1, R_2, R'_3 and R_4 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

7. Compounds according to claim 1 in which Ar' represents a 1,2-benzisoxazol-3-yl nucleus, which correspond to the benzisoxazoles of formula:



in which R_1, R_2, R'_3 and R_4 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds according to claim 1 in which Ar' represents an indazol-3-yl nucleus, which correspond to the indazoles of formula:



in which R_1, R_2, R'_3 and R_4 have the same meaning as in claim 1, the isomers, epimers and diastereoisomers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

9. Compound according to claim 1 which is N-[2-(5-methoxyindol-3-yl)ethyl]-trifluoroacetamide.

10. Compound according to claim 1 which is N-[2-(5-methoxyindol-3-yl)ethyl]-N'-propylurea.

11. Compound according to claim 1 which is N-[2-(5-methoxyindol-3-yl)ethyl]-N'-propylthiourea.

12. Compound according to claim 1 which is N-[2-(5-methoxyindol-3-yl)ethyl]-cyclopropylcarboxamide.

13. Compound according to claim 1 which is N-[2-(5-methoxybenzo[b]furan-3-yl)ethyl]-N'-propylurea.

14. Compound according to claim 1 which is N-[2-(5-methoxybenzo[b]thiophen-3-yl)ethyl]-N'-propylurea.

15. Compound according to claim 1 which is N-[2-(5-methoxyindol-3-yl)ethyl]-cyclobutylcarboxamide.

16. Compound according to claim 1 which is N-[2-(6-methoxybenzimidazol-1-yl)ethyl]-acetamide.

17. Compound according to claim 1 which is N-[2-(6-fluoro-5-methoxyindol-3-yl)ethyl]-cyclopropylcarboxamide.

18. Compound according to claim 1 which is N-[2-(6-fluoro-5-methoxyindol-3-yl)ethyl]-N'-propylurea.

19. Process for the preparation of the compounds of formula (I) according to claim 1, characterised in that there is used as starting material an amine of the general formula (IX):

$$Ar'-CH_2CH_2-NHR_2 \qquad (IX),$$

in which Ar' and R_2 have the same meaning as in claim 1, which is treated:

- with an acid chloride of formula (X):

$$Cl - \underset{\underset{O}{\|}}{C} - R_7 \qquad (X)$$

or with the corresponding acid anhydride of formula (XI):

$$R_7 - \underset{\underset{O}{\|}}{C} - O - \underset{\underset{O}{\|}}{C} - R_7 \qquad (XI)$$

in which formulae R_7 has the same meaning as in claim 1, to obtain the compounds of formula (Ia):

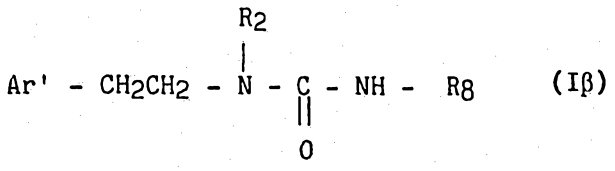
$$Ar' - CH_2CH_2 - \overset{\overset{R_2}{|}}{N} - \underset{\underset{O}{\|}}{C} - R_7 \qquad (Ia)$$

in which Ar', R_2 and R_7 have the same meaning as in claim 1,

- or with an isocyanate of formula (XII):

$$R_8\text{-}N{=}C{=}O \qquad \text{(XII)},$$

in which R_8 has the same meaning as in claim 1, to obtain the compounds of formula (Iβ):



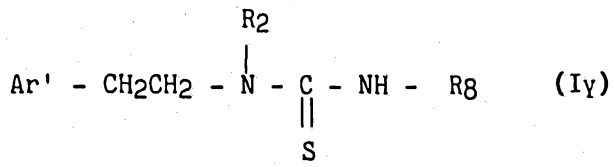
(Iβ)

in which Ar', R_2 and R_8 have the same meaning as in claim 1,

- or with an isothiocyanate of formula (XIII):

$$R_8\text{-}N{=}C{=}S \qquad \text{(XIII)},$$

in which R_8 has the same meaning as in claim 1, to obtain the compounds of formula (Iγ):



(Iγ)

in which Ar', R_2 and R_8 have the same meaning as in claim 1,

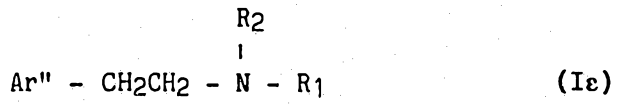
it being understood that the compounds of formulae (Iα), (Iβ) and (Iγ) form part of the invention and together constitute the compounds of formula (I) according to claim 1,

it being possible for the compounds of formula (I) according to claim 1 to be:

- purified by one or more purification methods selected from crystallisation, chromatography over a silica column, extraction, filtration, and passage over carbon and/or resin,

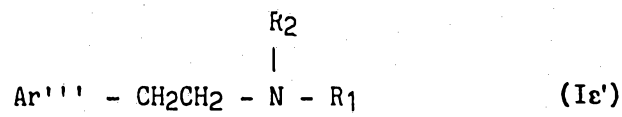
- separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers,
- and/or converted into salts by means of a pharmaceutically acceptable acid or base.

20. Process for obtaining the compounds of formula (Iε), which are a special case of the compounds of formula (I) according to claim 1:



(Iε)

in which R_1 and R_2 are as defined in claim 1 and Ar" represents a group Ar' as defined in claim 1 that is substituted by a group $-O-R_3"$ wherein $R_3"$ represents a group selected from optionally substituted aryl, optionally substituted arylalkyl or diarylalkyl, and cycloalkyl or cycloalkylalkyl (the terms "aryl", "arylalkyl", "diarylalkyl", "cycloalkyl", "cycloalkylalkyl" and "substituted" being as defined in claim 1),characterised in thata compound of formula (Iε'):



(Iε')

in which R_1 and R_2 are as defined above and Ar"' represents a group Ar' as defined in claim 1 that is substituted by a group $-O-R_3"'$ wherein $R_3"'$ represents a hydrogen atom, is reacted with a compound of formula (XIV):

(XIV),

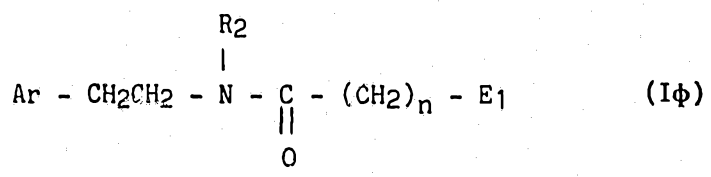
in which Hal represents a halogen atom and R" represents a group selected from optionally substituted aryl, optionally substituted arylalkyl or diarylalkyl, and cycloalkyl or cycloalkylalkyl (the terms "aryl", "arylalkyl", "diarylalkyl",

"cycloalkyl", "cycloalkylalkyl" and "substituted" being as defined in claim 1),

it being possible for the compounds of formula (I) to be:

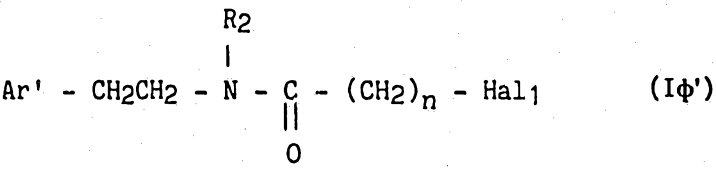
- purified by one or more purification methods selected from crystallisation, chromatography over a silica column, extraction, filtration, and passage over carbon and/or resin,
- separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers,
- and/or converted into salts by means of a pharmaceutically acceptable acid or base.

21. Process for the preparation of the compounds of formula (IΦ), which are a special case of the compounds of formula (I) according to claim 1:



(Iφ)

in which Ar', R_2, E_1 and n are as defined in claim 1,characterised in that a compound of formula (IΦ'):



(Iφ')

in which Ar', R_2 and n are as defined in claim 1 and Hal_1 represents a halogen atom, is reacted with a morpholine group or with a piperazine group that is unsubstituted or substituted by a radical $-(CH_2)_{n'}-E_2$ wherein n' and E_2 are as defined in formula (I),

it being possible for the compounds of formula (IΦ) to be:

purified by one or more purification methods selected from crystallisation, chromatography over a silica column, extraction, filtration, and passage over carbon and/or resin, separated, where applicable, in pure form or in the form of a mixture, into their possible optical isomers, and/or converted into salts by means of a pharmaceutically acceptable acid or base.

22. Pharmaceutical composition containing as active ingredient at least one compound according to one of claims 1 to 18 or an addition salt thereof with a pharmaceutically acceptable acid or base, on its own or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or vehicles.

23. A method of treatment of disorders of the melatoninergic system comprising the administration, to a patient suffering said disorder, of an effective amount of a pharmaceutical composition as claimed in claim 22.

24. A method of treatment of stress, of sleep disorders, of anxiety, of seasonal depression, of insomnia and fatigue due to jet lag, of schizophrenia, of panic attacks, of melancholia, of regulation of the appetite, of insomnia, of psychotic disorders, of epilepsy, of Parkinson's disease, of senile dementia, of disorders associated with normal or pathological ageing, of migraine, of memory loss, of Alzheimer's disease, as well as of disorders of cerebral circulation, of certain cancers, of psoriasis, of acne, and of seborrhoea, or as ovulation inhibitors, or in veterinary medicine in disorders of the fur comprising the administration, to a patient suffering said disorder, of an effective amount of a pharmaceutical composition as claimed in claim 22.

DATED this 16th day of March, 1994.

ADIR ET COMPAGNIE

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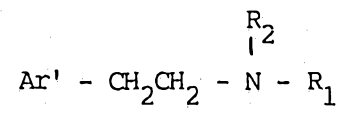
A B S T R A C T

The invention provides a new arylethylamine compound of the general formula



(I)

processes for the preparation thereof, and pharmaceutical compositions containing them