

**NEW INDOLE COMPOUNDS,
A PROCESS FOR THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

- 5 The present invention relates to new indole compounds, to a process for their preparation and to pharmaceutical compositions containing them

The compounds of the present invention are new and have pharmacological properties that are of great interest in relation to melatoninergetic receptors.

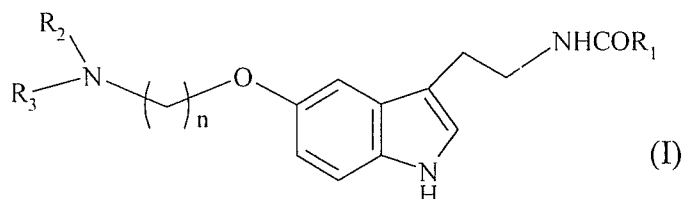
- 10 In the last ten years, numerous studies have demonstrated the major role played by melatonin (N-acetyl-5-methoxytryptamine) in a large number of physiopathological phenomena and in the control of circadian rhythms, but melatonin has a rather short half-life owing to the fact that it is rapidly metabolised. Great interest therefore lies in the possibility of making available to the clinician melatonin analogues that are metabolically more stable and have an agonist or antagonist character and of which the therapeutic effect
15 may be expected to be superior to that of the hormone itself.

- In addition to their beneficial action in respect of circadian rhythm disorders (J. Neurosurg. 1985, 63, pp. 321-341) and sleep disorders (Psychopharmacology, 1990, 100, pp. 222-226), ligands of the melatoninergetic system have valuable pharmacological properties in respect of the central nervous system, especially anxiolytic and antipsychotic properties
20 (Neuropharmacology of Pineal Secretions, 1990, 8 (3-4), pp. 264-272), and analgesic properties (Pharmacopsychiat., 1987, 20, pp. 222-223), and also for the treatment of Parkinson's disease (J. Neurosurg. 1985, 63, pp. 321-341) and Alzheimer's disease (Brain Research, 1990, 528, pp. 170-174). The compounds have also demonstrated activity in relation to certain cancers (Melatonin - Clinical Perspectives, Oxford University Press,
25 1988, pp. 164-165), ovulation (Science 1987, 227, pp. 714-720), diabetes (Clinical Endocrinology, 1986, 24, pp. 359-364), and in the treatment of obesity (International Journal of Eating Disorders, 1996, 20 (4), pp. 443-446).

Those various effects are exerted *via* the intermediary of specific melatonin receptors.

- Molecular biology studies have demonstrated the existence of a number of receptor subtypes that are capable of binding that hormone (Trends Pharmacol. Sci., 1995, 16, p. 50 ; WO 97.04094). It has been possible for some of those receptors to be located and characterised for different species, including mammals. In order to be able to understand the physiological functions of those receptors better, it is of great advantage to have available selective ligands. Moreover such compounds, by interacting selectively with one or another of those receptors, may be excellent medicaments for the clinician in the treatment of pathologies associated with the melatoninergic system, some of which have been mentioned above.
- 10 In addition to being new, the compounds of the present invention exhibit a very strong affinity for melatonin receptors.

The present invention relates more especially to compounds of formula (I) :



wherein :

- 15 ➤ R₁ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₃-C₈)-cycloalkyl group or a (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl group in which the alkyl moiety may be linear or branched,
- R₂ and R₃, together with the nitrogen atom carrying them, form a heterocycle having from 5 to 8 ring members,
- 20 ➤ and n represents 2, 3, 4, 5 or 6,

- wherein the heterocycle having from 5 to 8 ring members so defined does not contain an additional hetero atom, and may optionally be substituted by from one to three, identical or different linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, OH, carboxy,
- 25 amino (optionally substituted by one or two linear or branched (C₁-C₆)alkyl groups)

groups, or halogen atoms,

to their enantiomers and diastereoisomers, and also to addition salts thereof with a pharmaceutically acceptable acid or base.

5 Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulfonic acid, camphoric acid, oxalic acid etc..

10 Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine etc..

Preferred compounds according to the invention are those wherein *n* represents 2 or 3 and more preferably 2.

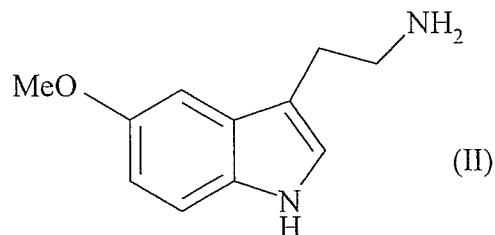
*R*₁ advantageously represents an alkyl group, such as, for example, a methyl, ethyl or propyl group.

Preferred *R*₂ and *R*₃ groups are those that, together with the nitrogen atom carrying them, form a piperidinyl group.

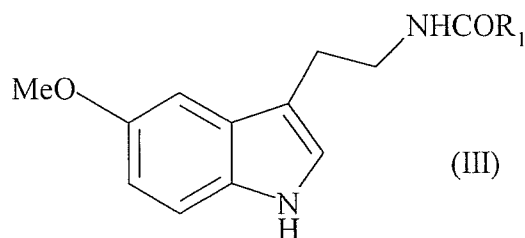
15 The invention relates even more especially to the following compounds : *N*-(2-{5-[2-(1-piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)acetamide, *N*-(2-{5-[2-(1-piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)propanamide, *N*-(2-{5-[2-(1-piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)-butanamide and *N*-(2-{5-[3-(1-piperidinyl)propoxy]-1*H*-indol-3-yl}ethyl)butanamide.

The enantiomers, diastereoisomers and also addition salts with a pharmaceutically acceptable acid or base of the preferred compounds of the invention form an integral part of the invention.

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

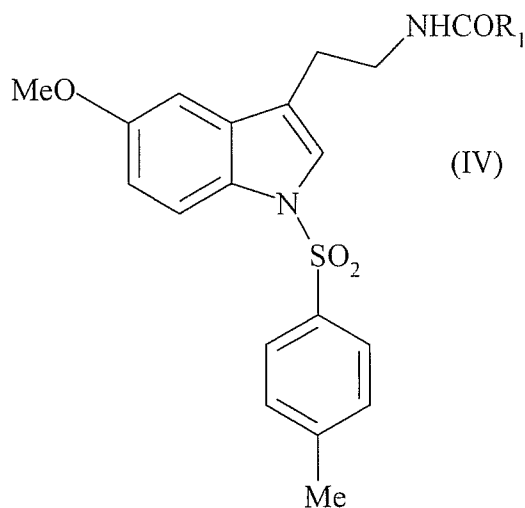


which is condensed with an acid chloride of formula $R_1\text{COCl}$, wherein R_1 is as defined for
5 formula (I), or with the corresponding symmetrical anhydride to yield a compound of formula (III) :



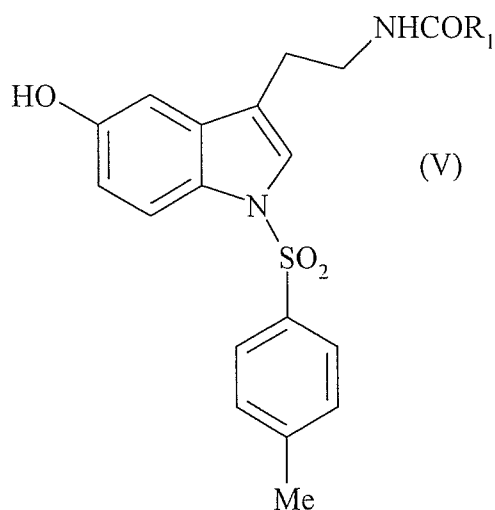
wherein R_1 is as defined hereinbefore,

which is subjected in basic medium to the action of tosyl chloride to yield a compound of
10 formula (IV) :



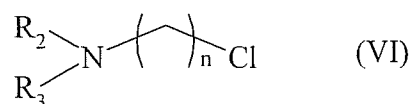
wherein R_1 is as defined hereinbefore,

which is placed under demethylation conditions to yield a compound of formula (V) :



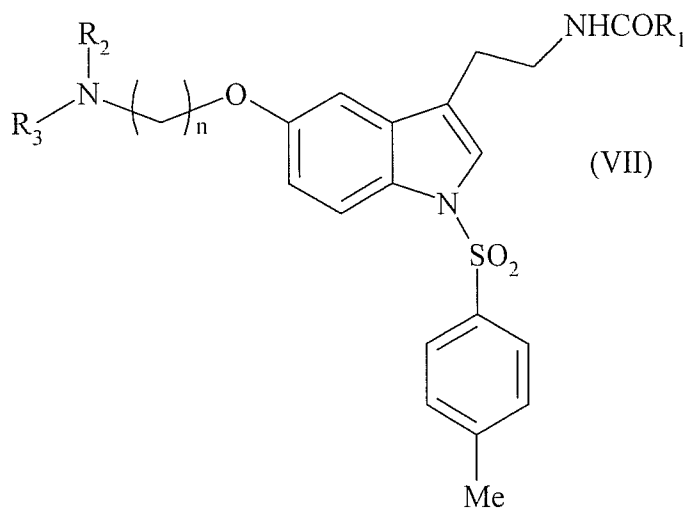
wherein R₁ is as defined hereinbefore,

which is condensed with a compound of formula (VI) :



5 wherein R₂, R₃ and n are as defined for formula (I),

to yield a compound of formula (VII) :



wherein R₁, R₂, R₃ and n are as defined hereinbefore,

which is subjected to the action of magnesium to yield a compound of formula (I),

10 which may be purified according to a conventional separation technique, is converted, if desired, into addition salts with a pharmaceutically acceptable acid or base, and the enantiomers of which may be separated on a chiral column according to a conventional separation technique.

A pharmacological study of the compounds of the invention has demonstrated that they are non-toxic, have a high selective affinity for melatonin receptors and have substantial activity in respect of the central nervous system and, especially, there have been revealed therapeutic properties in respect of sleep disorders, antidepressant properties, anxiolytic properties, antipsychotic properties, analgesic properties and also properties in respect of microcirculation, enabling it to be established that the products of the invention are useful in the treatment of stress, sleep disorders, anxiety, seasonal affective disorder or major depression, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, and in cerebral circulation disorders. In another field of activity, it appears that the products of the invention can be used in the treatment of sexual dysfunction, that they have ovulation-inhibiting and immunomodulating properties and that they lend themselves to use in the treatment of cancers.

The compounds will preferably be used in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, appetite disorders and obesity.

For example, the compounds will be used in the treatment of major depression, seasonal affective disorder and sleep disorders.

The present invention relates also to pharmaceutical compositions comprising at least one compound of formula (I) on its own or in combination with one or more pharmaceutically acceptable excipients.

Amongst the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral, nasal, per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration and especially

tablets or dragées, sublingual tablets, sachets, paquets, capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels and drinkable or injectable ampoules.

The dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the therapeutic indication or any associated treatments, and ranges from
5 0.01 mg to 1 g per 24 hours in one or more administrations.

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

Example 1 : *N*-(2-{5-[2-(1-Piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)acetamide

Step A : 5-Methoxy-3-[2-nitroethenyl]-1*H*-indole

Under argon, dissolve 3.59 g of 5-methoxy-1*H*-indole-3-carbaldehyde and 3.95 g of
10 ammonium acetate in 150 ml of nitromethane and heat at 80°C for 2 hours and 30 minutes.
Allow to return to ambient temperature and take up the reaction mixture in ethyl acetate.
Wash the organic phase with saturated aqueous sodium carbonate solution and then with
saturated aqueous sodium chloride solution. Dry the organic phase over sodium sulfate.
Following filtration and evaporation, the title compound is obtained in the form of an
15 orange solid.

Melting point : 151-152°C

Step B : 2-(5-Methoxy-1*H*-indol-3-yl)ethylamine

20 Under argon, add dropwise a solution of 4.48 g of the compound obtained in Step A in
100 ml of tetrahydrofuran to a solution of 7.80 g of lithium aluminium hydride in 100 ml
of tetrahydrofuran. Stir at ambient temperature for 20 hours. Cool to 0°C and hydrolyse
with water. Filter the reaction mixture over Celite and extract with ethyl acetate. Dry the
organic phase over sodium sulfate, filter and evaporate. The compound obtained is isolated
25 in the form of a brown solid.

Melting point : 101-102°C

Step C : *N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]acetamide

Under argon, dissolve 3.13 g of the compound obtained in Step B in 100 ml of tetrahydrofuran in the presence of 2.30 ml of triethylamine. Add 2.17 ml of acetic anhydride dropwise at 0°C, and stir the reaction at ambient temperature for 21 hours. Evaporate off the solvent and take up the residue in ethyl acetate. Wash the organic phase with saturated aqueous sodium carbonate solution and with saturated aqueous sodium chloride solution. Dry the organic phase over sodium sulfate, filter and evaporate. Purify the compound by column chromatography on silica gel using ethyl acetate as eluant. The title compound is obtained in the form of a white solid.

Melting point : 110-111°C

Step D : *N*-(2-{5-Methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}ethyl)-acetamide

Under nitrogen, dissolve 0.81 g of the compound obtained in Step C in 10 ml of dimethylformamide. Add 0.21 g of sodium hydride in small portions at 0°C and stir the reaction at 0°C for 30 minutes. Add 1 g of tosyl chloride at 0°C and stir the reaction at ambient temperature for 24 hours. Add water and extract with ethyl acetate. Wash the organic phase with saturated aqueous sodium carbonate solution and with saturated aqueous sodium chloride solution. Dry the organic phase over sodium sulfate, filter and evaporate. Purify the compound by column chromatography on silica gel using as eluant a 19/1 dichloromethane/ethanol mixture. Following evaporation and recrystallisation from diisopropyl ether, the title product is obtained in the form of a white solid.

Melting point : 132-133°C

Step E : *N*-(2-{5-Hydroxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}ethyl)-acetamide

Under nitrogen, dissolve 0.40 g of the compound obtained in Step D in 10 ml of dichloromethane and add dropwise 3.1 ml of a boron tribromide solution (1M) in

dichloromethane at 0°C. Stir the reaction at ambient temperature for 4 hours. Dilute the reaction mixture with dichloromethane. Wash the organic phase with saturated aqueous sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution. Dry the organic phase over sodium sulfate, filter and evaporate. The title product is isolated in the form of a white solid.

Melting point : 173-174°C

Step F : *N*-(2-{1-[(4-Methylphenyl)sulfonyl]-5-[2-(1-piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)acetamide

Dissolve 0.36 g of the compound obtained in Step E in 10 ml of dimethylformamide and add 0.40 g of potassium bicarbonate and 0.20 g of 1-(2-chloroethyl)piperidine hydrochloride and stir the reaction at 80°C for 48 hours. Add water to the reaction mixture and extract with ethyl acetate. Wash the organic phase with water and with saturated aqueous sodium chloride solution. Dry the organic phase over sodium sulphate, filter and evaporate. The title compound is obtained in the form of a brown solid.

Melting point : 65-66°C

Step G : *N*-(2-{5-[2-(1-Piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)acetamide

Dissolve 0.66 g of the compound obtained in Step F in 15 ml of methanol and add 0.51 g of magnesium and stir the reaction at ambient temperature for 20 hours. Hydrolyse with water and extract with ethyl acetate. Dry the organic phase over sodium sulfate, filter and evaporate. Purify the compound by column chromatography on silica gel using as eluant a 19/1 dichloromethane/ethanol mixture. The title product is isolated in the form of a white paste.

MS, $m/z = 331$ ($M+1$)

Example 2 : *N*-(2-{5-[2-(1-Piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)propanamide

The procedure is as in Example 1, with the replacement of acetic anhydride with propanoic anhydride in Step C.

The title product is obtained in the form of a brown paste.

MS, $m/z = 345$ ($M+1$)

Example 3 : *N*-(2-{5-[2-(1-piperidinyl)ethoxy]-1*H*-indol-3-yl}ethyl)butanamide

The procedure is as in Example 1, with the replacement of acetic anhydride with butanoic anhydride in Step C.

The title product is obtained in the form a brown paste and is then recrystallised.

Melting point : 113-114°C

5 *MS*, $m/z = 359$ ($M+1$)

Example 4 : *N*-(2-{5-[3-(1-Piperidinyl)propoxy]-1*H*-indol-3-yl}ethyl)butanamide

The procedure is as in Example 1, with the replacement of acetic anhydride with butanoic anhydride in Step C, and the replacement of 1-(2-chloroethyl)piperidine hydrochloride with 1-(3-chloropropyl)piperidine in Step F.

The title product is obtained in the form a brown paste.

PHARMACOLOGICAL STUDY

EXAMPLE A : Acute toxicity study

The acute toxicity was evaluated after oral administration to groups each comprising 8 mice (26 ± 2 grams). The animals were observed at regular intervals during the course of the first day, and daily for the two weeks following treatment. The LD₅₀ (dose that causes the death of 50% of the animals) was evaluated and demonstrated the low toxicity of the compounds of the invention.

EXAMPLE B : Forced swimming test

The compounds of the invention are tested in a behavioural model, the forced swimming test.

The apparatus is composed of a Plexiglas cylinder filled with water. The animals are tested individually for a session of 6 minutes. At the start of each test, the animal is placed in the centre of the cylinder. The time spent immobile is recorded. Each animal is judged to be immobile when it ceases to struggle and remains immobile at the surface of the water, making only those movements which allow it to keep its head above water.

Following administration 40 minutes before the start of the test, the compounds of the invention significantly reduce the time spent immobile, which indicates their anti-depressant activity.

EXAMPLE C : Melatonin MT₁ and MT₂ receptor binding study

The MT₁ or MT₂ receptor binding experiments are carried out using 2-[¹²⁵I]-iodomelatonin as reference radioligand. The radioactivity retained is determined using a liquid scintillation counter.

Competitive binding experiments are then carried out in triplicate using the various test compounds. A range of different concentrations is tested for each compound. The results enable the binding affinities (K_i) of the compounds tested to be determined.

The compounds of the invention have K_i values of less than 1 μ M. By way of example, the
5 compound of Example 3 has a K_i (MT_1) of 11 nM and a K_i (MT_2) of 19 nM.

**EXAMPLE D : Action of the compounds of the invention on the circadian rhythms
of locomotor activity of the rat**

The involvement of melatonin in the entrainment, by day/night alternation, of the majority
10 of physiological, biochemical and behavioural circadian rhythms has made it possible to establish a pharmacological model for use in the search for melatonergic ligands.

The effects of the compounds are tested on numerous parameters and, in particular, on the circadian rhythms of locomotor activity, which are a reliable indicator of the activity of the endogenous circadian clock.

15 In this study, the effects of such compounds on a particular experimental model, namely the rat placed in temporal isolation (permanent darkness), are evaluated.

Experimental protocol

One-month-old male rats are subjected, as soon as they arrive at the laboratory, to a light cycle of 12 hours of light per 24 hours (LD 12 : 12).

20 After 2 to 3 weeks' adaptation, they are placed in cages fitted with a wheel connected to a recording system in order to detect the phases of locomotor activity and thus monitor the nycthemeral (LD) or circadian (DD) rhythms.

As soon as the rhythms recorded show a stable entrainment by the light cycle LD 12 : 12, the rats are placed in permanent darkness (DD).

Two to three weeks later, when the free-running rhythm (rhythm reflecting that of the endogenous clock) is clearly established, the rats are given a daily administration of the compound to be tested.

The observations are made by means of visualisation of the activity rhythms :

- 5 - entrainment of the activity rhythms by the light rhythm,
- disappearance of the entrainment of the rhythms in permanent darkness,
- entrainment by the daily administration of the compound; transitory or durable effect.

A software package makes it possible :

- 10 - to measure the duration and intensity of the activity, the period of the rhythm of the animals in the free-running state and during treatment,
- to demonstrate by spectral analysis the existence of circadian and non-circadian (for example ultradian) components, where present.

Results

15 It clearly appears that the compounds of the invention have a powerful action on the circadian rhythm *via* the melatoninergetic system.

EXAMPLE E : Light/dark cages test

The compounds of the invention are tested in a behavioural model, the light/dark cages test, which enables the anxiolytic activity of the compounds to be demonstrated.

20 The apparatus consists of two polyvinyl boxes covered with Plexiglas. One of the boxes is in darkness. A lamp is placed above the other box, yielding a light intensity of approximately 4000 lux at the centre of the box. An opaque plastics tunnel separates the light box from the dark box. The animals are tested individually for a session of 5 minutes. The floor of each box is cleaned between each session. At the start of each test, the mouse
25 is placed in the tunnel, facing the dark box. The time spent by the mouse in the illuminated

box and the number of passages through the tunnel are recorded after the first entry into the dark box.

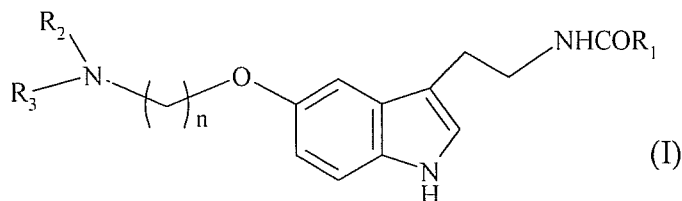
Following administration of the compounds 30 minutes before the start of the test, the compounds of the invention significantly increase the time spent in the illuminated cage
5 and the number of passages through the tunnel, which demonstrates the anxiolytic activity of the compounds of the invention.

EXAMPLE F : Pharmaceutical composition : tablets

10	1000 tablets each containing a dose of 5 mg of <i>N</i> -(2-{5-[2-(1-piperidinyloxy)]-1 <i>H</i> -indol-3-yl}ethyl)butanamide (Example 3)	5 g
	wheat starch	20 g
	maize starch	20 g
	lactose	30 g
15	magnesium stearate.....	2 g
	silica.....	1 g
	hydroxypropyl cellulose	2 g

CLAIMS

1- Compounds of formula (I) :



wherein :

- 5 ➤ R₁ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₃-C₈)cycloalkyl group or a (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl group in which the alkyl moiety may be linear or branched,
- R₂ and R₃, together with the nitrogen atom carrying them, form a heterocycle having from 5 to 8 ring members,
- 10 ➤ and n represents 2, 3, 4, 5 or 6,

wherein the heterocycle having from 5 to 8 ring members so defined does not contain an additional hetero atom, and may optionally be substituted by from one to three, identical or different linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, OH, carboxy, amino (optionally substituted by one or two linear or branched (C₁-C₆)alkyl groups) groups, or halogen atoms,

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their enantiomers and diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

20 2- Compounds of formula (I) according to claim 1, wherein n represents 2, their enantiomers, and also addition salts thereof with a pharmaceutically acceptable base.

3- Compounds of formula (I) according to claim 1, wherein R₁ represents an alkyl group,

their enantiomers, and also addition salts thereof with a pharmaceutically acceptable base.

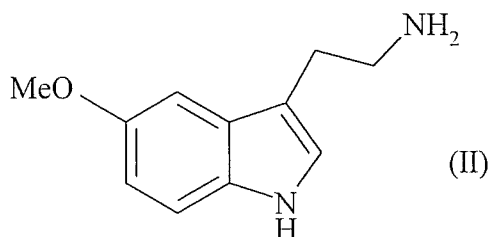
4- Compounds of formula (I) according to claim 1, wherein R₂ and R₃, together with the nitrogen atom carrying them, form a piperidiny1 group, their enantiomers, and also addition salts thereof with a pharmaceutically acceptable base.

5- Compound of formula (I) according to claim 1 which is *N*-(2-{5-[2-(1-piperidiny1)ethoxy]-1*H*-indol-3-yl}ethyl)acetamide, and also addition salts thereof with a pharmaceutically acceptable acid or base.

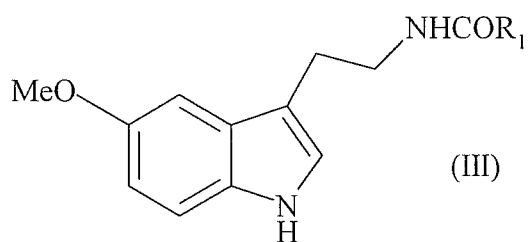
6- Compound of formula (I) according to claim 1 which is *N*-(2-{5-[2-(1-piperidiny1)ethoxy]-1*H*-indol-3-yl}ethyl)propanamide, and also addition salts thereof with a pharmaceutically acceptable acid or base.

7- Compound of formula (I) according to claim 1 which is *N*-(2-{5-[2-(1-piperidiny1)ethoxy]-1*H*-indol-3-yl}ethyl)butanamide, and also addition salts thereof with a pharmaceutically acceptable acid or base.

8- Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material the compound of formula (II) :

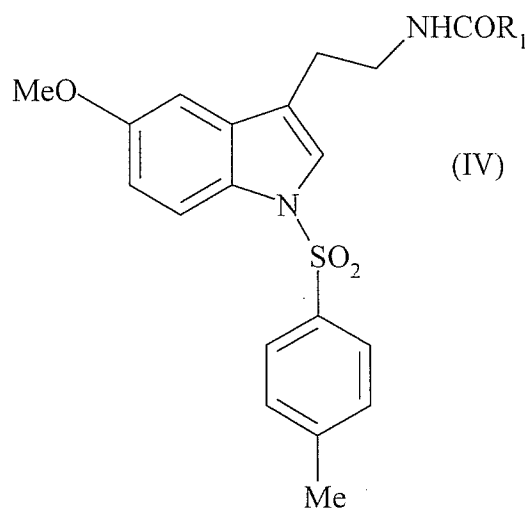


which is condensed with an acid chloride of formula R₁COCl, wherein R₁ is as defined for formula (I), or with the corresponding symmetrical anhydride to yield a compound of formula (III) :



wherein R₁ is as defined hereinbefore,

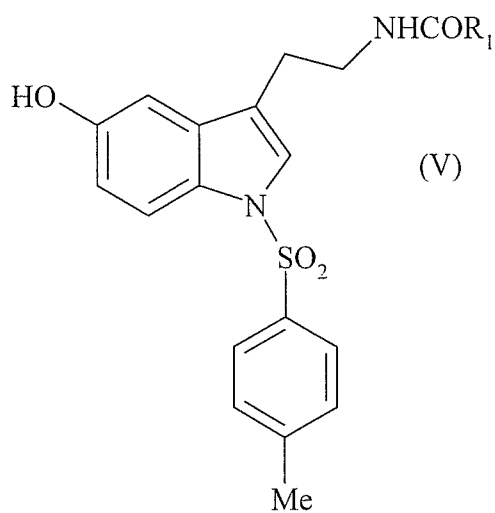
which is subjected in basic medium to the action of tosyl chloride to yield a compound of formula (IV) :



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wherein R₁ is as defined hereinbefore,

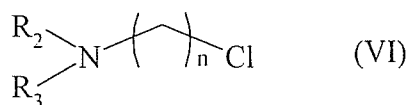
which is placed under demethylation conditions to yield a compound of formula (V) :



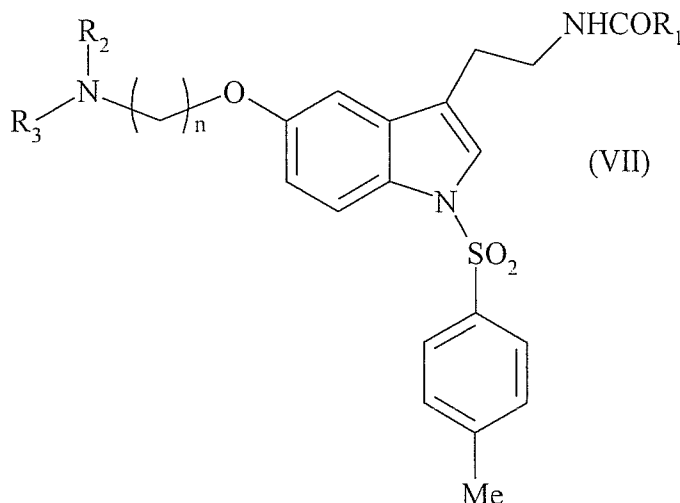
wherein R₁ is as defined hereinbefore,

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which is condensed with a compound of formula (VI) :



wherein R_2 , R_3 and n are as defined for formula (I),
to yield a compound of formula (VII) :



5 wherein R_1 , R_2 , R_3 and n are as defined hereinbefore,
which is subjected to the action of magnesium to yield a compound of formula (I),
which may be purified according to a conventional separation technique, is converted, if
desired, into addition salts with a pharmaceutically acceptable acid or base, and the
enantiomers of which may be separated on a chiral column according to a conventional
10 separation technique.

9- Pharmaceutical compositions comprising at least one compound of formula (I)
according to any one of claims 1 to 7 or an addition salt thereof with a pharmaceutically
acceptable acid or base in combination with one or more pharmaceutically acceptable
excipients.

15 **10-** Pharmaceutical compositions according to claim 9 for use in the manufacture of
 medicaments for treating disorders of the melatoninergetic system.

11- Pharmaceutical compositions according to claim 9 for use in the manufacture of
 medicaments for the treatment of sleep disorders, stress, anxiety, major depression or
 seasonal affective disorder, cardiovascular pathologies, pathologies of the digestive

system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, cerebral circulation disorders, and also in sexual dysfunction, as inhibitors of ovulation, immunomodulators, and in the treatment of cancers.