

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

The present invention relates to new naphthalene compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are new and have very valuable pharmacological characteristics relating to melatoninergetic receptors.

5 Numerous studies in the last ten years have demonstrated the key role of melatonin (N-acetyl-5-methoxytryptamine) in many physiopathological phenomena and in the control of circadian rhythms. Its half-life is quite short, however, owing to the fact that it is rapidly metabolised. Great interest therefore lies in the possibility of providing the clinician with melatonin analogues that are metabolically more stable, that have an agonist or antagonist
10 character and that may be expected to have a therapeutic effect that is superior to that of the hormone itself.

In addition to their beneficial action on 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
15 central nervous system, especially anxiolytic and antipsychotic properties (Neuropharmacology of Pineal Secretions, 1990, 8 (3-4), pp. 264-272) and analgesic properties (Pharmacopsychiat., 1987, 20, pp. 222-223) as well as 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). Those compounds have also demonstrated activity in
20 respect of certain cancers (Melatonin - Clinical Perspectives, Oxford University Press, 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).

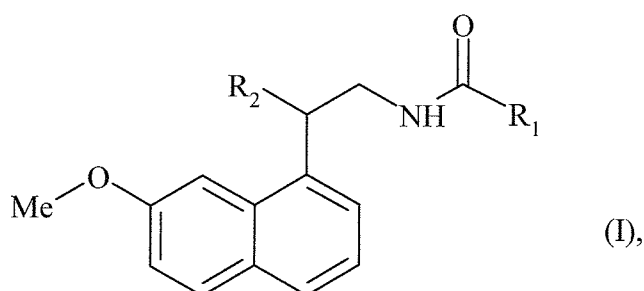
Those various effects are exerted *via* the intermediary of specific melatonin receptors.
25 Molecular biology studies have demonstrated the existence of a number of receptor subtypes that are capable of binding that hormone (Trends Pharmacol. Sci., 1995, 16, p. 50; WO 97.04094). For various species, including mammals, it has been possible for some of those receptors to be located and characterised. 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 other of those receptors, may be excellent medicaments for the clinician in the treatment of pathologies associated with the melatoninergetic system, some of which have been mentioned above.

Besides the fact that they are new, the compounds of the present invention exhibit a very strong affinity for melatonin receptors.

They moreover have a strong affinity for the 5-HT_{2C} receptor, which has the effect of reinforcing the properties observed in the case of melatoninergetic receptors, especially in the field of depression.

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



wherein:

R₁ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₁-C₆)alkenyl group, a linear or branched (C₁-C₆)haloalkyl group, a linear or branched (C₁-C₆)polyhaloalkyl group, a (C₃-C₈)cycloalkyl group, a (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl group in which the alkyl moiety may be linear or branched, an aryl group, an aryl-(C₁-C₆)alkyl group in which the alkyl moiety may be linear or branched, a heteroaryl group or a heteroaryl-(C₁-C₆)alkyl group in which the alkyl moiety may be linear or branched,

R₂ represents a fluorine atom or a linear or branched (C₁-C₆)alkyl group substituted by one or more fluorine atoms,

it being understood that:

- "aryl" means a phenyl, naphthyl or biphenyl group,
- "heteroaryl" means any mono- or bi-cyclic aromatic group containing from 1 to 3 hetero atoms selected from oxygen, sulphur and nitrogen,

5 it being possible for the aryl and heteroaryl groups so defined to be substituted by from 1 to 3 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, hydroxy, carboxy, formyl, nitro, cyano, linear or branched (C₁-C₆)haloalkyl, linear or branched (C₁-C₆)polyhaloalkyl, alkyloxycarbonyl and halogen atoms,

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

Among the pharmaceutically acceptable acids there may be mentioned by way of non-limiting example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid,
15 glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid etc..

Among the pharmaceutically acceptable bases there may be mentioned by way of non-limiting example sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc..

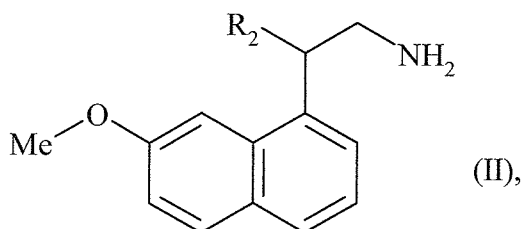
20 Preferred compounds of the invention are compounds of formula (I) wherein R₁ represents a linear or branched (C₁-C₆)alkyl group such as, for example, a methyl or ethyl group; or a (C₃-C₈)cycloalkyl group such as, for example, a cyclopropyl or cyclobutyl group; or a polyhaloalkyl group such as, for example, a fluoromethyl group.

The R₂ group advantageously represents a fluorine atom or a fluoromethyl group or a
25 1-fluoroethyl group.

The invention even more specifically relates to the compounds which are *N*-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]acetamide, *N*-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]-propanamide, *N*-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]cyclopropanecarboxamide, *N*-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]cyclobutanecarboxamide, *N*-[3-fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide, 2-fluoro-*N*-[3-fluoro-2-(7-methoxy-1-naphthyl)-propyl]acetamide and *N*-[4-fluoro-2-(7-methoxy-1-naphthyl)butyl]acetamide.

The addition salts of preferred compounds of the invention with a pharmaceutically acceptable base form an integral part of the invention.

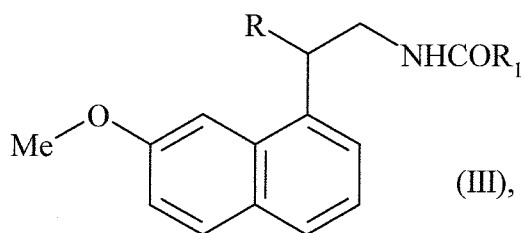
The invention relates also to a process for the preparation of the compound of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



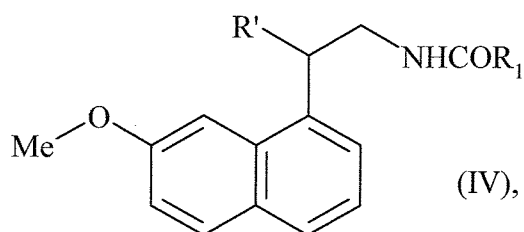
wherein R_2 is as defined for formula (I),

which is subjected to the action of the compound of formula $R_1\text{COCl}$, wherein R_1 is as defined for formula (I), to yield the compound of formula (I), which may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base, and which is separated, where appropriate, into its isomers according to a conventional separation technique.

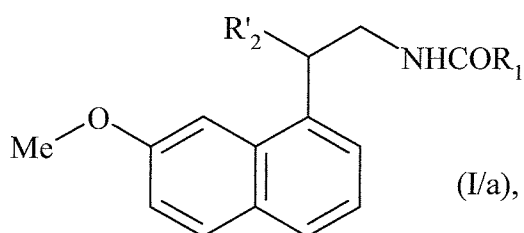
An advantageous embodiment relates to a process for the preparation of compounds of formula (I) wherein R_2 represents a linear or branched (C_1 - C_6)alkyl group substituted by one or more fluorine atoms, which process is characterised in that there is used as starting material the compound of formula (III):



wherein R_1 is as defined for formula (I) and R represents a linear or branched (C_1 - C_6)alkyl group substituted by one or more OH groups,
 which is subjected to the action of methanesulphonyl chloride to yield the compound of
 5 formula (IV):



wherein R_1 is as defined for formula (I) and R' represents a linear or branched (C_1 - C_6)alkyl group substituted by one or more OSO_2Me groups,
 which is subjected to the action of tetrabutylammonium fluoride to yield the compound of
 10 formula (I/a), a particular case of the compounds of formula (I):



wherein R'_2 represents a linear or branched (C_1 - C_6)alkyl group substituted by one or more fluorine atoms,
 which compounds of formula (I/a) may be purified according to a conventional separation
 15 technique, which are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base, and which are separated, where appropriate, into their isomers according to a conventional separation technique.

The compounds of formulae (II) and (III) are either commercially available or can be obtained by the person skilled in the art using conventional chemical reactions described in the literature.

Pharmacological study of the compounds of the invention has shown them to be atoxic, to
5 have strong selective affinity for melatonin receptors and to have significant activities in respect of the central nervous system; and, in particular, there have been found therapeutic properties in respect of sleep disorders, antidepressive, anxiolytic, antipsychotic and analgesic properties and properties in respect of microcirculation, enabling it to be established that the compounds of the invention are useful in the treatment of stress, sleep
10 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 and Alzheimer's
15 disease, and in cerebral circulation disorders. In another field of activity, it appears that, in treatment, the compounds of the invention can be used in sexual dysfunctions, that they have ovulation-inhibiting and immunomodulating properties and that they may potentially be used in the treatment of cancers.

The compounds will preferably be used in the treatment of major depression, seasonal
20 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
25 compound of formula (I) on its own or in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that 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,
5 creams, ointments, dermal gels, and drinkable or injectable ampoules.

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

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

10 **Example 1: N-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]acetamide**

Step A: 2-(7-Methoxy-1-naphthyl)ethyl methanesulphonate

2-(7-Methoxy-1-naphthyl)ethanol (25 mmol) and triethylamine (30 mmol) are dissolved in 50 ml of dichloromethane and the reaction mixture is cooled to 0°C using an ice bath. Mesyl chloride (30 mmol) is added dropwise and the reaction mixture is stirred at ambient
15 temperature for 2 hours and then poured into 100 ml of water. The organic phase is washed with 1M hydrochloric acid solution and then with water, dried over magnesium sulphate and evaporated. The oil obtained is precipitated from a mixture of diethyl ether/petroleum ether (1/1). The title product is filtered off under suction and then recrystallised from diisopropyl ether.

20 Melting point: 60-62°C

Step B: 7-Methoxy-1-vinylnaphthalene

The compound obtained in Step A (21.4 mmol) is dissolved in 120 ml of tetrahydrofuran, and potassium *tert*-butylate (64.2 mmol) is added in small portions. After stirring for 30 minutes at ambient temperature, the reaction mixture is evaporated to dryness. The

residue obtained is taken up in 150 ml of water and the aqueous phase is extracted twice with 60 ml of diethyl ether. The organic phase is washed with water, dried over magnesium sulphate, decolourised on vegetable carbon and evaporated. The residue obtained is purified on silica gel (eluant: petroleum ether) to yield the title product in the form of a yellow oil.

Step C: 1-(2-Bromo-1-fluoroethyl)-7-methoxynaphthalene

The compound obtained in Step B (5.4 mmol) is dissolved in 25 ml of dichloromethane, and then the resulting solution is cooled to 0°C using an ice bath. Triethylamine trihydrofluoride (16.3 mmol) and *N*-bromosuccinimide (6.5 mmol) are added. The reaction mixture is stirred for 30 minutes at 0°C and for 12 hours at ambient temperature. The reaction mixture is poured into ice-cold water, neutralised using 28 % ammonia solution and extracted with dichloromethane. The organic phase is washed with 0.1M hydrochloric acid solution, with 5 % sodium hydrogen carbonate solution and with water. The organic phase is dried over magnesium sulphate, and the solvent is evaporated off under reduced pressure. The residue obtained is purified by chromatography on silica gel (eluant: petroleum ether/dichloromethane 9/1) to yield the title product in the form of a brown oil.

Step D: 1-(2-Azido-1-fluoroethyl)-7-methoxynaphthalene

Sodium azide (15.3 mmol) is suspended in 10 ml of dimethylformamide, tetrabutylammonium bromide (200 mg) is added and the mixture is heated at 70°C for 30 minutes. The compound obtained in Step C, dissolved in 20 ml of dimethylformamide, is then added and the mixture is stirred at 70°C for 2 hours. At the end of the reaction, 40 ml of water are added and the aqueous phase is extracted 3 times using 60 ml of ether. The organic phase is then washed with 2M hydrochloric acid solution and then with water, is dried and is evaporated under reduced pressure to yield the title product in the form of a yellow oil.

Step E: 2-Fluoro-2-(7-methoxy-1-naphthyl)ethylamine hydrochloride

Aluminium chloride (80 mmol), dissolved in 200 ml of anhydrous ether, is added to a suspension of lithium aluminium hydride (80 mmol) at 0°C in 300 ml of anhydrous ether. After stirring for 10 minutes, the compound obtained in Step D (20 mmol), dissolved in 200 ml of anhydrous ether, is added. After 30 minutes, the mixture is hydrolysed, in the cold state and with caution, using sodium hydroxide solution (250 mmol). The inorganic precipitate formed is then filtered off and washed with copious amounts of ether. The residue obtained after evaporation is taken up in water and the aqueous phase is extracted with dichloromethane. The organic phase is then washed with water, dried and decolourised, and is then treated with gaseous HCl and evaporated. The oil obtained is precipitated from ethyl acetate and the precipitate formed is filtered off under suction and then recrystallised.

Step F: N-[2-fluoro-2-(7-methoxy-1-naphthyl)ethyl]acetamide

The compound obtained in Step E (20 mmol) is dissolved in a mixture of water/ethyl acetate (25 ml/75 ml) cooled to 0°C. Potassium carbonate (60 mmol) is added, and then acetyl chloride (26 mmol) is added dropwise to the reaction mixture. The mixture is stirred vigorously for 30 minutes at ambient temperature. The two phases are separated and the organic phase is washed with 0.1M aqueous hydrochloric acid solution and then with water. After drying over magnesium sulphate, the organic phase is evaporated under reduced pressure. The residue obtained is recrystallised from a mixture of toluene/cyclohexane (5/5) to yield the title product in the form of a white solid.

Melting point: 128-130°C

Elemental microanalysis:

	%	C	H	N
25	<i>Calculated:</i>	68.95	6.17	5.36
	<i>Found:</i>	68.40	6.14	5.19

Example 2: N-[2-Fluoro-2-(7-methoxy-1-naphthyl)ethyl]propanamide

The procedure is as in Example 1, replacing the acetyl chloride in Step F by propanoyl chloride. The title product, recrystallised from cyclohexane, is obtained in the form of a white solid.

5 Melting point: 139-141°C

Elemental microanalysis:

	%	C	H	N
Calculated:		69.80	6.59	5.09
Found:		69.80	6.71	5.12

10 **Example 3: N-[2-Fluoro-2-(7-methoxy-1-naphthyl)ethyl]cyclopropanecarboxamide**

The procedure is as in Example 1, replacing the acetyl chloride in Step F by cyclopropanoyl chloride. The title product, recrystallised from cyclohexane, is obtained in the form of a white solid.

Melting point: 115-117°C

15 Elemental microanalysis:

	%	C	H	N
Calculated:		71.06	6.31	4.87
Found:		70.91	6.21	4.68

Example 4: N-[2-Fluoro-2-(7-methoxy-1-naphthyl)ethyl]cyclobutanecarboxamide

20 The procedure is as in Example 1, replacing the acetyl chloride in Step F by cyclobutanoyl chloride. The title product, recrystallised from cyclohexane, is obtained in the form of a white solid.

Melting point: 112-114°C

Elemental microanalysis:

	%	C	H	N
Calculated:		71.74	6.69	4.65
Found:		71.66	6.78	4.51

5 **Example 5: N-[3-Fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide**

Step A: 3-Amino-2-(7-methoxy-1-naphthyl)-1-propanol hydrochloride

Aluminium chloride (80 mmol), dissolved in 200 ml of anhydrous ether, is added to a suspension of lithium aluminium hydride (80 mmol) at 0°C in 300 ml of anhydrous ether. After stirring for 10 minutes, methyl cyano(7-methoxy-1-naphthyl)acetate (20 mmol),
10 dissolved in 200 ml of anhydrous ether, is added. After 30 minutes, the mixture is hydrolysed, in the cold state and with caution, using sodium hydroxide solution (250 mmol). The inorganic precipitate formed is then filtered off and washed with copious amounts of ether. The residue obtained after evaporation is taken up in water and the aqueous phase is extracted with dichloromethane. The organic phase is then washed with
15 water, dried and decolourised, and is then treated with gaseous HCl and evaporated. The oil obtained is precipitated from ethyl acetate and the precipitate formed is filtered off under suction and then recrystallised from acetonitrile to yield the title product in the form of a white solid.

Melting point: 164-166°C

20 **Step B: N-[3-Hydroxy-2-(7-methoxy-1-naphthyl)propyl]acetamide**

The compound obtained in Step A (20 mmol) is dissolved in a mixture of water/ethyl acetate (25 ml/75 ml) cooled to 0°C. Potassium carbonate (60 mmol) is added, and then acetyl chloride (26 mmol) is added dropwise to the reaction mixture. The mixture is stirred vigorously for 30 minutes at ambient temperature. The two phases are separated and the
25 organic phase is washed with 0.1M aqueous hydrochloric acid solution and then with water. After drying over magnesium sulphate, the organic phase is evaporated under

reduced pressure. The residue obtained is recrystallised from acetonitrile to yield the title product in the form of a white solid.

Melting point: 136-138°C

Step C: 3-(Acetylamino)-2-(7-methoxy-1-naphthyl)propyl methanesulphonate

- 5 The compound obtained in Step B (10.9 mmol) is dissolved in 160 ml of dichloromethane, triethylamine (16.8 mmol) is added and the solution is cooled to 0°C using an ice bath. Methanesulphonyl chloride (16.8 mmol) is then added dropwise and the mixture is stirred at ambient temperature for 15 minutes. At the end of the reaction, the mixture is poured into water and the organic phase is washed with 0.5N hydrochloric acid solution, then with
10 5 % sodium hydrogen carbonate solution and with water. The organic phase is then dried and then evaporated in the cold state. The oil obtained after evaporation is precipitated from ether. The precipitate obtained is filtered off under suction but not recrystallised and yields the title product in the form of a white solid.

Melting point: 104-106°C

15 **Step D: N-[3-Fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide**

Tetrabutylammonium fluoride (25.6 mmol) is added to a solution of the compound obtained in Step C (8.5 mmol) in 20 ml of anhydrous tetrahydrofuran. The resulting solution is stirred at ambient temperature for 48 hours.

The reaction mixture is poured into water and extracted twice with 50 ml of diethyl ether.

- 20 The organic phase is dried over magnesium sulphate. The oil obtained after evaporating off the solvent is purified on silica gel (eluant: acetone/cyclohexane 4/6) to yield, after recrystallisation from cyclohexane, the title product in the form of a white solid.

Melting point: 87-89°C

Example 6: 2-Fluoro-N-[3-fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide

Step A: 3-Amino-2-(7-methoxy-1-naphthyl)-1-propanol hydrochloride

Aluminium chloride (80 mmol), dissolved in 200 ml of anhydrous ether, is added to a suspension of lithium aluminium hydride (80 mmol) at 0°C in 300 ml of anhydrous ether.

- 5 After stirring for 10 minutes, methyl cyano(7-methoxy-1-naphthyl)acetate (20 mmol), dissolved in 200 ml of anhydrous ether, is added. After 30 minutes, the mixture is hydrolysed, in the cold state and with caution, using sodium hydroxide solution (250 mmol). The inorganic precipitate formed is then filtered off and washed with copious amounts of ether. The residue obtained after evaporation is taken up in water and the
- 10 aqueous phase is extracted with dichloromethane. The organic phase is then washed with water, dried and decolourised, and is then treated with gaseous HCl and evaporated. The oil obtained is precipitated from ethyl acetate and the precipitate formed is filtered off under suction and then recrystallised from acetonitrile to yield the title product in the form of a white solid.

15 Melting point: 164-166°C

Step B: 2-Fluoro-N-[3-hydroxy-2-(7-methoxy-1-naphthyl)propyl]acetamide

The compound obtained in Step A (20 mmol) is dissolved in a mixture of water/ethyl acetate (25 ml/75 ml) cooled to 0°C. Potassium carbonate (60 mmol) is added, and then fluoroacetyl chloride (26 mmol) is added dropwise to the reaction mixture. The mixture is

20 stirred vigorously for 30 minutes at ambient temperature. The two phases are separated and the organic phase is washed with 0.1M aqueous hydrochloric acid solution and then with water. After drying over magnesium sulphate, the organic phase is evaporated under reduced pressure. The residue obtained is recrystallised from diisopropyl ether to yield the title product in the form of a white solid.

25 Melting point: 49-51°C

**Step C: 3-[(Fluoroacetyl)amino]-2-(7-methoxy-1-naphthyl)propyl
methanesulphonate**

The compound obtained in Step B (10.9 mmol) is dissolved in 160 ml of dichloromethane, triethylamine (16.8 mmol) is added and the solution is cooled to 0°C using an ice bath.

- 5 Methanesulphonyl chloride (16.8 mmol) is then added dropwise and the mixture is stirred at ambient temperature for 15 minutes. At the end of the reaction, the mixture is poured into water and the organic phase is washed with 0.5N hydrochloric acid solution, then with 5 % sodium hydrogen carbonate solution and with water. The organic phase is then dried and then evaporated in the cold state. The oil obtained after evaporation is precipitated
- 10 from ether. The precipitate obtained is filtered off under suction but not recrystallised and yields the title product in the form of a white solid.

Melting point: 122-124°C

Step D: 2-Fluoro-N-[3-fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide

- 15 Tetrabutylammonium fluoride (25.6 mmol) is added to a solution of the compound obtained in Step C (8.5 mmol) in 20 ml of anhydrous tetrahydrofuran. The resulting solution is stirred at ambient temperature for 48 hours.

The reaction mixture is poured into water and extracted twice with 50 ml of diethyl ether. The organic phase is dried over magnesium sulphate. The oil obtained after evaporating off the solvent is purified on silica gel (eluant: acetone/cyclohexane 4/6) to yield, after

20 recrystallisation from diisopropyl ether, the title product in the form of a white solid.

Melting point: 82-84°C

Example 7: N-[4-Fluoro-2-(7-methoxy-1-naphthyl)butyl]acetamide

- The compound is obtained starting from methyl 2-cyano-2-(7-methoxy-1-naphthyl)propanoate in accordance with the procedure described in Steps A to D of
- 25 Example 5.

Melting point: 81-82°C

PHARMACOLOGICAL STUDY

EXAMPLE A : Acute toxicity study

5 The acute toxicity was evaluated after oral administration to groups each comprising 8 mice (26 ± 2 g). 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

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

The apparatus is composed of a plexiglass 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. The animal is
15 considered to be immobile when it stops struggling and remains immobile on 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 antidepressant 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.

- 5 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 of the compounds tested (K_i) to be determined.

The K_i values found for the compounds of the invention accordingly demonstrate binding to one or other of the melatonergic binding sites, those values being $\leq 10\mu\text{M}$.

- 10 By way of example, the compound obtained in Example 5 has a $K_i(\text{MT}_1)$ of 0.1nM and a $K_i(\text{MT}_2)$ of 0.2nM.

EXAMPLE D : Serotonergic 5-HT_{2C} receptor binding study

The affinity of the compounds for the human 5-HT_{2C} receptor is evaluated on membrane preparations from CHO cells stably expressing that receptor.

- 15 Incubation is carried out in 50mM TRIS buffer, pH 7.4, containing 10mM MgCl₂ and 0.1 % BSA, in the presence of [³H]-mesulergine (1nM) and 25 fmol/ml of receptor. Non-specific binding is determined in the presence of 10 μM mianserin.

- The reaction is stopped by the addition of 50mM TRIS buffer, pH 7.4, followed by a filtration step and 3 successive rinses: the radioactivity bound to the membranes remaining
20 on the filters (GF/B pretreated with 0.1 % PEI) is determined by liquid scintillation counting.

The results obtained show that the compounds of the invention have affinity for the 5-HT_{2C} receptor, with K_i values $< 10\mu\text{M}$.

By way of example, the compound of Example 5 has a $K_i(5\text{-HT}_{2C})$ of 6 μM .

EXAMPLE E : 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 of physiological, biochemical and behavioural circadian rhythms has made it possible to
5 establish a pharmacological model for use in the search for melatoninerbic 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.

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

Experiment protocol

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

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

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

Two to three weeks later, when free running (rhythm reflecting that of the endogenous
20 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 rhythms of activity:

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

A software package makes it possible:

- 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

The compounds of the invention clearly appear to allow powerful action on the circadian
5 rhythm *via* the melatoninergetic system.

EXAMPLE F : Light/dark cages test

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

The apparatus consists of two polyvinyl boxes covered with plexiglass. One of the boxes is
10 in darkness. A lamp is placed above the other box, yielding a light intensity of approximately 4000 lux in the centre of the box. An opaque plastic 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 is placed in the tunnel, facing the dark box. The time spent by the mouse in the illuminated
15 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 and the number of passages through the tunnel, which demonstrates the anxiolytic activity
20 of the compounds of the invention.

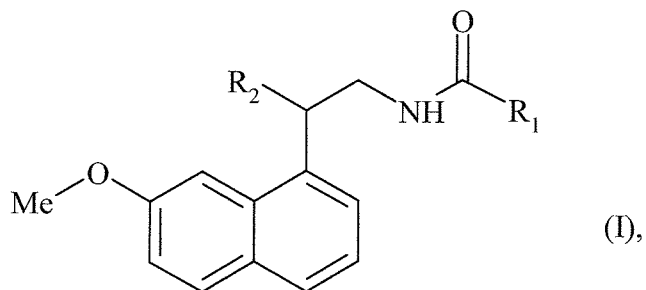
EXAMPLE G : Pharmaceutical composition : Tablets

1000 tablets each containing a dose of 5 mg of *N*-[3-fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide (Example 5) 5 g
Wheat starch 20 g
25 Maize starch..... 20 g

Lactose.....	30 g
Magnesium stearate	2 g
Silica	1 g
Hydroxypropylcellulose	2 g

CLAIMS

1- Compounds of formula (I):



wherein:

- 5 R_1 represents a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_1-C_6) alkenyl group, a linear or branched (C_1-C_6) haloalkyl group, a linear or branched (C_1-C_6) polyhaloalkyl group, a (C_3-C_8) cycloalkyl group, a (C_3-C_8) cycloalkyl- (C_1-C_6) alkyl group in which the alkyl moiety may be linear or branched, an aryl group, an aryl- (C_1-C_6) alkyl group in which the alkyl moiety may be linear or branched, a heteroaryl group or a heteroaryl- (C_1-C_6) alkyl group in which the alkyl moiety may be linear or branched,
- 10

R_2 represents a fluorine atom or a linear or branched (C_1-C_6) alkyl group substituted by one or more fluorine atoms,

it being understood that:

- 15 - "aryl" means a phenyl, naphthyl or biphenyl group,
- "heteroaryl" means any mono- or bi-cyclic aromatic group containing from 1 to 3 hetero atoms selected from oxygen, sulphur and nitrogen,
- it being possible for the aryl and heteroaryl groups so defined to be substituted by from 1 to 3 groups selected from linear or branched (C_1-C_6) alkyl, linear or branched

(C₁-C₆)alkoxy, hydroxy, carboxy, formyl, nitro, cyano, linear or branched (C₁-C₆)haloalkyl, linear or branched (C₁-C₆)polyhaloalkyl, alkyloxycarbonyl and halogen atoms,

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

2- Compounds of formula (I) according to claim 1, wherein R₂ represents a fluorine atom, their enantiomers and diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable base.

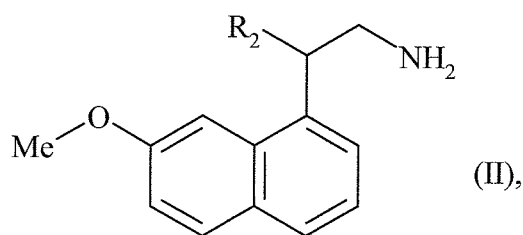
10 3- Compounds of formula (I) according to claim 1, wherein R₂ represents a linear or branched (C₁-C₆)haloalkyl group, their enantiomers and diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable base.

4- Compounds of formula (I) according to claim 3, wherein R₂ represents a fluoromethyl group or a 1-fluoroethyl group, their enantiomers and diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable base.

15 5- Compound of formula (I) according to claim 1, which is *N*-[3-fluoro-2-(7-methoxy-1-naphthyl)propyl]acetamide, and also addition salts thereof with a pharmaceutically acceptable base.

20 6- Compound of formula (I) according to claim 1, which is *N*-[4-fluoro-2-(7-methoxy-1-naphthyl)butyl]acetamide, and also addition salts thereof with a pharmaceutically acceptable base.

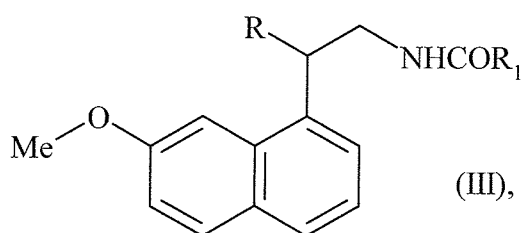
7- Process for the preparation of the compound of formula (I) according to claim 1, characterised in that there is used as starting material the compound of formula (II):



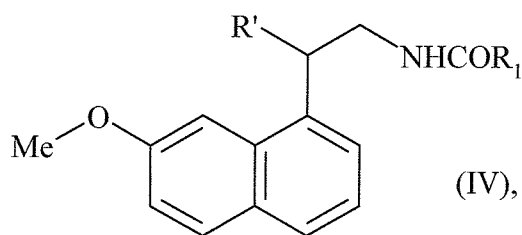
wherein R_2 is as defined in claim 1,

which is subjected to the action of the compound of formula R_1COCl , wherein R_1 is as defined in claim 1, to yield the compounds of formula (I), which may be purified according to a conventional separation technique, which are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base, and which are separated, where appropriate, into their isomers according to a conventional separation technique.

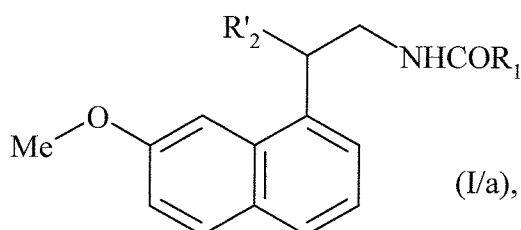
8- Process for the preparation of compounds of formula (I) according to claim 1 wherein R_2 represents a linear or branched (C_1-C_6) alkyl group substituted by one or more fluorine atoms, characterised in that there is used as starting material the compound of formula (III):



wherein R_1 is as defined in claim 1 and R represents a linear or branched (C_1-C_6) alkyl group substituted by one or more OH groups, which is subjected to the action of methanesulphonyl chloride to yield the compound of formula (IV):



wherein R_1 is as defined hereinbefore and R' represents a linear or branched (C_1-C_6) alkyl group substituted by one or more OSO_2Me groups,
 which is subjected to the action of tetrabutylammonium fluoride to yield the compound of
 5 formula (I/a), a particular case of the compounds of formula (I):



wherein R'_2 represents a linear or branched (C_1-C_6) alkyl group substituted by one or
 more fluorine atoms,

10 which compounds of formula (I/a) may be purified according to a conventional separation
 technique, which are converted, if desired, into addition salts thereof with a
 pharmaceutically acceptable acid or base, and which are separated, where appropriate,
 into isomers thereof according to a conventional separation technique.

9- Pharmaceutical compositions comprising at least one compound of formula (I)
 15 according to any one of claims 1 to 6 or an addition salt thereof with a pharmaceutically
 acceptable base in combination with one or more pharmaceutically acceptable
 excipients.

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

- 5 **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 or sexual dysfunctions, as ovulation-inhibitors or immunomodulators, or for the treatment of cancers.