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Synthesis of β-Substituted Naphth-1-yl Ethylamido Derivatives as New Melatoninergic Agonists

Monique Mathé-Allainmat, Marie Le Gall, Carole Jellimann, Jean Andrieux and Michel Langlois*

CNRS-BIOCIS (UPRES A 8076), Université de Paris-Sud, Faculté de Pharmacie, 5 rue J. B. Clément, 92296, Châtenay-Malabry, France

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Abstract—Naphthalene melatoninergic ligands with alkyl groups (Me, Et, Pr, Bz) in the β position of the ethylamido chain were synthesised. The affinity of the compounds for chicken brain melatonin receptors was evaluated using 2-[^{125}I]-iodomelatonin as the radioligand. An increase in the affinity was observed with the β-methyl derivatives and the greatest increase was seen with the (−) enantiomers. The introduction of a 2- or 7-MeO group on the naphthalene ring and the lengthening (Et, Pr) of the alkylamido chain gave potent compounds such as (−)**1h** ($K_i = 24$ pM). The functional activity of these compounds was evaluated by the aggregation of melanophores in *Xenopus laevis* tadpoles. The potency to produce lightening of the skin of *Xenopus laevis* was related to the affinities values of the molecules at melatonin chicken brain receptors. The most potent ligands were found to be full agonists and compound **1h** was 25 fold more potent than melatonin in this bioassay.

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone secreted during darkness.[1] It is now well recognised that it regulates the circadian rhythm[2] in a large number of animals and in man. It can be used to control diseases associated with circadian rhythm disorders.[3] Melatonin alleviates jet-lag, regulates delayed sleep phase syndrome[4] and induces sleep.[5] Conversely, it has been implicated in seasonal and winter depression.[6] Melatonin controls the breeding cycle in photoperiodic species and can be used to induce reproduction outside of the breeding season.[7] Melatonin has also been reported to have antiproliferative effects on mammary cell lines.[8]

It has been demonstrated that a number of the effects of melatonin are mediated through G protein-coupled receptors[9] which have been cloned[10] and coupling to one of the G_i family of G-proteins appears to be the common signalling pathway for the receptors characterised to date.[11] Recently, considerable interest has evolved in the search for new molecules capable of mimicking or antagonising the response to melatonin.[12,13] In particular, naphthalene derivatives were designed as bioisosteric melatonin compounds[14] and several of these, such as agomelatine (S 20098), were claimed to control circadian rhythm disorders.[15] Naphthalene melatoninergic ligands were structurally characterised by the position of the methoxy group which can occupy the melatonin-like position 7 or be located in the *ortho* position of the ethylamido chain.[16]

To date, few data on the influence of substitution of the ethylamido flexible chain have been reported: the unfavourable effect of the α-methyl group was noted in the naphthalene[16] and indole[17] derivatives, while an increase in anti-ovulatory activity with regard to melatonin was demonstrated with β-methyl 6-chloromelatonin and a marked affinity for melatonin receptors was demonstrated with the β-methyl 2-phenyltryptamine derivatives.[18] We report herein the results of preliminary structure–activity relationship studies on the influence of β-alkyl substitution and the corresponding chirality on the ethyl chain of the naphthalene melatonergic derivatives **1**, **10** and **11** which were evaluated by their affinity for chicken brain melatonin receptors and compared to the reference compounds, melatonin and agomelatine (S 20098). Their functional activity on melatonin receptors was evaluated by examining the potency of the compounds to lighten the skin

Key words: Melatonin; receptors; *N*-(2-methyl-2-(7-methoxy-naphth-1-yl)ethyl) butyramide; melanophore; agonist.

* Corresponding author. Tel.: +33-1-4-683-5738; fax: +33-1-4683-5740; e-mail: michel.langois@cep.u.psud.fr

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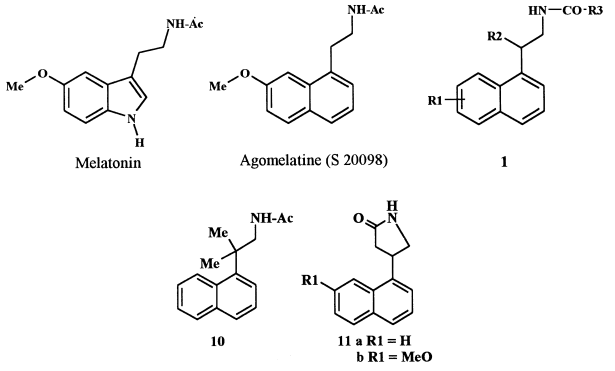
of *Xenopus laevis* tadpoles as it has been clearly demonstrated that melatonin mediates the aggregation of melanophores.[19,20] The degree of the dispersion of melanophores on the head and dorsal surface of the tadpoles observed under a microscope can be assessed using the melanophore index scale (1–5) of Hogben and Slome[21] and a concentration–effect curve (5 concentrations) can be plotted. The potency of each compound was expressed as the EC_{50} melatonin/EC_{50} compound ratio evaluated in the same experiment.



Chemistry

The compounds were synthesised according to the chemical pathway described in Scheme 1. Cyano derivatives **4a–c** were prepared (method A) by the reaction of TosMIC with the ketones **3a–c** in DME in the presence of *t*-BuOK while compounds **4d**, **5a** and **6a** were prepared by the alkylation of the corresponding cyano derivative **2** with methyl iodide or benzyl bromide in the presence of NaH in DMF at room temperature (method B). The monosubstituted cyano derivatives were isolated with moderate to good yields. Compounds **4a–d**, **5a** and **6a** were reduced to the amines **7a–d**, **8a**, **9a** by hydrogen at atmospheric pressure in the presence of Raney nickel in EtOH. The amines were acylated by the anhydride method (method C) or by the reaction of acyl chloride (method D) in the presence of Et_3N according to the processes already reported[16] to provide the compounds **1** (Table 1). For the purpose of comparison, the β,β′-dimethyl derivative **10** and compounds **11a–b** where the β-methyl ethylacetamido chain was introduced into the 2-pyrrolidone ring, were synthesised. Compound **10** was prepared by the double alkylation of **2** (Ar = naphth-1-yl) with methyl iodide. Compound **11a–b** were synthesised

Table 1. Biological data of compounds **1**,**10** and **11** for chicken brain melatonin receptors and *Xenopus laevis* melanophores

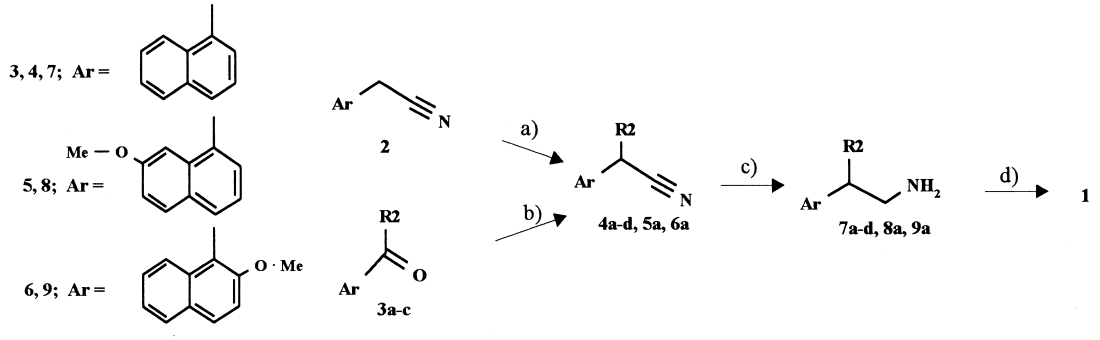
Compound	R1	R2	R3	[a]K_i (nM)	[b]*Xenopus* melanophores,[c] potency with regard to melatonin (=1)
1a	H	H	Me	321[290-370]	[d]NT
(±)**1b**	H	Me	Me	73[30-175]	[e]inactive
(±)**1b**	H	Me	Me	>1000	[d]NT
(−)**1b**	H	Me	Me	32[18-55]	[e]inactive
1c	H	Et	Me	130[82-206]	[e]inactive
1d	H	*n*-Pr	Me	96[64-147]	0.005(100%)
1e	H	Bz	Me	>1000	[d]NT
1f	7-MeO	Me	Me	0.16[0.12-0.22]	8 (100%)
1g	7-MeO	Me	Et	0.25 [0.16-0.38]	25 (100%)
(±)**1h**	7-MeO	Me	*n*-Pr	0.032 [0.021-0.047]	26 (100%)
(+)**1h**	7-MeO	Me	*n*-Pr	0.13 [0.055-0.31]	[d]NT
(−)**1h**	7-MeO	Me	*n*-Pr	0.024 [0.011-0.042]	[d]NT
1i	7-MeO	H	*n*-Pr	0.146[0.10-0.211]	[d]NT
1j	2-MeO	H	Me	2.68 [2-4.2]	0.4 (100%)
1k	2-MeO	Me	Me	1.23 [0.95-1.6]	0.4 (100%)
10				29[24-34]	[e]inactive
11a				>1000	[d]NT
11b				>1000	[d]NT
Agomelatine				0.53 [0.41-0.67]	0.8 (100%)
Melatonin				0.67 [0.41-0.67]	1 (100%)

[a] 2-[^{125}I]-iodomelatonin was used as the radioligand and the binding assays were carried out using membranes prepared from chicken brain. Non-specific binding was defined with 10 μM 2-iodomelatonin in melatonin and represented about 10% of the total binding. K_i values are expressed in nM and were calculated using the Cheng-Prussof equation from the IC_{50} values (PRISM software package), 95% limits are in brackets.

[b] *Xenopus laevis* tadpoles were placed in groups of 5 in 100 mL beakers. The compounds under test (5 concentrations) were dissolved in a final volume of 5 mL and added to the beaker. The degree of the melanophore response was determined by examination of the head and body surface using the melanophore index scale (1–5) of Hogben and Slome (reference 20). EC_{50} values were determined using PRISM and are the result of 2 separate experiments.

[c] The potency of the molecules was calculated as the EC_{50} melatonin/EC_{50} compound ratio determined in the same experiment. % represents the percentage of the maximum effect observed with regard to that of melatonin (100%).

[d] Not tested.



R2 **a** = Me; **b** = Et; **c** = n-Pr; **d** = Bz

Scheme 1. (a) MeI or BzBr, HNa, DMF, r.t., 1 h; (b) TosMIC, *t*-BuOK, DME, r.t.; (c) H_2, r.t., Raney Ni; (d) Ac_2O, AcONa, H_2O or R_3COCl, Et_3N, CH_2Cl_2, r.t.

according to the process already described for the 2-pyrrolidones.[19,20] Nitriles **2** (Ar = naphth-1-yl or 7-methoxy-naphth-1-yl) were alkylated with ethyl bromoacetate and then reduced with hydrogen in the presence of Raney nickel and aqueous ammoniac to give compounds **11a** and **11b** respectively. The different intermediates were characterised by their NMR spectra and thin layer chromatography. The new compounds **1**, **10** and **11** were characterised by NMR spectra and microanalysis. The (+) and (−) enantiomers of compounds **1b** and **1h** were isolated by semi-preparative enantiomeric HPLC separation using the CHIROS-BOND[22,23] column, containing a chiral stationary phase made with β-cyclodextrin linked to functionalised silica. Enantiomeric separation was achieved using a hexane/AcOEt/EtOH mobile phase. The enantiomers, obtained with a high enantiomeric purity (>99%), were characterised by their optical rotations: **1b** ($\alpha_D = +45°$ and $\alpha_D = -45°$, $c = 0.2$ in MeOH) and **1h** ($\alpha_D = +60°$ and $\alpha_D = -50°$, $c = 0.3$ in MeOH).

Results and Discussion

The affinity (K_i) of compounds **1**, **10** and **11** for chicken brain melatonin receptors was evaluated in binding assays using 2-[^{125}I]-iodomelatonin according to the method already described.[16] This assay was not predictive for the selectivity of the compounds as all melatonin receptors subtypes, mt_1, MT_2 and Mel_{1C}[24] are present in the chicken brain. The compounds were evaluated as agonists by the aggregation of the melanophores of *X. laevis* and the potency was expressed with regard to that of melatonin (= 1).

The results (Table 1) demonstrated, first, that the introduction of marked steric constraints in the ethylacetamido chain, as in compounds **11a** and **11b**, was not favourable because these compounds were inactive. These data also indicate that the *cis* orientation of the amide group was probably unfavourable for the fit with the binding site of the melatonin receptor. On the other hand, the presence of a methyl group (compound **1b**) in the β position of the ethylacetamido chain of **1a** ($K_i = 321$ nM) produced a clear increase in the affinity for melatonin receptors. The (−) enantiomer of **1b** was one order of magnitude more potent ($K_i = 32$ nM), while the effect of the ethyl and propyl substituents (compounds **1c** and **1d**) seemed to be less marked ($K_i = 130$ and $K_i = 96$ nM for the racemic mixtures, respectively). However, the introduction of a benzyl group at this position (compound **1e**) greatly reduced the affinity, indicating the limits of the favourable influence of steric factors in this domain of the receptor. β-Methyl substitution of the potent melatoninergic naphthalene compound, agomelatine (S 20098) and the corresponding 2-methoxy derivative **1j** gave compounds **1f** and **1k** ($K_i = 0.16$ nM and $K_i = 1.23$ nM, respectively). Their affinities were similar to those of the parent compounds, but with a small improvement for the β-methyl substituted compounds. This point was confirmed with the derivatives **1g** (R_3 = Et) and **1h** (R_3 = *n*-Pr) which resulted from the lengthening of the amido chain by ethyl and propyl groups, respectively. They were potent melatonin receptor ligands. In particular, (−) **1h** was one of the most potent compounds ($K_i = 24$ pM with regard to a $K_i = 146$ pM for the corresponding unsubstituted compound **1i**) synthesised by us.

The results obtained with the enantiomers of **1b** and **1h** indicated that they could not be correlated with the classical eudismic-affinity analysis rules because the enantioselectivity of melatonin receptors was more marked for **1b** than for the very potent compound, **1h**. This point was supported by the high enantiomeric purity of (+) **1h** which was not contaminated with the (−) enantiomer (<0.1%). However, these results confirmed the enantioselectivity of the melatonin receptor already observed for the partially constrained tricyclic indoles with a β chiral center.[25,26] On the other hand, the affinity of the β,β′-dimethyl derivative **10** ($K_i = 29$ nM), which was equipotent to (−) **1b** was unexpected. It was important to evaluate the selectivity of the molecules for the cloned human receptors mt_1 and MT_2. Preliminary results indicated that the compounds were not selective for the receptors expressed in HEK 293 cells[27] (**1f**, $IC_{50} = 0.053$ and 0.23 nM; **1b**, $IC_{50} = 7.4$ and 4.1 nM for mt_1 and MT_2 receptors, respectively).

The compounds **1f**, **1g**, (±) **1h**, (−)**1h**, **1k** with high affinity for chicken brain melatonin receptors were characterised as potent full agonists (Table 1) in the *X. laevis* melanophore assay and the potency of the compounds as agonists was correlated to their affinity for melatonin receptors. It is worth noting that **1g** and **1h** were 25-fold more potent than melatonin. These data indicate that the introduction of the β-methyl substitution on the ethyl amido chain does not influence the activation process of the receptor by the agonists, thus **1f** and **1k** were practically equipotent to agomelatine and to the 2-methoxy analogue **1j**. As has been shown previously, the lack of the 7-methoxy group brought about an important decrease in the efficacy, EC_{50} values could not be determined for (±) **1b**, (−)**1b**, **1c** and **10**, at 1 μM concentration, no activity on the lightening of the skin of *X. laevis* can be observed. In summary, the data reported here have shown that, in contrast to α substitution, introduction of β-methyl substitution on the ethylamido chain is a favourable steric parameter for recognition by melatonin receptors. In addition, the pharmacological profile of the compounds was not modified as several melatonin receptor full agonists, equipotent to the unsubstituted compounds were obtained.

Experimental

Melting points were determined on a KOFLER 7841 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a BRUCKER AC 200 or an AM 400 spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) in δ units. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), m (multiplet) and br (broad). Coupling constants are in Hertz. TLC was

performed on Silica Gel 60 F254 (Merck) with detection by UV light. Preparative chromatography was performed at atmospheric pressure with SDS Chromagel Silica 60, 70–200 mesh. All solvents and reagents were reagent grade unless otherwise noted. Elemental analyses were performed at the CNRS microanalysis service in Châtenay-Malabry (France). Starting materials and reactants were purchased from Aldrich-Chimie (Strasbourg). (Naphth-1-yl) ethylketone (**3b**) and (naphth-1-yl) propylketone (**3c**) were synthesised in methylene chloride according to the Friedel–Craft reaction.[28] The following cyano compounds **2**: 2-(naphth-1-yl) acetonitrile, 2-(2-methoxy-naphth-1-yl) acetonitrile and 2-(7-methoxy-naphth-1-yl) acetonitrile were synthesised according to the process reported elsewhere.[14,16] *N*-(2-(naphth-1-yl)ethyl) acetamide **1a**, *N*-(2-(7-methoxy-naphth-1-yl)ethyl) butyramide **1i**, *N*-(2-(2-methoxy-naphth-1-yl) ethyl) acetamide **1j** were synthesised according to the methods already reported.[14,16]

Synthesis of 2-(naphth-1-yl) alkylnitriles 4a–d, 5, 6.

Method A

2-(Naphth-1-yl) propionitrile (4a). A solution of acenaphtone (**1g**, 5.58 mmol) and TosMIC (2.29 g, 11.75 mmol) in 25 mL of 1,2-dimethoxy ethane (DME) was stirred at 0°C under nitrogen and a *t*-BuOK (1.65 g, 14.7 mmol) suspension in *t*-BuOH (14 mL) was added dropwise. The mixture was stirred for 15 min at 0°C and then for 20 h at room temperature under nitrogen. The solution was filtered and the organic solution was washed successively with a AcOH:H_2O mixture (4:100), water and a saturated $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was distilled ($Eb_{0.01}$: 110°C) to give 0.87 g (yield: 82%) of nitrile **4a** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96–7.83 (m, 3H, H_{ar}), 7.71 (d, 1H, H_{ar}), 7.64–7.46 (m, 3H, H_{ar}), 4.63 (q, 1H, CH), 1.79 (d, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 134.98, 133.64, 130.77 (C_{10}, C_9, C_1), 130.28, 129.91 (C_5, C_4), 127.90, 127.09, 126.53, 125.66 (C_8, C_7, C_6, C_3), 123.05 (C_2), 122.78 (CN), 29.21 (CH), 21.54 (CH_3).

2-(Naphth-1-yl) butyronitrile (4b). It was synthesised according to the previous method from (naphth-1-yl) ethylketone **3b** (1.84 g, 10 mmol), TosMIC (3.9 g, 20 mmol) and *t*-BuOK (3 g, 26 mmol). The compound was purified by column chromatography (silica gel) and eluted with Et_2O:petroleum ether (10:90). 0.66 g of **4b** was obtained as an oil (yield: 35%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, 1H, H_{ar}), 7.89 (d, 1H, H_{ar}), 7.84 (d, 1H, H_{ar}), 7.68 (d, 1H, H_{ar}), 7.6–7.57 (m, 2H, H_{ar}), 7.48 (t, 1H, H_{ar}), 4.51 (dd, 1H, CH), 2.08 (m, 2H, CH_2), 1.17 (t, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 133.80 (C_{10}), 132.15 (C_1), 129.85 (C_9), 129.17 (C_4), 128.75 (C_5), 126.69 (C_2), 125.92 (C_7), 125.44 (C_6), 125.27 (C_3), 121.95 (C_8), 120.83 (CN), 35.79 (CH), 27.92 (CH_2), 11.69 (CH_3).

2-(Naphth-1-yl) valeronitrile (4c). It was synthesised according to the previous method from (naphth-1-yl) propylketone **3c** (1.98 g, 10 mmol), TosMIC (3.9 g, 20 mmol) and *t*-BuOK (**3g**, 26 mmol). The compound was purified by column chromatography (silica gel) eluting with Et_2O:petroleum ether (10:90). 0.76 g of **4c** was obtained as an oil (yield: 35%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, 1H, H_{ar}), 7.89 (d, 1H, H_{ar}), 7.83 (d, 1H, H_{ar}), 7.69 (d, 1H, H_{ar}), 7.6–7.56 (m, 2H, H_{ar}), 7.48 (t, 1H, H_{ar}), 4.55 (t, 1H, CH), 1.99 (m, 2H, CH_2CH), 1.69 (m, 2H, CH_2CH_3), 1.03 (t, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 133.83 (C_{10}), 132.12 (C_1), 129.81 (C_9), 129.15 (C_4), 128.69 (C_5), 126.68 (C_2), 125.91 (C_7), 125.63 (C_6), 125.30 (C_3), 121.95 (C_8), 121.91 (CN), 36.59 (CH), 34.0 (CH_2CH), 20.57 (CH_2CH_3), 13.30 (CH_3).

Method B

2-(Naphth-1-yl)-3-phenyl propionitrile (4d). A solution of 2-(naphth-1-yl)acetonitrile (3 g, 18 mmol) in 25 mL of DMF was added dropwise to a 60% suspension of NaH in oil (0.65 g, 21.6 mmol). The mixture was stirred for 30 min at room temperature, benzyl bromide (2.4 mL, 18 mmol) in DMF was slowly added and the mixture was stirred for 1 h. The organic solution was poured into 200 mL cold water and the mixture was extracted with methylene chloride. The organic solution was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The compound was purified by column chromatography (silica gel) and eluted with ether, 4 g of **4d** were obtained as an oil (yield: 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9–7 (m, 12H, H_{ar}), 4.65 (q, 1H, CH), 3.2 (m, 2H, CH_2); ^{13}C NMR (200 MHz, $CDCl_3$): δ 136.78, 134.21, 130.57, 130.39, 130.03, 129.63, 128.89, 127.67, 127.23, 126.33, 126.13, 125.62, 122.09 (16 C_{ar}), 120.80 (CN), 41.02 (CH_2), 37.04 (CH).

2-(7-Methoxy-naphth-1-yl) propionitrile (5a). It was synthesised according to the previous process from (7-methoxy-naphth-1-yl) acetonitrile (2 g, 10.15 mmol), methyl iodide (1.44 mL, 10.15 mmol) and a 60% suspension of NaH (0.49 g, 12.18 mmol) in oil. It was purified by column chromatography (silica gel) and eluted with Et_2O. The compound was isolated as a colorless oil (1.8 g, yield: 84%) which crystallised slowly, mp: 70–72°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (t + d, 2H, H_{ar}), 7.63 (d, 1H, H_{ar}), 7.37 (d, 1H, H_{ar}), 7.25–7.18 (t + s, 2H, H_{ar}), 4.54 (q, 1H, CH), 3.95 (s, 3H, OCH_3), 1.79 (d, 3H, CH_3).

2-(2-Methoxy-naphth-1-yl) propionitrile (6a). It was synthesised according to the previous process from (2-methoxy-naphth-1-yl) acetonitrile (1 g, 5.07 mmol), methyl iodide (0.875 g, 6.08 mmol) and a 60% suspension of NaH (0.245 g, 6.08 mmol) in oil. It was purified by column chromatography (silica gel) and eluted with an Et_2O:petroleum ether mixture (20:80) and was isolated as a white amorphous product (0.65 g, yield: 61%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.09 (d, 1H, H_{ar}), 7.84 (2d, 2H, H_{ar}), 7.58 (t, 1H, H_{ar}), 7.40 (t, 1H, H_{ar}), 7.28 (d, 1H, H_{ar}), 4.95 (q, 1H, CH), 3.97 (s, 3H, OCH_3), 1.73 (d, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 154.29, 134.19, 130.46, 129.53, 129.22, 127.39, 123.86, 122.28 (8C, C_{ar}), 117.52 (CN), 113.46, 103.39 (2C, C_{ar}), 56.70 (OCH_3), 21.80 (CH), 18.62 (CH_3).

Synthesis of the arylalkylamines 7a–d, 8a, 9a, 2-(naphth-1-yl) propanamine, HCl (7a). 2-(naphth-1-yl) propionitrile **4a** (0.5 g, 2.76 mmol) was dissolved in 10 mL of EtOH with 0.1 mL of aqueous ammoniac (20%) in the

presence of Raney nickel (100 mg). The suspension was stirred under hydrogen at atmospheric pressure for 20 h at 40°C. The solution was filtered on Celite and the solvent was evaporated under reduced pressure. The crude material was dissolved in diethyl ether and an anhydrous HCl diethyl ether solution was added. The hydrochloride salt formed was collected by filtration and dried in vacuo, 0.37 g of **7a** was obtained as a white powder (yield: 72%). ^{1}H NMR (200 MHz, CD_3OD): δ 8.12 (d, 1H, H_{ar}), 7.85–7.72 (m, 2H, H_{ar}), 7.55–7.40 (m, 4H, H_{ar}) 4.03–3.93 (m, 1H, CH), 3.37–3.13 (m, 2H, NCH_2), 1.42 (d, 3H, CH_3); ^{13}C NMR (200 MHz, CD_3OD): δ 139.26, 135.81, 132.77 ($3C_{ar}$, C_{10}-C_9-C_1), 130.30, 129.02, 127.68, 126.98, 126.84, 124.21, 123.60 ($7C_{ar}$, C_2-C_3-C_4-C_5-C_6-C_7-C_8), 46.45 (CH_2), 33.61 (CH), 19.76 (CH_3).

2-(Naphth-1-yl) butanamine (7b). The compound (0.2 g, yield: 67%) was synthesised according to the previous process from 2-(naphth-1-yl)-butyronitrile **4b** (0.29 g, 1.5 mmol), it was purified by column chromatography (neutral aluminum oxyde) and eluted with a CH_2Cl_2: MeOH mixture (98:2) and isolated as the amine.^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 (dd, 1H, H_{ar}), 7.75 (dd, 1H, H_{ar}), 7.6 (d, 1H, H_{ar}), 7.45–7.30 (m, 3H, H_{ar}), 7.22 (dd, 1H, H_{ar}), 3.55–3.4 (m, 1H, CH), 2.92–2.85 (dd, 2H, CH_2), 2.2 (brs, 2H, NH_2), 1.88–1.49 (m, 2H, CH_2), 0.72 (t, 3H, CH_3).

2-(Naphth-1-yl) pentanamine, HCl (7c). The compound (0.459 g, yield: 60%) was synthesised according to the previous process described for **7a** (0.76 g, 3.4 mmol).^{1}H NMR (200 MHz, CD_3OD): δ 8.2 (d, 1H, H_{ar}), 7.90 (d, 1H, H_{ar}), 7.88 (d, 1H, H_{ar}), 7.57–7.45 (m, 4H, H_{ar}) 3.83 (m, 1H, CH), 3.31 (d, 2H, NCH_2), 1.84 (m, 2H, $CHCH_2$), 1.16 (m, 2H, CH_3CH_2), 0.84 (t, 3H, CH_3).

3-Phenyl-2-(naphth-1-yl) propanamine, HCl (7d). The compound (1.32 g, yield: 82%) was synthesised according to the previous process described for **7a** (1.65 g, 6.05 mmol).^{1}H NMR (200 MHz, CD_3OD): δ 8.11 (d, 1H, H_{ar}), 7.99–7.79 (2d, 2H, $2H_{ar}$), 7.64–7.48 (m, 4H, H_{ar}), 1.22 (brs, 5H, H_{ar}), 4.42–4.24 (m, 1H, CH), 3.52–3.29 (m, 2H, CH_2), 3.12 (d, 2H, CH_2).

2-(7-Methoxy-naphth-1-yl) propanamine (8a). The amine (0.3 g, yield: 33%) was synthesised according to the previous process described for **7a** from 2-(7-methoxy-naphth-1-yl) propionitrile **5a** (0.9 g, 4.26 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H, H_{ar}), 7.65 (m, 1H, H_{ar}), 7.45 (s, 1H, H_{ar}), 7.32 (d + t, 2H, H_{ar}), 7.15 (dd, 1H, H_{ar}), 3.95 (s, 3H, OCH_3), 3.6 (q, 1H, CH), 3.05 (m, 2H, NCH_2), 1.4 (d + s, 5H, CH_3 et NH_2); ^{13}C NMR (200 MHz, $CDCl_3$): δ 157.88, 139.64, 133.21, 130.6, 126.59, 123.43, 123.31, 117.88, 102.2, ($10C_{ar}$), 55.44 (OCH_3), 48.57 (CH_2), 37.47 (CH), 19.23 (CH_3).

2-(2-Methoxy-naphth-1-yl) propanamine, HCl (9a). The compound (0.37 g, yield: 55%) was synthesised according to the process described for **7a** from 2-(2-methoxy-naphth-1-yl) propionitrile **6a** (0.78 g, 3.69 mmol). ^{1}H NMR (200 MHz, CD_3OD): δ 7.99 (d, 1H, H_{ar}), 7.76 (2d, 2H, $2H_{ar}$), 7.46–7.22 (m, 3H, $3H_{ar}$), 4.10–3.85 (m, 1H, CH), 3.85 (s, 3H, CH_3), 3.55–3.33 (m, 2H, CH_2N), 1.39 (d, 3H, CH_3).

Synthesis of the alkylamido derivatives 1b–h, 1k, 10. Method C

***N*-(2-methyl-2-(naphth-1-yl)ethyl) acetamide (1b).** To a stirred solution of the hydrochloride salt of the corresponding amine **7a** (0.26 g, 1.17 mmol) in water (15 mL) were added successively AcONa (1.4 g, 17.03 mmol) and acetic anhydride (2.7 mL, 28.62 mmol). After these additions, the reaction mixture was stirred at room temperature for 30 min. The amide was extracted from water with CH_2Cl_2 (3×20 mL) The organic solution was successively washed with a saturated $NaHCO_3$ solution and water. The organic extract was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography (silica gel) and eluted with a CH_2Cl_2:MeOH (98:2) mixture to give 0.25 g of a solid, mp: 105°C (yield: 80%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.09 (d, 1H, H_{ar}), 7.79 (dd, 1H, H_{ar}), 7.67 (d, 1H, H_{ar}), 7.5–7.3 (m, 4H, H_{ar}), 4.30 (brs, 1H, NH), 3.89–3.75 (m, 1H, CH), 3.67–3.37 (m, 2H, CH_2), 1.76 (s, 3H, $COCH_3$), 1.33 (d, 3H, CH_3CH); ^{13}C NMR (200 MHz, $CDCl_3$): δ 170.24 (CO), 140.18, 134.06, 132.06, 129, 127.19, 126.22, 125.70, 125.64, 123.14, 122.68 (10C, C_{ar}), 45.98 (NCH_2), 33.67 (CH), 23.32 ($COCH_3$), 19.33 (CH_3CH). Anal. ($C_{15}H_{17}NO + 1/3\ H_2O$); calc. C.77.22, H 7.63, N 6.00; F. C 77.59, H 7.63, N 6.00.

Method D

***N*-(2-ethyl-2-(naphth-1-yl)ethyl) acetamide (1c).** To a stirred solution of the amine **7b** (0.26 g, 1.3 mmol) in anhydrous CH_2Cl_2 (10 mL) under an Ar atmosphere and at 0°C were added dropwise Et_3N (0.27 mL, 1.95 mmol) and then acetyl chloride (0.11 mL, 1.56 mmol). After these additions, the reaction mixture was stirred for 30 min. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The compound was purified by column chromatography (silica gel) and eluted with a CH_2Cl_2: MeOH (98:2) mixture to give a white solid, mp: 88–89°C (yield: 64%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (m, 1H, H_{ar}), 7.80 (m, 1H, H_{ar}), 7.67 (d, 1H, H_{ar}), 7.45–7.31 (m, 4H, H_{ar}), 5.15 (brs, 1H, NH), 3.84–3.75 (m, 1H, NCH2), 3.71–3.58 (m, 1H, CH), 3.38–3.25 (m, 1H, NCH_2), 1.84–1.49 (m, 2H, CH_2CH_3), 1.69 (s, 3H, $COCH_3$), 0.78 (t, 3H, CH_3CH_2). Anal. ($C_{16}H_{19}NO$); calc. C.79.63, H 7.93, N 5.80; F. C 79.45, H 7.96, N 5.78.

***N*-(2-propyl-2-(naphth-1-yl)ethyl) acetamide (1d).** It was synthesised according to the previous process from the amine **7c** (0.14 g, 0.65 mmol), Et_3N (0.1 mL, 0.65 mmol) and acetyl chloride (0.065 mL, 0.65 mmol). The compound was isolated as an amorphous compound (0.14 g, yield: 84%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (m, 1H, H_{ar}), 7.86 (m, 1H, H_{ar}), 7.75 (d, 1H, H_{ar}), 7.56–7.25 (m, 4H, H_{ar}), 5.21 (brs, 1H, NH), 3.92–3.75 (m, 2H, CH et NCH_2), 3.41–3.32 (m, 1H, NCH_2), 1.81–1.63 (m, 2H, CH_2), 1.71 (s, 3H, $COCH_3$), 1.33–1.16 (m, 2H, CH_2), 0.85 (t, 3H, CH_3CH_2). Anal. ($C_{17}H_{21}NO$); calc. C.79.96, H 8.29, N 5.48; F. C 79.74, H 8.32, N 5.41.

***N*-(3-phenyl-2-(naphth-1-yl)propyl) acetamide (1e).** It was synthesised according to the process described for compound **1c** from the amine **7d** (0.22 g, 0.85 mmol),

Et_3N (0.118 mL, 0.85 mmol) and acetyl chloride (0.060 mL, 0.85 mmol). The compound was isolated as an amorphous compound (0.19 g, yield: 75%). ^1H NMR (200 MHz, $CDCl_3$): δ 8.13 (m, 1H, H_{ar}), 7.86 (m, 1H, H_{ar}), 7.75 (d, 1H, H_{ar}), 7.56–7.39 (m, 4H, H_{ar}), 7.25–7.09 (m, 5H, H_{ar}), 5.15 (brs, 1H, NH), 4.14–4.03 (m, 1H, CH), 3.85–3.72 (m, 1H, NCH_2), 3.63–3.42 (m, 1H, NCH_2), 3.19–2.98 (m, 2H, $PhCH_2$), 1.71 (s, 3H, $COCH_3$). Anal. ($C_{21}H_{21}NO$); calc. C.83.13, H 6.97, N 4.61; F. C 81.19, H 7.27, N 4.30.

***N*-(2-methyl-2-(7-methoxy-naphth-1-yl)ethyl) acetamide (1f).** It was synthesised according to the process described for compound **1c** from the amine **8a** (0.230 g, 1.06 mmol), Et_3N (0.166 mL, 1.2 mmol) and acetyl chloride (0.085 mL, 1.2 mmol). The compound was purified by column chromatography (silica gel) and eluted with CH_2Cl_2:MeOH (98:2) and crystallised in a CH_2Cl_2:diisopropyl ether mixture to give a solid, mp: 83–85°C (0.11 g, yield: 40%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, 1H, H_{ar}), 7.68 (dd, 1H, H_{ar}), 7.53 (sd, 1H, H_{ar}), 7.38–7.26 (m, 2H, H_{ar}), 7.17 (dd, 1H, H_{ar}), 5.49 (brs, 1H, NH), 3.98 (s, 3H, OCH_3), 3.94–3.77 (m, 1H, $CHCH_2$), 3.66–3.43 (m, 2H, $CHCH_2$), 1.87 (s, 3H, $COCH_3$), 1.41 (d, 3H, CH_3). Anal. ($C_{16}H_{19}NO_2$); calc. C.74.68, H 7.44, N 5.44; F. C 74.54, H 7.49, N 5.46.

***N*-(2-methyl-2-(7-methoxy-naphth-1-yl)ethyl) propionamide (1g).** It was synthesised according to the process described for compound **1c** from the amine **8a** (0.435 g, 2.4 mmol), Et_3N (0.33 mL, 2.4 mmol) and propionyl chloride (0.206 mL, 2.4 mmol). The compound was purified by column chromatography (silica gel) and eluted with a CH_2Cl_2:MeOH mixture (98:2) and crystallised in diisopropyl ether to give a solid, mp: 98–100°C (0.3 g, yield: 55%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, 1H, H_{ar}), 7.67 (dd, 1H, H_{ar}), 7.51 (sd, 1H, H_{ar}), 7.35–7.25 (m, 2H, H_{ar}), 7.15 (dd, 1H, H_{ar}), 5.38 (brs, 1H, NH), 3.97 (s, 3H, OCH_3), 3.87–3.84 (m, 1H, $CHCH_2$), 3.56 (t, 2H, NCH_2), 2.06 (q, 2H, $COCH_2$), 1.40 (d, 3H, CH_3); 1.03 (t, 3H, CH_3CH_2). Anal. ($C_{17}H_{21}NO_2$); calc. C.75.24, H 7.80, N 5.16; F. C 74.54, H 7.97, N 5.11.

***N*-(2-methyl-2-(7-methoxy-naphth-1-yl)ethyl) butyramide (1h).** It was synthesised according to the process described for compound **1c** from the amine **8a** (0.347 g, 1.6 mmol), Et_3N (0.127 mL, 1.92 mmol) and butyryl chloride (1.92 mmol). The compound was purified by column chromatography (silica gel) and eluted with a CH_2Cl_2: MeOH mixture (98:2) and crystallised in diisopropyl ether to give a solid, mp: 68–70°C (0.23 g, yield: 50%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, 1H, H_{ar}), 7.67 (dd, 1H, H_{ar}), 7.52 (sd, 1H, H_{ar}), 7.35–7.25 (m, 2H, H_{ar}), 7.16 (dd, 1H, H_{ar}), 5.45 (brs, 1H, NH), 3.97 (s, 3H, OCH_3), 3.90–3.79 (m, 1H, $CHCH_2$), 3.61–3.51 (m, 2H, NCH_2), 2.02 (t, 2H, $COCH_2$), 1.60–1.39 (m, 2H, CH_2CH_3); 1.40 (d, 3H, CH_3CH), 0.85 (t, 3H, CH_3CH_2). Anal. ($C_{18}H_{23}NO_2$); calc. C.75.75, H 8.12, N 4.90; F. C 75.91, H 8.29, N 4.91.

***N*-(2-methyl-2-(2-methoxy-naphth-1-yl)ethyl) acetamide (1j).** It was synthesised according to the process described for compound **1c** from the amine **9a** (0.420 g, 1.93 mmol), Et_3N (0.32 mL, 2.3 mmol) and acetyl chloride (0.16 mL, 2.3 mmol). The compound was recrystallised in a CH_2Cl_2: diisopropyl ether mixture to give a solid, mp: 136–138°C (0.27 g, yield: 40%). ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, 1H, H_{ar}), 7.80–7.36 (2d, 2H, $2H_{ar}$), 7.46 (td, 1H, H_{ar}), 7.32 (td, 1H, H_{ar}), 7.26 (d, 1H, H_{ar}), 5.54 (brs, 1H, NH), 4.03–3.82 (m, 2H, CH et CH_2), 3.93 (s, 3H, OCH_3), 3.69–3.56 (m, 1H, CH_2), 1.75 (s, 3H, $COCH_3$), 1.44 (d, 3H, CH_3). Anal. ($C_{16}H_{19}NO_2$); calc. C.74.68, H 7.44, N 5.44; F. C 74.74, H 7.61, N 5.34.

***N*-(2,2-Dimethyl-2-(naphth-1-yl)ethyl) acetamide (10).** 2-(Naphth-1-yl)-2-methyl-propionitrile was synthesised according to method B from (naphth-1-yl) acetonitrile (3 g, 18 mmol), methyl iodide (2.24 mL, 36 mmol) and a 60% suspension of NaH (1.43 g, 36 mmol) in oil. It was purified by column chromatography (silica gel) and eluted with an Et_2O:petroleum ether mixture (20:80). The compound was isolated as a clear oil (yield: 78%). ^1H NMR (200 MHz, $CDCl_3$): δ 8.55 (d, 1H, H_{ar}), 7.92 (d, 1H, H_{ar}), 7.84 (dd, 1H, H_{ar}), 7.64–7.40 (m, 4H, H_{ar}), 3.2 (s, 6H, $2CH_3$). The previous compound (1.5 g) was reduced to 2-(naphth-1-yl)-2-methyl propanamine, HCl (1.4 g, yield: 77%) according to the process used for the preparation of **7a**.^1H NMR (200 MHz, CD_3OD): δ 8.28 (d, 1H, H_{ar}), 7.85 (dd, 1H, H_{ar}), 7.65 (d, 1H, H_{ar}), 7.5–7.35 (m, 4H, H_{ar}), 3.58 (s, 2H, NCH_2), 1.60 (s, 6H, $2\times CH_3$); ^{13}C NMR (200 MHz, CD_3OD): δ 139.26, 135.81, 132.77 (3C, C_{ar}), 130.30, 129.02, 127.68, 126.98, 126.84, 124.21, 123.60 (7C, C_{ar}), 46.45 (CH_2), 33.61 (CH), 19.76 (CH_3). **10** was synthesised according to the method D from the previous free amine (0.3 g, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol) and acetyl chloride (0.128 mL, 1.8 mmol). The compound was purified by column chromatography (silica gel) and eluted with CH_2Cl_2:MeOH (98:2) and crystallised in a CH_2Cl_2: diisopropyl ether mixture to give a solid, mp: 138–140°C (0.12 g, yield: 33%). ^1H NMR (200 MHz, $CDCl_3$): δ 8.44 (m, 1H, H_{ar}), 7.89 (m, 1H, H_{ar}), 7.76 (d, 1H, H_{ar}), 7.55–7.38 (m, 4H, H_{ar}), 5.06 (brs, 1H, NH), 3.92 (d, 2H, NCH_2), 1.83 (s, 3H, $COCH_3$), 1.62 (s, 6H, $2\times CH_3$). Anal. ($C_{16}H_{19}NO$); calc. C.79.63, H 7.9, N 5.8; F. C 79.47, H 7.92, N 5.74.

4-(Naphth-1-yl) 2-pyrrolidone (11a). 2 g of a 60% suspension of NaH (50 mmol) in oil was dissolved in 75 mL of THF and the mixture was stirred at room temperature under an argon atmosphere. 1-Naphthylacetonitrile (7.5 g, 45 mmol) were added and the mixture was heated at 50°C for 1 h under an argon atmosphere. 9 g of methyl bromoacetate was added dropwise at 0°C and the mixture was refluxed for 1 h. The solution was poured onto ice and extracted twice with ether. The organic layers were washed with water and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure to give an oil which was purified by column chromatography (silica gel, cyclohexane:Et_2O, 40:60) to give 7.8 g (yield: 72%) of methyl 3-cyano-3-(naphth-1-yl) propionate. ^1H NMR (200 MHz, $CDCl_3$): δ 7.95–7.40 (7H, H_{ar}), 5.03 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 3.04 (m, 2H, CH_2). 4.8 g (20 mmol) of the previous compound were dissolved in a mixture of EtOH (100 mL) and a concentrated solution of NH_4OH (6 mL), then 0.5 g of Raney nickel was added. The mixture was stirred with H_2 under atmospheric pressure at 45°C for 48 h. The catalyst was filtered and the

solvent was evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) and was crystallised with a CH_2Cl_2:Et_2O mixture to give a white solid, mp: 134–135°C (3.3 g, yield: 78%). ^{1}H NMR (200 MHz, $CDCl_3$): δ: 8.20–7.40 (m, 7H, H_{ar}), 6.80 (s, 1H, NH), 5.50 (m, 1H, CH), 3.60–3.95 (m, 2H, $C\underline{H}_2$), 2.80 (m, 2H, $COCH_2$). Anal. ($C_{14}H_{13}NO$); calc. C.79.58, H 6.22, N 6.63; F. C 79.42, H 6.41, N 6.51.

4-(7-Methoxy-naphth-1-yl) 2-pyrrolidone (11b). The compound was prepared according to the process described for **11a**: 2-(7-methoxy-naphth-1-yl) acetonitrile gave methyl 3-cyano-3-(7-methoxy-naphth-1-yl) propionate which was crystallised as a white solid, mp: 116°C (yield: 67%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90–7.10 (m, 6H, H_{ar}), 4.90 (m, 1H, CH), 3.90 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.05 (m, 2H, CH_2). Anal. ($C_{16}H_{15}NO_3$); calc. C.71.36, H 5.62, N 5.20, F. C 71.35, H 5.68, N 5.15. This compound was reduced with hydrogen and Raney nickel according to the previous process used for the preparation of compound **11a**. Compound **11b** was obtained as a white solid, mp: 146–147°C (yield: 82%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85–7.15 (m, 6H, H_{ar}), 6.85 (s, 1H, NH), 4.30 (m, 1H, CH), 3.95 (s, 3H, OCH_3), 3.58–3.97 (m, 2H, CH_2), 2.80 (m, 2H, $COCH_2$). Anal. ($C_{15}H_{15}NO_2$); calc. C.74.66, H 6.27, N 5.81; F. C 74.44, H 6.42, N 5.83.

Separation of the enantiomers of *N*-(2-methyl-2-(naphth-1-yl)ethyl) acetamide (1b) and *N*-(2-methyl-2-(7-methoxy-naphth-1-yl)ethyl) butyramide (1h). A direct chromatographic method using a semipreparative chiral HPLC column (CHIROS-BOND C1) 10 μm−250× 10 mm (Chiralsep; Parc d'activités de la Boissiére-La Frenaye-76170 France) gave the pure enantiomers of **1b** and **1h**. The conditions for the semi-preparative separations were estimated by analytical runs on an analytical chiral HPLC CHIROSE BOND C1 column (5 μm−250× 4.5 mm). A 150 μL loop was used to introduce samples. The concentrations chosen varied between 10 and 20 mg/mL in a mixture depending on the resolution of the compound. The mobile phase consisted of a hexane:AcOEt:EtOH mixture (90:9:2) which was degassed by sonication. The solvent delivery system was a Varian 5000 HPLC pump set at a flow rate of 4 mL/min. Detection at 254 nm was carried out using a Varian 2050 tuneable absorbance detector. The chromatograms were registered with a Varian 4270 integrator. The enantiomers of **1b** and **1h** were separated on a milligram scale and their purity was controlled by analytical HPLC (>99%). Optical rotations α_D were measured on a Polartronic C-Schimdt-Haensch for each enantiomer at 589 nm. They were uncorrected. (+) **1b**: $\alpha_D = +45°$ (c = 0.2, MeOH); (−) **1b**: $\alpha_D = -45°$ (c = 0.2, MeOH); (+) **1h**: $\alpha_D = +60°$ (c = 0.3, MeOH); (−) **1h**: $\alpha_D = -50°$ (c = 0.3, MeOH).

Melatonin receptor binding assay

Chickens (Red Brook, male or female, 4 months (3–4 Kg); Cellubio, France) were decapitated at 12 p.m. The brains were quickly removed and stored at −80°C. They were homogenised (Polytron) in 10 vol of ice-cold Tris–HCl buffer (50 mM, pH 7.4) and washed twice by centrifugation (44 000 g, 25 min, 4°C). The resulting pellet was resuspended in 10 volumes of the same buffer to a final concentration of 5 or 6 mg protein/mL. The membrane aliquots (30 μL) were incubated in a total volume of 0.25 ml Tris–HCl buffer (50 mM, pH 7.4) with 0.05 nM 2-[^{125}I]iodomelatonin and seven concentrations of the compound under test. Each binding assay was performed in triplicate. The incubation (25°C, 60 min) was stopped by the addition of 3 mL of ice-cold buffer and immediate vacuum filtration through glass fibre filters (GF/B Whatman strips) presoaked in 0.1% poly(ethyleneimine) using a Brandel cell harvester. The filters were washed (3×4 mL) with buffer, dried, and counted on a γ-counter (Crystal–Packard). Non-specific binding was defined with 10 μM melatonin and represented 10% of the total binding. K_i values are expressed and were calculated using the Cheng-Prussof equation from the corresponding IC_{50} values using PRISM program.

Melanophore contraction in *X. laevis* tadpoles

The *X. laevis* tadpoles (stage 41) used in this study were obtained from the Laboratoire de Biologie Cellulaire et Reproduction CNRS (Rennes, France). They were maintained in an aquarium in the laboratory at 22°C under natural illumination for 8 days and fed daily with powdered fish food. Prior to the bioassay, tadpoles of uniform stage, size, and colour, were selected, removed from the aquarium, and placed in groups of 5 in 100 mL beakers placed on a dark background and filled with 45 mL of pool water, 18 h before the experiments. They were lit with artificial light (60 W) for 3 h before the experiments which were performed at midday. The compound under test was dissolved in a DMF and water mixture in a final volume of 5 mL and added to the liquid in the beaker (45 mL) to achieve the final selected concentration. After 15 min, the experiment was terminated by the addition of a 37% formaldehyde solution. The degree of the melanophore response in each tadpole was determined by examination of the melanophore configuration under a microscope (Leitz, magnification ×4) and evaluated according to the melanophore index scale (1–5) of Hogben and Slome.[21] The data are the results of the sum of the determinations of the melanophore index on the body and the dorsal surface of the tadpole. EC50 values for the compounds were determined from the concentration-effect curve obtained with 5 concentrations in the range of 0.1 to 100×K_i values for chicken brain receptors. The mean of the control data (animals with vehicle) represented 100%. Variations in the EC_{50} values of melatonin (1–10 nM, $n = 10$) and the reference compounds were observed between batches of tadpoles at different times of the year. Consequently the potency of the molecule was calculated as the ratio between the EC_{50} melatonin/EC_{50} compound ratio determined in the same experiment.

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References

1. Reiter, R. J. *Endocrinol. Rev.* **1991**, *12*, 151.
2. Klein, D. C.; Roseboom, P. H.; Coon, S. L. *TEM* **1996**, *7*, 106.
3. Arendt, J.; Deacon, S. *Chronobiol. Int.* **1997**, *14*, 185.
4. Arendt, J.; Deacon, S.; English, J.; Hampton, S.; Morgan, L. *J. Sleep Res.* **1995**, *4*, 74.
5. Wirz-Justice, A.; Amstrong, S. M. *J. Sleep Res.* **1996**, *5*, 137.
6. Blehar, M. C.; Lewy, A. J. *Psychopharmacol. Bull.* **1990**, *4*, 465.
7. Reiter, R. J. *Endocrinol. Rev.* **1980**, *1*, 109.
8. Ying, S-W.; Niles, L. P.; Crocker, C. *Eur. J. Pharmacol.-Mol. Pharmacol. Section,* **1993**, *246*, 89.
9. Stankov, B.; Fraschini, F.; Reiter, R. *J. Brain. Res. Rev.* **1991**, *16*, 245.
10. Reppert, S. M.; Weaver, D. R.; Godson, C. *TIPS* **1996**, *17*, 100.
11. Morgan, P. J.; Barrett, P.; Hazlerigg, D.; Milligan, G.; Lawson, W.; MacLean, A.; Davidson, G. *J. Neuroendocrinol.* **1995**, *7*, 361.
12. Mahle, C. D.; Takaki, K. S.; Watson, A. J. In: *Annual Reports in Medicinal Chemistry*; Bristol J.A., Ed.; Academic Press: London, 1997; vol. 32, pp. 31.
13. Mathé-Allainmat, M.; Andrieux, J.; Langlois, M. *Exp. Opin. Ther. Patents* **1997**, *7*, 1447.
14. Depreux, P.; Lesieur, D.; Mansour, H. A.; Morgan, P.; Howell, H. E.; Renard, P.; Caignard, D. H.; Pfeiffer, B.; Delagrange, P.; Guardiola, B.; Yous, S.; Demarque, A.; Adam, G.; Andrieux, J. *J. Med. Chem.* **1994**, *37*, 3231.
15. Mason, R.; Delagrange, P.; Guardiola, B. *Br. J. Pharmacol.* **1993**, *108*, 32P.
16. Langlois, M.; Brémont, B.; Shen, S.; Poncet, A.; Andrieux, J.; Sicsic, S.; Serraz, I.; Mathé-Allainmat, M.; Renard, P.; Delagrange, P. *J. Med. Chem.* **1995**, *38*, 2050.
17. Frohn, M. A.; Seaborn, C. J.; Johnson, D. W. *Life Sci.* **1980**, *27*, 2043.
18. Eli Lilly and Co, EP-655243-A (1995); Garratt, P. J.; Jones, R.; Tocher, D. A.; Sugden, D. *J. Med. Chem.* **1995**, *38*, 1132.
19. Rollag, M. D. *Pineal Res. Rev.* **1988**, *6*, 67.
20. Sudgen, D.Br. *J. Pharmacol.* **1991**, *104*, 922.
21. Hogben, L.; Slome, D. *Proc. R. Soc. (London), Ser B* **1931**, *108*, 10.
22. Langlois, M.; Maillard, *J. Bull. Soc. Chim.* **1971**, 2976.
23. CHIRALSEP (76170, La Fresnaye, France).
24. Dubocovich, M. L.; Cardinali, D. P.; Guardiola-Lemaitre, B.; Hagan, R. M.; Krause, D. N.; Yocca, F. D.; Vanhoutte, P. M. In *The IUPHAR Compendium of Receptor Characterization and Classification*, Girdlestone, D., Ed; IUPHAR Media: London, 1998, 187.
25. Sugden, D.; Davies, D. J.; Garratt, P. J.; Jones, R.; Vonhoff, S. *Eur. J. Pharmacol.* **1995**, *287*, 239.
26. Davies, D. J.; Garratt, P. J.; Tocher, D. A.; Vonhoff, S.; Davies, J.; Teh, M-T.; Sudgen, D. *J. Med. Chem.* **1998**, *41*, 451.
27. Conway, S.; Drew, E. J.; Canning, S. J.; Barett, P.; Jockers, R.; Strosberg, A. D.; Guardiola-Lemaitre, B.; Delagrange, Ph.; Morgan, P. J. *FEB Lett.* **1997**, *407*, 121.
28. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R., Eds.; Langman Scientific and Technical: Harlow, UK, p. 1006.