Articles

Synthesis of Phenalene and Acenaphthene Derivatives as New Conformationally Restricted Ligands for Melatonin Receptors

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Conformationally restricted phenalene and acenaphthene derivatives **5** were synthesized from phenalen-1-one and acenaphthen-1-one derivatives using the Horner−Emmons reaction. The amines were prepared through the corresponding isocyanates by the Curtius reaction on the acids or by the reduction of the nitriles. Amido derivatives (R_3 = Me, Et, *n*-Pr, *c*-Pr) were prepared by acylation of the amines with the appropriate anhydrides or acid chlorides or by the reductive acylation of the nitriles. The affinities of the compounds for melatonin binding sites were evaluated in vitro in binding assays using chicken brain melatonin and the human mt_1 and MT_2 receptors expressed in HEK-293 cells. The functionality of the compounds was determined by the potency to lighten the skin of *Xenopus laevis* tadpoles. Highly potent compounds were obtained. The data highlighted the role of the methoxy group located in the *ortho* position to the ethylamido chain as compounds with picomolar affinities such as **14c** were obtained (chicken brain, hmt_1, hMT_2 K_i values = 0.02, 0.008, 0.069 nM, respectively). Compound **14c** was equipotent to the corresponding dimethoxy derivative **15c** (chicken brain, hmt_1, hMT_2 K_i values = 0.07, 0.016, 0.1 nM, respectively). On the other hand, the restricted conformation of the amido chain did not influence selectivity for the cloned hmt_1 and hMT_2 receptors. These compounds were also potent agonists of melanophore aggregation in *X. laevis*. **15a**,**c** were several hundred fold more potent than melatonin (EC_{50} = 0.025, 0.004 nM, respectively). Conformational studies indicated that the minimum energy folded conformation of the ethylamido chain could constitute the putative active form in the receptor site in agreement with previous results.

Introduction

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

A number of the effects of melatonin have been shown to be mediated through G protein-coupled receptors,[8] and coupling to one of the G_i family of G-proteins appears to be the common signaling pathway for the receptors characterized to date. Cloning studies have revealed two recombinant mammalian melatonin receptors recently termed mt_1 and MT_2.[9,10]

In recent years considerable interest has evolved in the search for new molecules capable of mimicking or antagonizing the responses to melatonin.[11,12] These novel compounds were derived from the indole ring or the bioisosteric naphthalene moiety and include agomelatine, which was claimed to control circadian rhythm disorders.[13] The development of high-affinity, conformationally locked compounds has also constituted an important field of investigation to obtain a clear insight into the structural parameters implicated in the binding of melatonin with the receptor site. Several tricyclic structures were synthesized where the ethylamido chain was introduced in a ring. These compounds were either derivatives of tricyclic indoles,[14,15] such as **1** and **2** where the ethylamido chain was partially constrained, or totally locked phenalene derivatives, such as **3** recently described by us[16a,b] (Chart 1). These studies have

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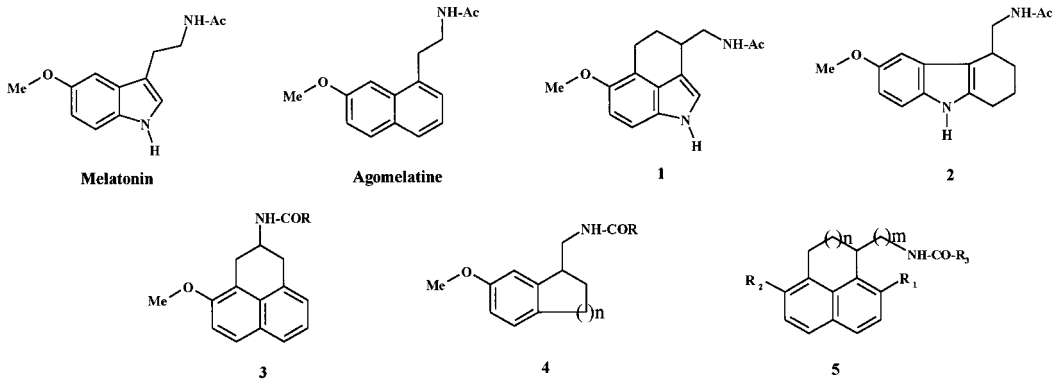
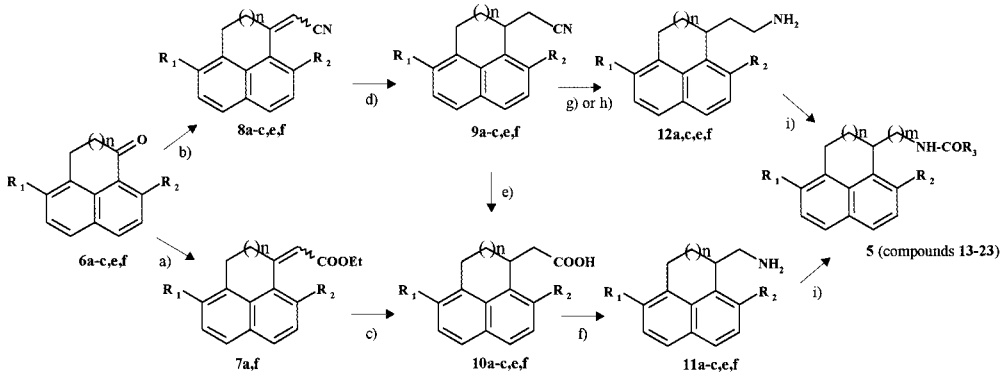
Chart 1



Scheme 1[a]



a R_1 = OMe, R_2 = H, n =1 ; **b** R_1 = H, R_2 = OMe, n =1 ; **c** R_1 = OMe, R_2 = OMe, n =1
d R_1 = H, R_2 = H, n =1 ; **e** R_1 = H, R_2 = MeO, n =0 ; **f** R_1 = H, R_2 = H, n =0

[a] Reagents: (a) $(EtO)_2POCH_2COOEt$, NaH, THF; (b) $(EtO)_2POCH_2CN$, NaH, THF; (c) $PdCl_2$, $NaBH_4$, MeOH, H_2, rt, 2 N KOH, MeOH/H_2O, △; (d) $PdCl_2$, $NaBH_4$, MeOH, H_2, rt; (e) 30% NaOH, MeOH or EtOH, △, 48 h; (f) EtOCOCl, Et_3N, acetone, 0 °C, NaN_3, H_2O, 0 °C, toluene, △, H_2O, 20% HCl; (g) H_2, Raney Ni, THF, NH_4OH, rt; (h) H_2, Raney Ni, THF, $(R_3CO)_2O$, **12** was not isolated; (i) $(R_3CO)_2O$, Na_2CO_3, CH_2Cl_2, H_2O or R_3COCl, CH_2Cl_2, Et_3N.

demonstrated the advantage of the partially constrained ethylamido chain over the total rigid structure for increasing the potency of binding to the receptor. Thus, we have demonstrated recently that compounds with nanomolar potency were obtained with a simple bicyclic structure derived from tetraline or indan **4**.[17] On the other hand totally rigid structures such as that of phenalene **3** had a different pharmacological profile as they were shown to possess an antagonist profile in the aggregation of the melanophores in *Xenopus laevis* tadpoles.[16b]

It has been demonstrated that the naphthalene ring is a good bioisosteric moiety of indole for the melatonin receptor[12] and that potent compounds[18] could be obtained by the introduction of a methoxy group in the *ortho* position of the ethylamido chain. With the goal to obtain information about the exact role of this secondary group in the binding with the receptor and its influence on the pharmacological profile, new phenalene and acenaphthene derivatives **5** (compounds **13**−**23**, Table 1; R_1, R_2 = MeO or H, n = 1 or 0, m = 1 or 2), where the ethylamido chain was partially constrained, were synthesized. They can be compared to the indolic derivatives recently synthesized by Spadoni.[15]

The synthesis of the different compounds **5** and the isolation of the corresponding (+) and (−) enantiomers for a number of them are reported herein. The compounds were evaluated for their affinity for chicken brain melatonin and for the recombinant human mt_1 and MT_2 receptors.[19] Pharmacological profiles were determined for the potency of the compounds to lighten the skin of *X. laevis* in tadpoles.[21] Recently we have shown that naphthalenic derivatives could be potent agonists in this biossay. [22]

Chemistry

Compounds **13**−**15** and **17**−**23** were synthesized from phenalenones **6a**−**d** and acenaphthenones **6e**−**f** according to the synthetic pathway described in Scheme 1. Ketones **6a**−**c**,**e**−**f** were prepared by the cyclization reaction of the corresponding naphthylpropionic or -acetic acids with polyphosphoric acid at 120 °C or by Friedel−Craft reaction of the acid chloride at 0 °C according to methods already described.[23] Compound **6d** (R_1 = R_2 = H) was prepared from reduction and oxidation of the commercially available 1*H*-phenalenone.[24]

The side chain of the tricyclic moiety was introduced by the reaction of Horner−Emmons with triethyl monophosphonoacetate or diethyl cyanomethylphosphonate to give the unsaturated esters **7a**,**f** or the nitriles **8a**−**c**,**e**,**f**, respectively, with a good yield. These compounds isolated as a mixture of *E* and *Z* isomers were characterized by ^1H NMR spectra. They were directly transformed into the corresponding saturated compounds by hydrogenation reaction at atmospheric pressure in the presence of $PdCl_2$ previously reduced with $NaBH_4$ in methanol.[25] This method prevented the hydrogenation

of the naphthalene ring and the formation of additional products observed using classical conditions with Pd on charcoal (5%). The esters were directly saponified in a 2 N KOH methanol solution into the acids **10a**,**f**. The acids **10b,c**,**e**, were prepared by hydrolysis of the corresponding nitriles **9** with a 30% NaOH solution in an EtOH:H_2O mixture (1/1). The amines **11a**−**c**,**e**,**f** were prepared from the acids **10** by Curtius reaction using thermal rearrangement of the acyl azides into the corresponding isocyanates followed by acid hydrolysis with 20% HCl in H_2O. Amine **11d** was synthesized from the reduction with hydrogen of 1-cyano-2,3-dihydrophenalene prepared by a process already reported by us.[26] The amines **11** were isolated as the bases or hydrochlorides and were transformed into acetamido, propionamido, butyramido and cyclopropylcarboxamido derivatives (compounds **13a**−**d**, **14a**,**c**, **15a**−**d**, **16a,c**, **20a**−**d**, **21a**−**d**) according to the methods previously described by us.[18]

The nitriles **9** were used as the starting materials to prepare the corresponding amides **17a**−**d**, **18a**,**c**, **19a**−**d**, **22a**−**d,** and **23a**−**d** possessing the flexible two-carbon side chain. Acetamido, propionamido, and butyramido derivatives were directly obtained by the reduction reaction of the nitriles in THF in the presence of Raney nickel and the corresponding anhydrides. On the other hand, cyclopropylcarboxamido derivatives were obtained from the isolated amines **12a,c,e,f** and cyclopropanecarbonyl chloride.

Final compounds were characterized by microanalysis and ^1H and ^{13}C NMR spectra. The (+) and (−) enantiomers of the racemic compounds **13c**, **15c**, and **20c** were isolated by semipreparative enantiomeric HPLC preparation. The separation was made with a new chiral 3D-reticulated matrix.[27] Enantiomeric separation was achieved using a heptane/EtOAc/EtOH or heptane/EtOH mobile phase. The enantiomers obtained with a high enantiomeric purity (>99%) were characterized by their optical rotation (α_D) and mass spectra.

Results and Discussion

The affinities of the compounds for melatonin binding sites were evaluated in vitro in binding assays using chicken brain membranes where all the receptors subtypes (mt_1, MT_2, and Mel_{1C}) are present.[9,28] The potential selectivity of the compounds was evaluated in binding assays with the human mt_1 and MT_2 receptors expressed in HEK-293 cells. 2-[^{125}I]Iodomelatonin was used as the radioligand. The functional activity of the compounds was evaluated by examining the potency of the compounds to lighten the skin of *X. laevis* tadpoles as it has been demonstrated previously that melatonin mediates the degree of aggregation of melanophores.[21,22] Agonist (EC_{50}) action was evaluated using the melanophore index scale of Hogben and Slome.[29]

The results of the binding assays are presented in Table 1. The data emphasized the lack of good selectivity for the different receptors and the good agreement between the affinities for the chicken brain melatonin and the cloned human receptors. Comparison of the different acetamido derivatives (**13**−**23a)** showed, as has been observed previously,[18,30] that the introduction of methoxy groups in the melatonin-like position and/or in the *ortho* position of the ethylamido chain was essential to obtain compounds with subnanomolar affinity (compounds **13a**, **14a**, **20a**, **22a**). However, the favorable influence of steric constraints was clearly marked with the unsubstituted phenalene and acenaphthene derivatives **16a** and **21a**, respectively, which were particularly potent with regard to the corresponding naphthalenic derivative.[22] In particular, compounds **16a** and **21a** had nanomolar affinity (K_i = 0.22, 0.5 nM, respectively) for MT_2 receptors. This increase in affinity can be explained either by the presence of the cyclic system, which imposes a favorable conformation on the amido group for binding to the receptor, or by the decrease of the unfavorable entropic term due to the reduction of the degrees of freedom. However, this increase was not seen with compound **13a** which was equipotent to the conformationally flexible reference compounds agomelatine and melatonin. On the other hand, it was clearly present with compound **14a** with a methoxy group in the *ortho* position of the ethylamido chain which was more potent than the corresponding flexible naphthalene derivatives.[18] These data again confirm the existence of a secondary binding site capable of productive interactions with the methoxy group in the *ortho* position of the ethylamido chain and explain the potent affinity of the 2-methoxynaphthalene derivatives previously described.[18] In contrast to the naphthalenic derivatives where the flexible chain can be directed in two orientations,[18] the locked conformations of **13a** and **14a** proved clearly the different spatial positions of the methoxy groups with regard to those of the amido function. The introduction of both methoxy groups in the melatonin-like position and in the *ortho* position of the ethylamido chain (compounds **15a**−**d**) gave compounds with picomolar affinities, equipotent to the most active compounds already described in the naphthalene series[18,22] but not much more potent than compounds **14**. The favorable influence of these groups in the binding with the receptor site was confirmed as has been observed previously in the naphthalene and phenalene series.[16a,b,18]

The butyramido derivatives (**13**−**23c**) of the different moieties had the highest affinity, although the effect of this group was less marked than those previously observed.

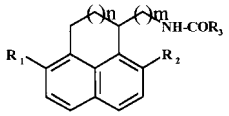
The equipotency of compounds **15a**,**c** and **14a**,**c** **(**chicken brain K_i = 54, 70, 40, 20 pM, respectively) was unexpected with regard to the previous results[16,18] where the dimethoxy derivatives were more potent.

Comparison of the affinities of the phenalene and acenaphthene derivatives (compounds **14**, **20**) showed that the totally rigid acenaphthene moiety has a less favorable fit to the receptor as only compounds with nanomolar affinity were obtained.

Examination of the results of the compounds with a two-carbon side chain (compounds **17**−**19, 22, 23**) showed that lengthening of the amido chain was less favorable. These findings are in contrast to the results obtained by us[18,31] and other groups with derivatives possessing only one benzene ring.[32,33] However, compounds with nanomolar affinity were again obtained with the dimethoxy substitution (compounds **19a**−**c**).

Several reports have indicated the enantioselectivity of melatonin receptors: the partially constrained tricyclic indoles **1** and **2** with a β chiral center,[14b,34] the

Table 1. Binding Affinity of Compounds **5** for Chicken Brain Melatonin Receptors and Human mt_1 and MT_2 Melatonin Receptors



5

						K_i (nM)		
compd	R_1	R_2	*n*	*m*	R_3	chicken brain[a]	hmt_1 receptors[b]	hMT_2 receptors[b]
13a	MeO	H	1	1	Me	0.9 ± 0.2	0.8 ± 0.02	0.41 ± 0.037
13b	MeO	H	1	1	Et	0.7 ± 0.17	0.19 ± 0.05	0.13 ± 0.056
(±)13c	MeO	H	1	1	nPr	0.36 ± 0.1	0.45 ± 0.2	0.11 ± 0.07
(−)13c	MeO	H	1	1	nPr	0.8 ± 0.4	0.11 ± 0.005	0.068 ± 0.004
(+)13c	MeO	H	1	1	nPr	21.7 ± 13	2.9 ± 0.05	4.07 ± 0.03
13d	MeO	H	1	1	cPr	4.6 ± 3	0.95 ± 0.33	0.79 ± 0.03
14a	H	MeO	1	1	Me	0.04 ± 0.005	0.010 ± 0.002	0.094 ± 0.003
14c	H	MeO	1	1	nPr	0.02 ± 0.007	0.008 ± 0.002	0.069 ± 0.011
15a	MeO	MeO	1	1	Me	0.054 ± 0.016	0.015 ± 0.004	0.145 ± 0.005
15b	MeO	MeO	1	1	Et	0.011 ± 0.004	0.012 ± 0.001	0.153 ± 0.01
(±)15c	MeO	MeO	1	1	nPr	0.07 ± 0.015	0.016 ± 0.005	0.10 ± 0.024
(−)15c	MeO	MeO	1	1	nPr	0.034 ± 0.026	NT[c]	NT
(+)15c	MeO	MeO	1	1	nPr	0.31 ± 0.25	NT	NT
15d	MeO	MeO	1	1	cPr	0.13 ± 0.05	0.026 ± 0.008	0.26 ± 0.09
16a	H	H	1	1	Me	5.5 ± 1.7	1.2 ± 0.3	0.22 ± 0.03
16c	H	H	1	1	nPr	3.2 ± 0.9	1.3 ± 0.4	0.18 ± 0.03
17a	MeO	H	1	2	Me	145 ± 32	8.90 ± 0.5	11.8 ± 1.8
17b	MeO	H	1	2	Et	31.7 ± 11	2.08 ± 0.08	4.03 ± 0.54
17c	MeO	H	1	2	nPr	28.1 ± 6	NT	NT
17d	MeO	H	1	2	cPr	43.4 ± 25	1.89 ± 0.2	13.2 ± 8
18a	H	MeO	1	2	Me	24.4 ± 32	0.10 ± 0.004	0.39 ± 0.07
18c	H	MeO	1	2	nPr	0.43 ± 0.25	NT	NT
19a	MeO	MeO	1	2	Me	3.6 ± 2.8	0.20 ± 0.029	0.55 ± 0.17
19b	MeO	MeO	1	2	Et	0.8 ± 0.4	0.070 ± 0.005	0.55 ± 0.17
19c	MeO	MeO	1	2	nPr	0.14 ± 0.02	0.057 ± 0.0007	0.19 ± 0.055
19d	MeO	MeO	1	2	cPr	11.2 ± 3.5	0.66 ± 0.004	1.59 ± 0.24
20a	H	MeO	0	1	Me	2.95 ± 1.0	0.12 ± 0.026	0.12 ± 0.036
20b	H	MeO	0	1	Et	0.9 ± 0.3	0.1 ± 0.056	0.085 ± 0.014
(±)20c	H	MeO	0	1	nPr	0.16 ± 0.060	0.37 ± 0.14	0.35 ± 0.024
(−)20c	H	MeO	0	1	nPr	0.15 ± 0.05	0.030 ± 0.002	0.034 ± 0.010
(+)20c	H	MeO	0	1	nPr	4.3 ± 1.0	3.9 ± 3	7.4 ± 1.1
20d	H	MeO	0	1	cPr	3.8 ± 1.5	1.32 ± 0.017	0.31 ± 0.25
21a	H	H	0	1	Me	36.1 ± 10	4.24 ± 0.66	0.51 ± 0.11
21b	H	H	0	1	Et	14.3 ± 9	2.65 ± 2.0	0.22 ± 0.025
21c	H	H	0	1	nPr	4.3 ± 0.9	0.79 ± 0.05	0.093 ± 0.03
21d	H	H	0	1	cPr	40.5 ± 12	1.06 ± 0.14	0.57 ± 0.12
22a	H	MeO	0	2	Me	2.7 ± 0.9	0.41 ± 0.005	0.59 ± 0.07
22b	H	MeO	0	2	Et	4.75 ± 1.1	0.22 ± 0.079	0.24 ± 0.079
22c	H	MeO	0	2	nPr	2.4 ± 0.8	0.37 ± 0.011	0.34 ± 0.11
22d	H	MeO	0	2	cPr	97.1 ± 39	10.0 ± 2.1	41.8 ± 23
23a	H	H	0	2	Me	123.3 ± 10	6.5 ± 1.3	3.83 ± 0.1
23b	H	H	0	2	Et	101.8 ± 18	4.34 ± 0.31	1.86 ± 0.45
23c	H	H	0	2	nPr	73.7 ± 45	6.41 ± 1	1.86 ± 0.45
23d	H	H	0	2	cPr	399 ± 115	6.48 ± 1.4	16.2 ± 7.7
agomelatine						0.53 ± 0.13	0.18 ± 0.1	0.45 ± 0.15
melatonin						0.7 ± 0.4	0.2 ± 0.1	0.53 ± 0.15

[a] 2-[^{125}I]Iodomelatonin was used as the radioligand and the binding assays were carried out using membranes prepared from chicken brain. Membrane aliquots (30 μL) were incubated in a total volume of 0.25 mL of Tris-HCl buffer (50 mM, pH 7.4) with 0.05 nM 2-[^{125}I]iodomelatonin. Each binding assay was performed in triplicate. Nonspecific binding was defined with 10 μM melatonin and represented about 10% of the total binding. [b] Binding assays were carried out as above using membranes prepared from HEK-293 cells which expressed human mt_1 or MT_2 receptors. Membrane aliquots were incubated for 2 h at 37 °C with 0.025 and 0.2 nM 2-[^{125}I]iodomelatonin for hmt_1 and hMT_2 receptors, respectively. Nonspecific binding was defined with 10 μM 2-iodomelatonin. Experiments were performed twice and the mean value is given with ±SEM. [c] NT, not tested.

β-methylnaphth-1-ylethylamido derivatives,[22] and, more recently, the melatoninergic indanyl and tetralin derivatives **4**.[17] Several racemic mixtures (compounds **13c**, **15c**, **20c**) were separated with chiral HPLC; the purity of the enantiomers was examined by analytical chiral HPLC and the enantiomeric purity was >99%. The data showed that the activity resided in the (−) enantiomers and that compounds such as **15c** were characterized by a weak selectivity for the chicken brain melatonin receptors (34, 310 pM).

As noted previously, steric constraints on the melatoninergic pharmacophore do not contribute to selectivity for the receptor subtypes mt_1 and MT_2 because the compounds reported herein had very weak selectivity. Doubtless, melatonin binds both receptors with the same conformers due to the structural similarity between the structures of the binding site.

On the other hand, the introduction of constraints in the melatoninergic pharmacophore might modify the ability of the molecule to activate the receptor, and therefore the pharmacological profiles of these compounds were evaluated on the dermal melanocytes of

Table 2. Biological Data of Compounds **5** for *X. laevis* Melanophores

compd	EC_{50} (nM) for melanophore aggregation[a]	potency with regard to melatonin (=1)[b]
13a	57.8 [15.3−218]	0.11
13c	1.61 [15.3−218]	13.3
14a	0.1 [0.04−0.28]	67.9
14c	0.08 [0.028−0.26]	84.8
15a	0.025 [0.007−0.084]	271.6
15c	0.004 [0.007−0.002]	1697
17a	>1000 (50%)	ne
18a	428	0.007
19a	2.65	2.5
19c	0.18 [0.09−7.3]	37.7
20a	5.08 [1.9−13.3]	1.33
20c	0.46 [0.18−1.2]	14.7
21a	>1000 (<50%)	ne
21c	26 (<50%)	ne
23a	>1000 (<50%)	ne
22a	>1000 (50%)	ne
agomelatine	0.53 [0.41−0.67]	0.8

[a] *X. 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 (ref 29). EC_{50} values were determined using the PRISM software package and are the result of 2 separate experiments. The mean value is given with the range of values in brackets. [b] The potency of the molecules was calculated as the EC_{50}(melatonin)/EC_{50}(compound) ratio determined in the same experiment. Percent (%) represents the percentage of the maximum effect observed with regard to that of melatonin (100%). [c] ne, not capable of evaluation.

X. laevis tadpoles.[21,29] Melatonin, naphthalenic,[22] and indolic[14b] compounds have been shown to be potent agonists in this biossay.

A number of the compounds synthesized were studied in the functional assay, and their EC_{50} values are reported in the Table 2. Variations in the EC_{50} values of melatonin have been observed between batches of tadpoles at different times of the year; consequently the potency of the molecules was calculated as the EC_{50}-(melatonin)/EC_{50}(compound) ratio determined in the same experiment. Several compounds were more potent full agonists than melatonin. In particular, the dimethoxy derivatives **15a,c**, with EC_{50} values = 25 and 4 pM, respectively, were more than 100-fold more potent than melatonin, confirming the favorable influence of both methoxy groups in these positions. On the other hand, these data demonstrated that the pharmacological profile was not influenced by the partially constrained ethylamido side chain, in contrast to the phenalene derivatives previously reported by us.[16b] Potent agonist activities were observed with the monomethoxy compounds **13a**,**c**, **14a**,**c**, and **20a,c**. As was observed with the affinity values in the binding assays for melatonin receptors, compounds **14a**,**c** with the methoxy group in the *ortho* position were more potent (potency ratios = 67, 84, respectively) than the isomers **13a,c** (potency ratios = 0.1, 13.3, respectively) with the methoxy group in the melatonin-like position. Although this group is lacking in melatonin, it is capable with the phenalene and acenaphthene derivatives (**14a**,**c**, **20a**,**c**) to facilitate the activation of the receptor and to enhance the transduction process. As was observed in the binding assays, lengthening of the ethylamido chain was not a favorable structural parameter because these compounds were either less potent (**19a**,**c**, **18a**) or partial agonists with very weak potency (**17a**, **22a**). The lack of the methoxy group greatly reduced the efficacy (**16a, 21a**,**c**, **23a**), as has been reported previously in the naphthalene and indole series. However, it is worth noting the nanomolar affinities of **16a** and **21a**, suggesting that this moiety may constitute information to design potent antagonists for these receptors.

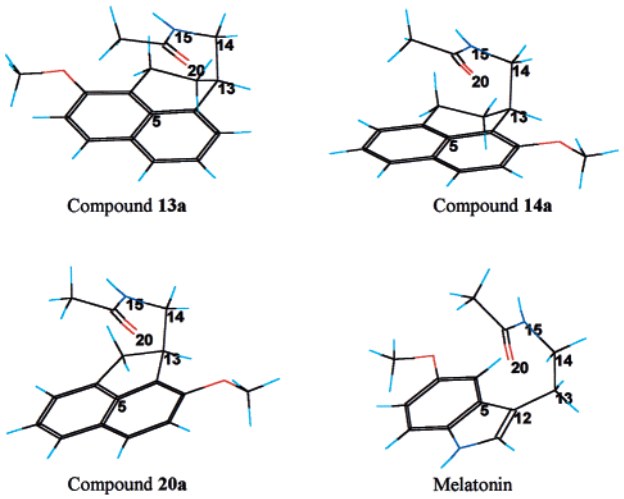


Figure 1. Minimum energy folded conformers of **13a**, **14a**, and **20a**. They have been selected by a conformational search (Alchemy 2000, version 3.2) and by their structural similarity with the CoMFA model of the pharmacophore previously described (ref 36). The *S*-configuration was represented. Conformer of melatonin was calculated by conformational search where the values of 3 ± 0.2 Å were imposed to the distances between the carbon atom C(5) and the nitrogen atom N(15) and the oxygen atom O(20). The fit of the four conformers on the carbon atom C(5), the oxygen atom O(20), and the nitrogen atom N(15) gave the rms value of 0.1.

The reduced number of permissible conformers of these compounds could provide additional information about the active conformation in the binding site. Recently, we proposed using 3D-QSAR studies with a limited number of locked compounds as a model of the pharmacophore structure with the folded ethylamido chain.[36] It was worth confirming this model by examining the different minimum energy conformers calculated by the conformational search using Alchemy 2000 (version 3.2). Conformational search was performed on acenaphthene **20a** and phenalenes **13a** and **14a**. Calculations made around the two rotatable bonds C(13)−C(14) and C(14)−N(15) (Figure 1) of the ethylamido chain gave a large number of conformers in a range of 5 kcal/mol (n > 50). Almost of all the permissible conformers of **13a** and **14a** preferred the axial stereochemistry. In agreement with our previous results, we selected the different conformers with the ethylamido chain in the folded conformation (values of C(13)−C(14) dihedral angle between +90° and −90°), and they were minimized using the Tripos force field. Three minimum energy conformers were found for the phenalene **14a** and the acenaphthene **20a,** while four minimum energy conformers were calculated for the phenalene **13a**. One of them, structurally related to the previous CoMFA model,[36] was selected and they are represented in the Figure 1. Geometrical parameters (3 ± 0.2 Å) representing the distance between the aromatic carbon C(5) and the nitrogen N(15) and the oxygen O(20) atoms of the amidic function were calculated and were imposed for

the conformational search performed on the melatonin. Only one conformer were found to fill these geometrical criteria. A fit of these structures was calculated with regard to the nitrogen and oxygen atoms of the amide function and the fused aromatic carbons. The rms value (0.1) indicated an excellent agreement between these conformers and the importance of the folded conformation of melatonin for binding to the receptor site.

In summary, the conformationally restricted phenalene and acenaphthene derivatives **5** constitute a new class of melatoninergic naphthalene derivatives. They highlighted the role of the methoxy group located in the *ortho* position to the ethylamido chain as compounds with picomolar affinities such as **14c** were obtained which were equipotent to the corresponding dimethoxy derivatives. This finding suggests that this group binds an essential part of the melatonin receptor as **14a**,**c** were potent agonists of melanophore aggregation in *X. laevis*. In this assay, dimethoxy derivatives, such as **15a**,**c**, which were several hundred fold more potent than melatonin were obtained. Similarly to the other class of naphthalene derivatives, the methoxy groups were essential for the efficacy of the molecules. Compounds such as **16a** and **21a** were very weak agonists, while their affinities for melatonin receptors were in the 10 nM range. Conformational studies indicated that the minimum energy folded conformation of the ethylamido chain could constitute the active form in the receptor site and confirmed the previous results using 3D-QSAR and a set of flexible molecules. On the other hand, the restricted conformation of the amido chain did not influence selectivity for the cloned hmt_1 and hMT_2 receptors.

Experimental Section

Melting points were determined on a KOFLER 7841 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AC 200 or AM 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as the internal standard. ^{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 (Hz). TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light. Preparative chromatography was performed under pressure with SDS Chromagel silica 60, 35−70 mesh. All solvents and reagents were reagent grade unless otherwise noted. Elemental analyses were performed at the CNRS microanalysis service in Châtenay-Malabry, France.

4-Methoxy-2,3-dihydrophenalen-1-one **(6a)**, 9-methoxy-2,3-dihydrophenalen-1-one **(6b)**, 4,9-dimethoxy-2,3-dihydrophenalen-1-one **(6c)** and 8-methoxyacenaphthen-1-one **(6e)** were synthesized from the corresponding acids according to the process already described.[23] 2,3-Dihydrophenalen-1-one **(6d)** was synthesized from the commercially available 1*H*-phenalenone.[24] Acenaphthenone **(6f)** was commercially available.

Preparation of Nitriles 9a−c,e,f. General Method. 0.433 g (10.8 mmol) of a 60% NaH oil suspension was washed with pentane and THF (15 mL) was added. Diethyl cyanomethylphosphonate (1.75 mL, 10.8 mmol) was added dropwise under an argon atmosphere to this suspension and the mixture was stirred for 50 min at room temperature. The ketone (94.2 mmol) in 15 mL of THF was added for 10 min and the mixture was stirred overnight. It was quenched with water, filtered through Celite and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and evaporated under reduced pressure. The oil residue was purified by column chromatography (silica gel, CH_2Cl_2/petroleum ether: 60/40), The unsaturated nitrile **8** was obtained as an orange-yellow oil and the presence of *E* and *Z* isomers (55/45) was determined by ^{1}H NMR spectra and CPG.

$PdCl_2$ (55 mg) in methanol (5 mL) was treated with $NaBH_4$ (25 mg) for 15 min. The ethylenic compound in methanol (15 mL) was added to the solution which was stirred for 2.5 h under hydrogen atmosphere. The mixture was filtered through Celite, washed several times with MeOH and the organic solution was evaporated under reduced pressure. The saturated compound was obtained as a white solid. The following compounds were prepared according to this process.

(4-Methoxy-2,3-dihydrophenalen-1-yl)acetonitrile (9a). It was obtained from 4-methoxy-2,3-dihydrophenalen-1-one **(6a)** as a colorless oil: yield 90%; ^{1}H NMR ($CDCl_3$) δ 2.10−2.20 (m, 2H), 2.55−2.59 (m, 2H), 2.85−3.01 (ddd, 1H, J = 6.5 Hz, J = 17.7 Hz, J = 9.6 Hz), 3.15−3.29 (dt, 1H, J = 5.0 Hz, J = 17.7 Hz), 3.34−3.46 (m, 1H), 3.98 (s, 3H, OCH_3), 7.26−7.36 (m, 3H, H_{Ar}), 7.70−7.78 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 19.84, 23.43, 26.50, 36.39, 56.49, 113.08, 119.19, 119.32, 123.46, 124.60, 127.65, 127.81, 129.26, 129.96, 134.61, 153.60. Anal. ($C_{16}H_{15}NO$) C, H, N.

(9-Methoxy-2,3-dihydrophenalen-1-yl)acetonitrile (9b). It was obtained from 9-methoxy-2,3-dihydrophenalen-1-one **(6b)** as a white solid: yield 96%; mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 1.97−2.55 (m, 3H), 2.76−2.86 (dd, 1H, J = 4.4 Hz, J = 16.5 Hz), 3.00−3.16 (m, 2H), 3.84−3.98 (m, 1H), 3.98 (s, 3H, OCH_3), 7.24−7.32 (m, 3H, H_{Ar}), 7.62−7.67 (m, 1H, H_{Ar}), 7.78 (d, 1H, J = 9,1 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 20.72, 24.98, 24.99, 29.73, 56.06, 112.43, 119.25, 119.97, 123.42, 125.07, 126.18, 128.71, 128.72, 129.69, 133.23, 153.04. Anal. ($C_{16}H_{15}NO$) C, H, N.

(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)acetonitrile (9c). It was obtained from 4,9-dimethoxy-2,3-dihydrophenalen-1-one **(6c)** as a white solid: yield 94%; mp 81 °C; ^{1}H NMR ($CDCl_3$) δ 1.85−3.37 (m, 6H), 3.84−3.95 (m, 1H), 3.95−3.96 (2s, 6H), 7.09−7.15 (2d, 2H, J = 9.1 Hz, J = 9.0 Hz, H_{Ar}), 7.63−7.72 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 17.75, 20.68, 24.21, 29.14, 56.04, 56.18, 110.37, 110.81, 117.81, 118.74, 119.33, 124.30, 127.15, 128.57, 130.60, 153.32, 153.58. Anal. ($C_{17}H_{17}NO_2$) C, H, N.

(8-Methoxyacenaphthen-1-yl)acetonitrile (9e). It was obtained from 8-methoxyacenaphthen-1-one **(6e)** as a solid: yield 92%; ^{1}H NMR ($CDCl_3$) δ 2.60−2.73 (dd, 1H, J = 9.5 Hz, J = 16.6 Hz), 3.15−3.32 (m, 2H), 3.69−3.82 (dd, 1H, J = 8.3 Hz, J = 17.5 Hz), 3.96 (s, 3H, OCH_3), 4.05−4.18 (m, 1H), 7.22−7.37 (m, 3H, H_{Ar}), 7.57 (d, 1H, J = 8,1 Hz, H_{Ar}), 7.70 (d, 1H, J = 8.8 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 22.31, 37.42, 38.65, 55.99, 114.74, 119.10, 119.98, 122.64, 125.98, 126.35, 126.69, 127.34, 139.70, 141.61, 152.46. Anal. ($C_{15}H_{13}NO$) C, H, N.

(Acenaphthen-1-yl)acetonitrile (9f). It was obtained from acenaphthen-1-one **(6f)** as an oil: yield 71%; ^{1}H NMR ($CDCl_3$) δ 2.63−2.87 (2dd, 2H, J = 7.7 Hz, J = 6.8 Hz, J = 16.6 Hz), 3.13−3.24 (dd, 1H, J = 3.3 Hz, J = 17.5 Hz), 3.71−3.84 (dd, 1H, J = 8.0 Hz, J = 17.5 Hz), 3.97−4.08 (m, 1H), 7.31 (d, 1H, J = 7.1 Hz, H_{Ar}), 7.41−7.54 (m, 3H, H_{Ar}), 7.63−7.71 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 24.03, 37.58, 39.53, 118.71, 119.36, 119.89, 122.95, 124.17, 127.99, 128.35, 131.58, 138.09, 142.28, 145.06. Anal. ($C_{14}H_{11}N$) C, H, N.

Preparation of Acids 10a,f. General Method. 16.3 mmol of a 60% NaH oil suspension was washed with pentane and THF (24 mL) was added. Triethyl phosphonoacetate (3.22 mL, 16.3 mmol) was added dropwise under an argon atmosphere and the mixture was stirred for 50 min at room temperature. Ketone (14.1 mmol) in 20 mL of THF was added for 10 min and the mixture was stirred overnight. It was quenched with water, filtered through Celite and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and evaporated under reduced pressure. The oil residue was purified by column chromatography (silica gel, CH_2Cl_2/petroleum ether: 60/40). The ethylenic compound was obtained as an orange-yellow oil which crystallized and the presence of *E* and *Z* isomers (55/45) was determined by ^{1}H NMR spectra.

$PdCl_2$ (55 mg) in methanol (5 mL) was treated with $NaBH_4$ (25 mg) for 15 min. The unsaturated ester above (3.5 mmol) in methanol (15 mL) was added to the solution and the mixture was stirred for 2.5 h under a hydrogen atmosphere. The

mixture was filtered through Celite, washed several times with MeOH and the organic solution was evaporated under reduced pressure. The saturated ester was obtained as a white solid. It (7 mmol) was saponified with KOH (4 g, 71 mmol) in a mixture of water (16 mL) and MeOH (16 mL) under reflux overnight. The solution was evaporated under reduced pressure and then the residue was diluted with water and extracted with diethyl ether. The aqueous cooled solution was neutralized with an HCl solution and the organic compound was extracted several times with ethyl acetate. The organic solution was washed with water and dried over $MgSO_4$. The solvent was evaporated and a pure solid compound was obtained. The following compounds were obtained according to this process.

(4-Methoxy-2,3-dihydrophenalen-1-yl)acetic Acid (10a). It was obtained from 4-methoxy-2,3-dihydrophenalen-1-one **(6a)** and isolated as a white solid: yield 84%; mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 2.09−2.14 (m, 2H), 2.65−2.78 (m, 2H, J = 7 Hz, J = 15.4 Hz), 2.94−3.03 (td, 1H, J = 7.7 Hz, J = 17.5 Hz), 3.17−3.23 (td, 1H, J = 4.9 Hz, J = 17.5 Hz), 3.64−3.79 (m, 1H), 3.97 (s, 3H, OCH_3), 7.26−7.31 (m, 3H, H_{Ar}), 7.78 (dd, 1H, J = 7.5 Hz, J = 2 Hz, H_{Ar}), 7.74 (d, 1H, J = 9.0 Hz, H_{Ar}), 11.2 (brs, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 19.78, 26.35, 35.61, 40.07, 56.17, 112.64, 119.81, 123.15, 123.77, 126.68, 126.97, 128.95, 129.94, 136.68, 152.97, 179.21. Anal. ($C_{16}H_{16}O_3$) C, H.

(Acenaphthen-1-yl)acetic Acid (10f). It was obtained from acenaphthen-1-one **(6f)** and isolated as a yellow solid: yield 65%; mp 123 °C; ^{1}H NMR ($CDCl_3$) δ 2.64−2.77 (dd, 1H, J = 9.5 Hz, J = 16.4 Hz), 2.96−3.07 (dd, 1H, J = 5.6 Hz, J = 16.4 Hz), 3.11−3.21 (dd, 1H, J = 3.4 Hz, J = 17.5 Hz), 3.72−3.84 (dd, 1H, J = 8.0 Hz, J = 17.5 Hz), 4.08−4.22 (m, 1H), 7.29−7.34 (m, 2H, H_{Ar}), 7.45−7.53 (m, 2H, H_{Ar}), 7.62−7.69 (m, 2H, H_{Ar}), 9.52 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ: 38.99, 40.28, 41,-97, 60.60, 119.90, 120.48, 123.54, 124.33, 128.87, 129.08, 132.50, 139.10, 144.59, 148.15, 180.16. Anal. ($C_{14}H_{12}O_2$) C, H.

Preparation of Acids 10b,c,e from Nitriles 9b,c,e. A mixture of nitrile **9** (2.11 mmol) and a 30% NaOH solution (8 mL) in a mixture of ethanol (8 mL) and water (8 mL) was refluxed for 48 h. The solution was poured into an ice/water mixture and the solution was acidified with a HCl solution. The organic compound was extracted several times with EtOAc and once with methylene chloride. The organic solutions were washed with water and brine. They were dried over $MgSO_4$ and evaporated under reduced pressure. The acid was obtained as a pale yellow solid. The following compounds were prepared according to this process.

(9-Methoxy-2,3-dihydrophenalen-1-yl)acetic Acid (10b). It was obtained from the nitrile **9b**: yield 97%; mp 147 °C; ^{1}H NMR ($CDCl_3$) δ 1.72−2.09 (m, 2H), 2.28−2.64 (m, 2H, J = 15.1 Hz, J = 10.6 Hz, J = 4.3 Hz), 2.70−3.23 (m, 2H), 3.71 (s, 3H, OCH_3), 3.86−3.99 (m, 1H), 6.97−7.08 (m, 3H, H_{Ar}), 7.78 (dd, 1H, J = 7.0 Hz, J = 2.2 Hz, H_{Ar}), 7.50 (d, 1H, J = 9.0 Hz, H_{Ar}), 11.6 (brs, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 25.43, 25.56, 29.54, 37.93, 56.08, 112.69, 122.46, 123.32, 124.77, 126.11, 127.98, 129.00, 130.21, 134.16, 152.89, 179.84. Anal. ($C_{16}H_{16}O_3$) C, H.

(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)acetic Acid (10c). It was obtained from the nitrile **9c** (yield 63%) after purification by column chromatography (CH_2Cl_2/MeOH: 98/2) as a brown solid: mp 181 °C; ^{1}H NMR ($CDCl_3$) δ 1.80−3.32 (m, 6H), 3.95−3.96 (2s, 6H), 3.94−4.05 (m, 1H), 7.13 (2d, 2H, J = 9.0 Hz, H_{Ar}), 7.63−7.70 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 18.06, 24.63, 28.80, 37.55, 56.00, 56.25, 110.60, 110.81, 118.69, 121.15, 124.44, 126.87, 127.71, 130.60, 152.97, 153.28, 179.57. Anal. ($C_{17}H_{18}O_3$) C, H.

(8-Methoxyacenaphthen-1-yl)acetic Acid (10e). It was obtained from the nitrile **9e** (yield 94%) as a brown solid: mp 114 °C; ^{1}H NMR ($CDCl_3$) δ 2.40−2.54 (dd, 1H, J = 10.8 Hz, J = 16.2 Hz), 3.04−3.15 (dd, 1H, J = 3.2 Hz, J = 17.5 Hz), 3.33−3.43 (dd, 1H, J = 3.8 Hz, J = 16.2 Hz), 3.65−3.78 (dd, 1H, J = 8.1 Hz, J = 17.5 Hz), 3.91 (s, 3H, OCH_3), 4.10−4.27 (m, 1H), 7.15−7.31 (m, 3H, H_{Ar}), 7.52 (d, 1H, J = 8,1 Hz, H_{Ar}), 7.63 (d, 1H, J = 8.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ: 38.19, 38.36, 39.04, 56.08, 115.15, 119.58, 122.31, 125.45, 125.81, 126.80, 129.67, 139.89, 142.96, 152.31, 179.57. Anal. ($C_{15}H_{14}O_3$) C, H.

Preparation of Amines 11 from Acids 10. (4-Methoxy-2,3-dihydrophenalen-1-yl)methylamine Hydrochloride (11a). To a cooled solution of acid **10a** (1.03 g, 4.02 mmol) in an acetone/water (17 mL/1 mL) mixture were added triethylamine (645 μL, 4.63 mmol) and ethyl chloroformate (500 μL, 5.23 mmol). After 30 min at 0 °C, sodium azide (0.35 g, 5.23 mmol) in water (1.7 mL) was added and the reaction mixture was stirred at 0 °C for 1 h. It was poured on to ice and extracted with diethyl ether. The organic layers were washed with water, dried over Na_2SO_4, and evaporated in vacuo at room temperature. The resulting azide, diluted with 10 mL of dry toluene, was heated at 80 °C until the gas had been removed. After evaporation of the solvent, the resulting isocyanate was heated at 100 °C with a 20% HCl solution (8 mL) for 3 h. After stirring at room temperature overnight, dilution with water and filtration, the liquid phase was extracted with diethyl ether. The aqueous phase was made alkaline with Na_2CO_3 and then extracted with CH_2Cl_2. The organic phases were washed with water and dried over K_2CO_3. After evaporation, in vacuo, the amine was converted to the hydrochloride salt with 4 N HCl in diethyl ether to give 0.76 g of solid: yield 72%; mp 237 °C; ^{1}H NMR (CD_3OD) δ 1.99−2.27 (m, 2H, CH_2), 2.82−2.99 (m, 1H,), 3.05−3.25 (m, 3H), 3.37−3.47 (m, 1H, CH), 3.95 (s, 3H, OMe), 7.23−7.38 (m, 2H, H_{ar}), 7.67−7.78 (m, 2H, H_{ar}); ^{13}C NMR (CD_3OD) δ 18.31, 19.95, 38.68, 43.97, 56.63, 113.97, 119.85, 124.12, 126.00, 128.44, 128.70, 130.57, 131.03, 134.12, 154.74. Anal. ($C_{15}H_{18}ClNO$) C, H, N.

(9-Methoxy-2,3-dihydrophenalen-1-yl)methylamine (11b). The compound was obtained according to the process described above for **11a** from the acid **10b** (0.515 g, 2.01 mmol). After the usual workup, 0.36 g of the free amine was obtained as an oil: yield 79%; ^{1}H NMR ($CDCl_3$) δ 1.69 (brs, 2H), 1.78−2.35 (m, 2H), 2.70−3.24 (m, 4H), 3.43−3.52 (m, 1H), 3.91 (s, 3H), 7.18−7.25 (m, 3H, H_{Ar}), 7.58 (dd, 1H, J = 8.5 Hz, H_{Ar}), 7.69 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.14, 25.36, 44.36, 44.39, 56.25, 112.84, 114.83, 117.92, 123.16, 124.60, 125.86, 127.50, 128.97, 134.32, 153.07.

(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)methylamine (11c). The compound was obtained according to the process described above for **11a** from the acid **10c** (1.3 g, 4.54 mmol). After the usual workup, 0.83 g of the free amine was obtained as an oil: yield 71%; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 2H), 1.71−3.24 (m, 6H), 3.45−3.56 (m, 1H), 3.92−3.93 (2s, 6H), 7.09−7.14 (2d, 2H, J = 9.0 Hz, H_{Ar}), 7.61−7.67 (2d, 2H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 18.31, 22.49, 35.46, 44.76, 56.20, 56.21, 110.73, 110.90, 118.99, 121.22, 124.55, 126.76, 127.35, 131.17, 153.26, 153.27.

(8-Methoxyacenaphthen-1-yl)methylamine (11e). The compound was obtained according to the process described above for **11a** from the acid **10e** (1.17 g, 4.83 mmol). After the usual workup, the free amine was isolated as an oil: 0.96 g, yield 93%; ^{1}H NMR ($CDCl_3$) δ 1.40 (brs, 2H), 2.99−3.22 (m, 3H); 3.47−3.60 (dd, 1H, J = 8.2 Hz, J = 17.4 Hz), 3.82−3.92 (m, 1H, CH), 3.92 (s, 3H), 7.20−7.36 (m, 3H, H_{Ar}), 7.56 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.65 (d, 1H, J = 8.8 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 35.48, 35.72, 46.07, 56.20, 115.33, 119.48, 122.24, 125.26, 125.76, 126.96, 129.48, 140.76, 143.56, 152.46.

(Acenaphthen-1-yl)methylamine Hydrochloride (11f). The compound was obtained according to the process described above for **11a** from the acid **10f** (4.62 g, 21.8 mmol). After the usual workup, 1.63 g of hydrochloride salt was obtained as a white solid: yield 55%; mp > 250 °C; ^{1}H NMR (free amine, $CDCl_3$) δ 1.31 (brs, 2H), 3.06−3.22(m, 3H), 3.52−3.65 (dd, 1H, J = 8.1 Hz, J = 17.2 Hz), 3.71−3.80 (m, 1H), 7.26−7.34 (m, 2H, H_{Ar}), 7.42−7.51 (m, 2H, H_{Ar}), 7.60−7.66 (m, 2H, H_{Ar}); ^{13}C NMR (hydrochloride, DMSO-d_6) δ 35.42, 41.43, 43.57, 119.76, 119.82, 122.42, 123.49, 128.04, 128.31, 131.17, 138.05, 143.50, 144.82. Anal. ($C_{13}H_{14}ClN$) C, H, N.

Preparation of Amines 12a,c,e,f from Nitriles 9. (4-Methoxy-2,3-dihydrophenalen-1-yl)ethylamine Hydrochloride (12a). NH_4OH solution (1 mL) was added to a solution of the nitrile **9a** (1.26 g, 5.31 mmol) in 15 mL of MeOH. The solution was vigorously stirred under a hydrogen

atmosphere in the presence of a catalytic amount of Raney nickel for 48 h at room temperature. The mixture was filtered through Celite and the solid was washed with methanol. The organic solution was evaporated under reduced pressure and the residue was dissolved in 4 N HCl diethyl ether solution. The hydrochloride salt was recrystallized in a EtOH/Et_2O mixture to give 0.66 g (yield 45%) of a white solid: mp 223 °C; ^{1}H NMR (CD_3OD) δ 1.85−2.12 (m, 4H), 2.83−3.31 (m, 5H), 3.94 (s, 3H), 7.18−7.28 (m, 2H, H_{Ar}), 7.33 (d, 1H, J = 9.0 Hz, H_{Ar}), 7.65 (d, 1H, J = 7.1 Hz, H_{Ar}), 7.73 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR (CD_3OD) δ 20.33, 27.34, 33.59, 37.79, 39.10, 56.57, 113.74, 120.38, 123.88, 125.21, 127.8, 128.22, 130.62, 130.99, 137.82, 154.54. Anal. ($C_{16}H_{20}ClNO$) C, H, N.

(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)ethylamine (12c). The compound was synthesized according to the process described above for **12a** from the nitrile **9c** (0.5 g, 1.87 mmol). It was isolated as an oil: 0.45 g, yield 89%; ^{1}H NMR ($CDCl_3$) δ 1.61−2.15 (m, 6H), 2.71−3.24 (m, 4H), 3.56−3.64 (m, 1H), 3.93−3.94 (2s, 6H), 7.12 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.65 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.50, 25.34, 28.39, 38.17, 40.23, 56.13, 56.22, 110.77, 110.78, 119.09, 123.32, 124.66, 126.76, 127.04, 130.97, 152.77, 153.28.

2-(8-Methoxyacenaphthen-1-yl)ethylamine (12e). The compound was synthesized according to the process described above for **12a** from the nitrile **9e** (0.650 g, 2.91 mmol). It was isolated as an oil: 0.6 g, yield 91%; ^{1}H NMR ($CDCl_3$) δ 1.6−1.8 (m, 3H), 2.1−2.35 (m, 1H), 2.78−2.85 (m, 2H), 3−3.02 (dd, 1H, J = 17.3 Hz), 3.48−3.61 (dd, 1H, J = 8.1 Hz, J = 17.3 Hz), 3.79−3.90 (m, 1H), 3.95 (s, 3H), 7.17−7.34 (m, 3H, H_{Ar}), 7.54 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.63 (d, 1H, J = 8.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 37.56, 38.93, 39.84, 40.50, 56.21, 115.43, 119.32, 122.16, 124.85, 125.65, 126.89, 131.70, 140.01, 143.55, 152.17.

2-(Acenaphthen-1-yl)ethylamine (12f). The compound was synthesized according to the process described above for **12a** from the nitrile **9f** (0.9 g, 4.66 mmol). It was isolated as an oil: 0.84 g, yield 92%; ^{1}H NMR ($CDCl_3$) δ 1.72 (brs, 2H), 1.72−2.18 (m, 2H), 2.80−2.95 (m, 2H), 3.00−3.11 (dd, 1H, J = 3.2 Hz, J = 17.0 Hz), 3.52−3.65 (dd, 1H, J = 7.9 Hz, J = 17.0 Hz), 3.69−3.80 (m, 1H), 7.25−7.28 (m, 2H, H_{Ar}), 7.41−7.50 (m, 2H, H_{ar}), 7.59−7.63 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 38.46, 41.26, 41.37, 42.01, 119.73, 120.17, 123.30, 123.66, 128.74, 128.82, 132.43, 139.46, 145.34, 150.04.

Preparation of Amide Derivatives 13a,b, 14a, 15a, 20a,b, and 21a,b. Anhydride Method. The free amine or the hydrochloride salt (1.14 mmol) was taken up in a CH_2Cl_2/water (17 mL/17 mL) biphasic system with sodium carbonate (854 mg, 7.96 mmol). Acetic anhydride (110 μL, 1.17 mmol) was slowly added at 0 °C. The reaction mixture was stirred for 20 min at room temperature. It was washed with water, saturated $NaHCO_3$, and brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude acetamido derivative was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 99/1). Recrystallization from hexane/ethyl acetate mixture gave a white solid. According to this process the following compounds were prepared.

***N*-[(4-Methoxy-2,3-dihydrophenalen-1-yl)methyl]acetamide (13a).** It was obtained from the amine **11a** and acetic anhydride: yield 74%; mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.01−2.11 (m, 2H), 2.95 (ddd, 1H, J = 6 Hz, J = 17.6 Hz, J = 10.1 Hz), 3.15 (td, 1H, J = 5.0 Hz, J = 17.6 Hz), 3.24−3.41 (m, 2H), 3.59−3.75 (m, 1H), 3.95 (s, 3H), 5.57 (brs, 1H), 7.20−7.31 (m, 3H, H_{Ar}), 7.65−7.75 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 20.47, 24.11, 25.29, 39.46, 43.84, 56.90, 113.45, 119.88, 122.93, 124.34, 126.76, 126.93, 128.99, 130.15, 135.19, 153.05, 170.11. Anal. ($C_{17}H_{19}NO_2$) C, H, N.

***N*-[(4-Methoxy-2,3-dihydrophenalen-1-yl)methyl]propanamide (13b).** The compound was obtained from the amine **11a** and propionic anhydride: yield 51%; mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7.6 Hz), 2.01−2.10 (m, 2H), 2.21 (q, 2H, J = 7.6 Hz), 2.86−3.09 (ddd, 1H, J = 5.9 Hz, J = 17.6 Hz, J = 10.5 Hz), 3.16 (td, 1H, J = 4.9 Hz, J = 17.6 Hz), 3.26−3.42 (m, 2H), 3.62−3.77 (m, 1H), 3.96 (s, 3H), 5.49 (brs, 1H), 7.20−7.31 (m, 3H, H_{Ar}), 7.65−7.75 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.90, 19.74, 24.56, 29.84, 38.81, 43.00, 56.20, 112.76, 119.93, 122.93, 124.42, 126.75, 126.93, 129.00, 130.20, 135.28, 153.06, 173.84. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***N*-[(9-Methoxy-2,3-dihydrophenalen-1-yl)methyl]acetamide (14a).** The compound was obtained from the amine **11b** and acetic anhydride. It was purified by chromatography (ethyl acetate/petroleum ether: 40/60) to give a white solid: yield 56%; mp 192 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 1.88−2.21 (m, 2H), 2.90−3.70 (m, 5H), 3.99 (s, 3H), 6.16 (brs, 1H), 7.24−7.31 (m, 3H, H_{Ar}), 7.63 (dd, 1H, J = 8.5 Hz, H_{Ar}), 7.75 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.20, 24.65, 25.43, 32.02, 43.54, 56.29, 112.59, 121.33, 123.37, 124.87, 125.75, 127.97, 129.11, 129.94, 134.00, 152.58, 169.88. Anal. ($C_{17}H_{19}NO_2$) C, H, N.

***N*-[(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)methyl]acetamide (15a).** The compound was obtained from the amine **11c** and acetic anhydride: yield 70%; mp 184 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H), 1.76−1.88, 2.11−2.22 (m, 2H), 2.81 (ddd, 1H, J = 5 Hz, J = 17.8 Hz, J = 13.6 Hz), 3.14−3.59 (m, 3H), 3.60−3.75 (m, 1H), 3.93−3.97 (2s, 6H), 6.18 (s, 1H), 7.13 (d, 2H, J = 9.2 Hz, H_{Ar}), 7.63−7.71 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 18.54, 23.28, 24.19, 31.26, 43.95, 56.14, 56.38, 110.67, 111.02, 118.84, 120.21, 124.73, 126.81, 127.97, 130.92, 152.92, 153.54, 170.05. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***N*-[(8-Methoxyacenaphthen-1-yl)methyl]acetamide (20a).** The compound was obtained from the amine **11e** and propionic anhydride: yield 58%; mp 148 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 3.03−3.13 (dd, 1H, J = 2.9 Hz, J = 17.5 Hz), 3.36−3.49 (m, 1H), 3.51−3.64 (m, 1H, J = 8.1 Hz, J = 17.5 Hz), 3.65−3.99 (m, 2H), 4.00 (s, 3H), 6.47 (s, 1H); 7.20−7.36 (m, 3H, H_{Ar}), 7.56 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.69 (d, 1H, J = 8.8 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.50, 36.00, 42.24, 44.28, 56.43, 115.13, 119.77, 122.35, 125.86, 126.06, 127.17, 129.19, 140, 142.81, 151.93, 170.25. Anal. ($C_{16}H_{17}NO_2$) C, H, N.

***N*-[(8-Methoxyacenaphthen-1-yl)methyl]propanamide (20b).** The compound was obtained from the amine **11e** and propionic anhydride: yield 66%; mp 160 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7.5 Hz), 2.08−2.19 (m, 2H), 3.01−3.11 (dd, 1H, J = 3.0 Hz, J = 17.3 Hz), 3.35−3.61 (m, 2H), 3.74−3.95 (m, 2H), 3.96 (s, 3H), 6.44 (brs, 1H), 7.16−7.32 (m, 3H, H_{Ar}), 7.53 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.65 (d, 1H, J = 9.1 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.92, 29.94, 36.08, 42.30, 44.17, 56.44, 115.16, 119.73, 122.32, 125.83, 126.04, 127.15, 129.27, 140.30, 142.85, 151.95, 173.98. Anal. ($C_{17}H_{19}NO_2$) C, H, N.

***N*-[(Acenaphthen-1-yl)methyl]acetamide (21a).** The compound was obtained from the amine **11f** and acetic anhydride: yield 57%; mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H), 3.08−3.18 (dd, 1H, J = 3.2 Hz, J = 17.2 Hz), 3.50−3.82 (m, 3H), 3.8−4.00 (m, 1H), 5.54 (s, 1H), 7.26−7.32 (m, 2H, H_{Ar}), 7.43−7.51 (m, 2H, H_{Ar}), 7.60−7.68 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 24.29, 36.1, 43.97, 44.82, 120.02, 120.54, 123.41, 124.39, 128.70, 129.06, 132.48, 139.81, 144.86, 146.80, 171.40. Anal. ($C_{15}H_{15}NO$) C, H, N.

***N*-[(Acenaphthen-1-yl)methyl]propanamide (21b).** The compound was obtained from the amine **11f** and propionic anhydride: yield 82%; mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.6 Hz), 2.12 (q, 2H, J = 7.6 Hz), 3.08−3.18 (dd, 1H, J = 3.2 Hz, J = 17.5 Hz), 3.50−3.83 (m, 3H), 3.89−3.99 (m, 1H), 5.46 (brs, 1H), 7.26−7.32 (m, 2H, H_{Ar}), 7.42−7.51 (m, 2H, H_{Ar}), 7.60−7.69 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.86, 29.81, 35.31, 43.18, 43.86, 119.13, 119.62, 122.50, 123.49, 127.81, 128.17, 131.57, 138.93, 144.03, 146.0, 174.18. Anal. ($C_{16}H_{17}NO$) C, H, N.

Preparation of Amido Derivatives 13c,d, 14c, 15b−d, 17c,d, 19d, 20c,d, 21c,d, 22d, and 23d. Acid Chloride Method. The free amine (0.8 mmol) was dissolved in dry CH_2Cl_2 (8 mL) with triethylamine (167 μL, 1.2 mmol). Acid chloride (0.8 mmol) was added at 0 °C and the reaction mixture was stirred for 40 min. According to the process described above, the compound was purified by columm chromatography and recrystallized under the same conditions to give the pure compound. The following compounds were prepared.

***N*-[(4-Methoxy-2,3-dihydrophenalen-1-yl)methyl]butanamide (13c).** It was prepared from the amine **11a** and

butanoyl chloride. A white solid was obtained: yield 44%; mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.56−1.75 (m, 2H), 1.97−2.10 (m, 2H), 2.14 (t, 2H, J = 7.3 Hz), 2.86−3.02 (ddd, 1H, J = 5.4 Hz, J = 17.4 Hz, J = 10.7 Hz), 3.08−3.38 (m, 3H), 3.53−3.67 (m, 1H), 3.91 (s, 3H), 6.01 (brs, 1H), 7.20−7.29 (m, 3H, H_{Ar}), 7.62−7.71 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 14.00, 19.41, 19.84, 24.53, 38.85, 39.04, 43.27, 56.30, 112.87, 120.11, 123.14, 124.64, 126.84, 127.08, 129.15, 130.38, 135.60, 153.18, 173.47. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***N*-[(4-Methoxy-2,3-dihydrophenalen-1-yl)methyl]cyclopropylcarboxamide (13d).** It was obtained from the amine **11a** and cyclopropanecarbonyl chloride: yield 43%; mp 119 °C; ^{1}H NMR ($CDCl_3$) δ 0.65−0.83 (m, 2H), 0.92−1.40 (m, 2H), 1.26 (m, 1H), 1.97−2.14 (m, 2H), 2.87−3.04 (ddd, 1H, J = 5.4 Hz, J = 17.5 Hz, J = 10.6 Hz), 3.16 (td, 1H, J = 4.9 Hz, J = 17.5 Hz), 3.26−3.49 (m, 2H), 3.60−3.76 (m, 1H), 3.96 (s, 3H), 5.77 (brs, 1H), 7.25−7.31 (m, 3H, H_{Ar}), 7.66−7.76 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 7.72, 8.71, 15.52, 20.45, 25.22, 39.59, 43.95, 56.89, 113.43, 120.66, 123.67, 125.11, 127.39, 127.60, 129.68, 136.03, 153.72, 174.30. Anal. ($C_{19}H_{21}NO_2$) C, H, N.

***N*-[(9-Methoxy-2,3-dihydrophenalen-1-yl)methyl]butanamide (14c).** The compound was obtained from the amine **11b** and butyryl chloride: yield 81%; mp 114 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz), 1.45−1.75 (m, 2H), 1.80−2.20 (m, 2H, CH_2), 2.15 (t, 2H, J = 7.4 Hz), 2.87−3.75 (m, 5H), 3.92 (s, 3H), 6.53 (brs, 1H), 7.20−7.29 (m, 3H, H_{Ar}), 7.61 (dd, 1H, J = 7.8 Hz, H_{Ar}), 7.72 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.85, 19.16, 24.62, 25.64, 32.34, 38.84, 43.20, 56.42, 112.78, 121.56, 123.51, 125.00, 125.92, 128.10, 129.26, 130.18, 134.28, 152.81, 173.08. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***N*-[(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)methyl]propanamide (15b).** The compound was obtained from the amine **11c** and propionyl chloride: yield 35%; mp 158 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.6 Hz), 1.75−2.21 (m, 2H), 2.15 (q, 2H, J = 7.6 Hz), 2.73−2.91 (ddd, 1H, J = 4.9 Hz, J = 17.9 Hz, J = 13.5 Hz), 3.14−3.69 (m, 3H), 3.60−3.75 (m, 1H), 3.93−3.97 (2s, 6H), 6.19 (brs, 1H), 7.13 (d, 2H, J = 8.9 Hz, H_{Ar}), 7.63−7.71 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.85, 18.64, 24.13, 29.79, 31.38, 43.62, 56.18, 56.38, 110.70, 111.04, 118.94, 120.31, 124.77, 126.87, 127.99, 131.02, 153.02, 153.59, 173.81. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

***N*-[(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)methyl]butanamide (15c).** The compound was obtained from the amine **11c** and butyryl chloride: yield 48%; mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 7.6 Hz), 1.55−1.75 (m, 2H), 1.75−2.22 (m, 2H), 2.12 (t, 2H, J = 7.6 Hz), 2.69−2.93 (ddd, 1H), 3.13−3.60 (m, 3H), 3.61−3.74 (m, 1H), 3.93−3.97 (2s, 6H), 6.18 (s, 1H), 7.13 (d, 2H, J = 8.9 Hz, H_{ar}), 7.63−7.71 (2d, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 13.78, 18.62, 19.06, 31.32, 38.88, 43.79, 56.20, 56.41, 110.69, 111.08, 118.95, 120.32, 124.77, 126.82, 127.97, 130.98, 152.94, 153.59, 172.92. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

***N*-[(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)methyl]cyclopropylcarboxamide (15d).** The compound was obtained from the amine **11c** and cyclopropanecarbonyl chloride: yield 60%; mp 192 °C; ^{1}H NMR ($CDCl_3$) δ 0.64−0.70 (m, 2H), 0.91−0.96 (m, 2H), 1.21−1.32 (m, 1H), 1.73−2.22 (m, 2H), 2.70−2.91 (ddd, 1H), 3.13−3.61 (m, 3H), 3.62−3.75 (m, 1H), 3.95−3.98 (2s, 6H), 6.27 (s, 1H), 7.13 (2d, 2H, J = 8.9 Hz, J = 9.1 Hz, H_{ar}), 7.63−7.71 (2d, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 6.81, 14.86, 18.58, 24.11, 31.47, 43.84, 56.19, 56.36, 110.69, 111.03, 118.97, 120.3, 124.73, 126.79, 127.91, 131.00, 153.01, 173.36. Anal. ($C_{20}H_{23}NO_3$) C, H, N.

***N*-[2-(4-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]butanamide (17c).** The compound was obtained from the amine **12a** and butyryl chloride as a colorless oil: yield 24%; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J = 7.3 Hz), 1.50−1.65 (m, 2H), 1.66−1.80 (m, 2H), 1.99−2.06 (t, m, 4H, J = 7.3 Hz), 2.79−3.55 (m, 5H), 3.90 (s, 3H), 5.63 (s, 1H), 7.12−7.24 (m, 3H, H_{ar}), 7.60 (dd, 1H, J = 7.6 Hz, J = 1.8 Hz, H_{ar}), 7.66 (d, 1H, J = 9.0 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 13.79, 19.23, 19.63, 26.38, 34.67, 36.85, 37.56, 38.72, 56.21, 112.60, 120.07, 123.05, 124.19, 126.33, 126.92, 129.04, 129.97, 137.89, 152.96, 173.09.

***N*-[2-(4-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]cyclopropylcarboxamide (17d).** The compound was obtained from the amine **12a** and cyclopropanecarbonyl chloride: yield 38%; mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 0.67−0.72 (m, 2H), 0.92−0.96 (m, 2H), 1.22−1.28 (m, 1H), 1.74−1.89 (m, 2H), 1.99−2.09 (m, 2H), 2.88−3.18 (m, 3H), 3.25−3.56 (m, 2H), 3.95 (s, 3H), 5.57 (s, 1H, NH), 7.20−7.27 (m, 3H, H_{ar}), 7.63 (dd, 1H, J = 7.9 Hz, J = 1.5 Hz, H_{ar}), 7.71 (d, 1H, J = 9.0 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 7.00, 14.67, 19.68, 26.42, 34.72, 36.80, 37.83, 56.22, 112.61, 120.15, 123.06, 124.19, 126.28, 126.91, 129.06, 130.00, 137.32, 152.96, 173.62. Anal. ($C_{20}H_{23}NO_2$) C, H, N.

***N*-[2-(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)ethyl]cyclopropylcarboxamide (19d).** The compound was obtained from the amine **12c** and cyclopropanecarbonyl chloride: yield 31%; mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 0.67−0.74 (m, 2H), 0.92−0.99 (m, 2H), 1.26−1.34 (m, 1H), 1.51−2.15 (m, 4H), 2.78 (ddd, 1H, J = 5.0 Hz, J = 17.8 Hz, J = 13.5 Hz), 3.03−3.59 (m, 4H), 3.92−3.94 (2s, 6H), 6.18 (brs, 1H), 7.08−7.13 (2d, 2H, J = 9.0 Hz, H_{ar}), 7.62−7.66 (2d, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 6.90; 14.88, 18.47, 25.40, 28.63, 33.66, 37.90, 56.17, 56.34, 110.81, 118.97, 122.74, 124.72, 126.83, 127.36, 130.90, 152.72, 153.42, 173.34. Anal. ($C_{21}H_{25}NO_3$) C, H, N.

***N*-[(8-Methoxyacenaphthen-1-yl)methyl]butanamide (20c).** The compound was obtained from the amine **11e** and butyryl chloride: yield 48%; mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.3 Hz), 1.54 (m, 2H), 2.07 (t, 2H, J = 7.3 Hz), 3.01−3.11 (dd, 1H, J = 3.0 Hz, J = 17.3 Hz), 3.37−3.60 (m, 2H), 3.74−3.93 (m, 2H), 3.96 (s, 3H), 6.40 (brs, 1H), 7.15−7.32 (m, 3H, H_{Ar}), 7.52 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.65 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.73, 19.13, 36.00, 38.93, 42.30, 43.96, 56.36, 115.09, 119.68, 122.26, 125.76, 125.98, 127.08, 129.18, 140.27, 142.81, 151.89, 173.10. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***N*-[(8-Methoxyacenaphthen-1-yl)methyl]cyclopropylcarboxamide (20d).** The compound was obtained from the amine **11e** and cyclopropanecarbonyl chloride: yield 71%; mp 185 °C; ^{1}H NMR ($CDCl_3$) δ 0.64−0.69 (m, 2H), 0.91−0.94 (m, 2H), 1.19−1.31 (m, 1H), 3.01−3.12 (dd, 1H, J = 3.0 Hz, J = 17.4 Hz), 3.40−3.61 (m, 2H), 3.74−3.93 (m, 2H), 3.97 (s, 3H), 6.61 (s, 1H), 7.16−7.33 (m, 3H, H_{Ar}), 7.53 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.66 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 6.97, 7.02, 14.98, 36.03, 42.42, 44.31, 56.46, 115.26, 119.74, 122.32, 125.79, 126.03, 127.16, 129.32, 140.34, 142.91, 152.02, 173.69. Anal. ($C_{18}H_{19}NO_2$) C, H, N.

***N*-[(Acenaphthen-1-yl)methyl]butanamide (21c).** The compound was obtained from the amine **11f** and butyryl chloride: yield 76%; mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.4 Hz), 1.57 (m, 2H, J = 7.4 Hz), 2.07 (t, 2H), 3.08−3.18 (dd, J = 3.0 Hz, J = 17.6 Hz), 3.42−3.85 (m, 3H), 3.89−3.99 (m, 1H), 5.43 (s, 1H), 7.26−7.32 (m, 2H, H_{Ar}), 7.42−7.51 (m, 2H, H_{Ar}), 7.60−7.68 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.65, 19.11, 35.29, 38.74, 43.16, 43.78, 119.09, 119.60, 122.47, 123.46, 127.78, 128.13, 131.54, 138.91, 143.98, 145.96, 173.38. Anal. ($C_{17}H_{19}NO$) C, H, N.

***N*-[(Acenaphthen-1-yl)methyl]cyclopropylcarboxamide (21d).** The compound was obtained from the amine **11f** and cyclopropanecarbonyl chloride: yield 79%; mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 0.55−0.64 (m, 2H), 0.83−0.90 (m, 2H), 1.09−1.22 (m, 1H), 3.0−3.10 (dd, J = 3.4 Hz, J = 17.5 Hz), 3.40−3.74 (m, 3H), 3.79−3.96 (m, 1H), 5.69 (s, 1H), 7.17−7.25 (m, 2H, H_{Ar}), 7.34−7.43 (m, 2H, H_{Ar}), 7.51−7.59 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 7.14, 7.22, 14.78, 35.33, 43.25, 44.11, 119.20, 119.64, 122.49, 123.45, 127.83, 128.14, 131.59, 138.94, 144.07, 146.06, 173.99. Anal. ($C_{17}H_{17}NO$) C, H, N.

***N*-[2-(8-Methoxyacenaphthen-1-yl)ethyl]cyclopropylcarboxamide (22d).** The compound was obtained from the amine **12e** and cyclopropanecarbonyl chloride: yield 73%; mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 0.63−0.72 (m, 2H), 0.88−0.95 (m, 2H), 1.15−1.30 (m, 1H), 1.75−2.31 (m, 2H), 3.02−3.61 (m, 4H), 3.73−3.88 (m, 1H), 3.92 (s, 3H), 5.71 (s, 1H), 7.15−7.31 (m, 3H, H_{Ar}), 7.63 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.71 (d, 1H, J = 8.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 7.0, 14.79, 34.65, 37.63, 38.00, 39.73, 56.21, 115.24, 119.54, 122.19, 125.12, 125.80, 126.95, 131.10, 140.00, 143.35, 152.11, 173.44. Anal. ($C_{19}H_{21}NO_2$) C, H, N.

***N*-[2-(Acenaphthen-1-yl)ethyl]cyclopropylcarboxamide (23d).** The compound was obtained from the amine **12f** and cyclopropanecarbonyl chloride: yield 92%; mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 0.66−0.76 (m, 2H), 0.92−1.00 (m, 2H), 1.22−1.34 (m, 1H), 1.76−2.23 (m, 2H), 3.05−3.79 (m, 5H), 5.71 (s, 1H), 7.25−7.30 (m, 2H, H_{Ar}), 7.41−7.49 (m, 2H, H_{Ar}), 7.58−7.64 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 7.10, 14.78, 36.46, 37.43, 37.94, 41.05, 118.89, 119.37, 122.41, 122.92, 127.81, 127.99, 131.53, 138.49, 144.23, 148.57, 173.54. Anal. ($C_{18}H_{19}NO$) C, H, N.

Preparation of Amides from Nitriles 9. A solution of nitrile **9** (1.85 mmol) in THF (12 mL) was stirred under a hydrogen atmosphere in the presence of anhydride (4.56 mmol) and Raney nickel for 8 h at room temperature. The mixture was filtered through Celite and evaporated under reduced pressure. The organic material was diluted in CH_2Cl_2, washed with water, a saturated $NaHCO_3$ solution, brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The amido derivative was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 99/1) and crystallized in hexane/ethyl acetate mixture to give a white solid. According to this process the following compounds were prepared.

***N*-[2-(4-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]acetamide (17a).** It was obtained from the nitrile **9a** and acetic anhydride as a colorless oil (yield 67%) after chromatography: ^{1}H NMR ($CDCl_3$) δ 1.71−1.86 (m, 2H), 1.91 (s, 3H), 1.99−2.09 (m, 2H), 2.82−3.58 (m, 5H), 3.95 (s, 3H), 5.43 (s, 1H), 7.17−7.28 (m, 3H, H_{Ar}), 7.65 (dd, 1H, J = 7.6 Hz, J = 1.8 Hz, H_{Ar}), 7.71 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 19.59, 23.19, 26.35, 34.47, 36.76, 37.70, 56.17, 112.56, 120.00, 122.97, 124.11, 126.27, 126.85, 128.98, 129.91, 137.74, 152.90, 170.16. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***N*-[2-(4-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]propanamide (17b).** It was obtained from the nitrile **9a** and propionic anhydride as a pale yellow oil (yield 77%) after chromatography: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.6 Hz), 1.70−1.81 (m, 2H), 1.99−2.06 (m, 2H), 2.12 (q, 2H, J = 7.6 Hz), 2.82−3.50 (m, 5H), 3.92 (s, 3H), 5.89 (s, 1H), 7.16−7.26 (m, 3H, H_{Ar}), 7.62 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz, H_{Ar}), 7.68 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.94, 19.61, 26.34, 29.60, 34.53, 36.77, 37.54, 56.12, 112.55, 120.03, 122.98, 124.11, 126.24, 126.86, 129.00, 129.94, 137.87, 152.91, 174.05. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***N*-[2-(9-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]acetamide (18a).** It was obtained from the nitrile **9b** and acetic anhydride after purification by chromatography (AcOEt/petroleum ether: 30/50) as a white solid: yield 73%; mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 1.63−2.18 (m, 4H), 2.00 (s, 3H), 2.87−3.75 (m, 5H), 3.97 (s, 3H), 5.88 (s, 1H), 7.23−7.30 (m, 3H, H_{Ar}), 7.62 (d, 1H, J = 7.1 Hz, H_{Ar}), 7.73 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.25, 25.33, 25.74, 29.33, 33.47, 37.94, 56.30, 112.82, 123.29, 124.14, 124.74, 125.89, 127.44, 129.14, 129.96, 134.25, 152.44, 170.23. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***N*-[2-(9-Methoxy-2,3-dihydrophenalen-1-yl)ethyl]butanamide (18c).** It was obtained from the nitrile **9b** and butyric anhydride (yield 55%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.58−1.85 (m, 2H), 1.85−2.35 (m, 6H), 2.88−3.60 (m, 5H), 3.94 (s, 3H), 6.10 (s, 1H), 7.09−7.29 (m, 3H, H_{Ar}), 7.61 (d, 1H, J = 7.1 Hz, H_{Ar}), 7.71 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.82, 19.29, 25.36, 25.89, 29.24, 33.64, 37.77, 38.88, 56.41, 112.85, 123.90, 124.18, 124.83, 125.91, 127.52, 129.23, 129.99, 134.30, 152.45, 173.32.

***N*-[2-(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)ethyl]acetamide (19a).** It was obtained from the nitrile **9c** and acetic anhydride (yield 51%) as a white solid: mp 125 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 1.60−2.14 (m, 4H), 2.78 (ddd, 1H, J = 5.2 Hz, J = 17.9 Hz, J = 13.5 Hz), 3.02−3.65 (m, 4H), 3.94−3.96 (2s, 6H), 5.89 (brs, 1H), 7.09−7.15 (2d, 2H, J = 9.0 Hz, H_{Ar}), 7.63−7.68 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 18.30, 23.37, 25.29, 28.42, 33.41, 37.61, 56.04, 56.27, 110.66, 110.72, 118.83, 122.52, 124.59, 126.68, 127.27, 130.73, 152.53, 153.32, 169.71. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

***N*-[2-(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)ethyl]propanamide (19b).** It was obtained from the nitrile **9c** and propionic anhydride (yield 70%) as a white solid: mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.6 Hz), 1.61−2.14 (m, 4H), 2.21 (q, 2H, J = 7.6 Hz), 2.79 (ddd, 1H, J = 4.9 Hz, J = 17.7 Hz, J = 13.5 Hz), 3.01−3.62 (m, 4H), 3.94−3.95 (2s, 6H), 5.89 (s, 1H), 7.10−7.15 (2d, 2H, J = 9.0 Hz, H_{Ar}), 7.63−7.68 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 10.02, 18.46, 25.28, 28.69, 29.74, 33.53, 37.65, 56.03, 56.22, 110.69, 110.77, 118.84, 122.70, 124.70, 126.84, 127.33, 130.88, 152.69, 153.38, 173.78. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

***N*-[2-(4,9-Dimethoxy-2,3-dihydrophenalen-1-yl)ethyl]butanamide (19c).** It was obtained from the nitrile **9c** and butyric anhydride (yield 50%) as a white solid: mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.53−2.14 (m, 6H), 2.14 (t, 2H, J = 7.3 Hz), 2.78 (ddd, 1H, J = 5.0 Hz, J = 17.8 Hz, J = 13.5 Hz), 3.02−3.58 (m, 4H), 3.93−3.95 (2s, 6H), 5.89 (brs, 1H, NH), 7.09−7.14 (2d, 2H, J = 9.0 Hz, H_{Ar}), 7.62−7.67 (2d, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.79, 18.41, 19.23, 25.40, 28.49, 33.60, 37.46, 38.99, 56.14, 56.39, 110.79, 118.95, 122.66, 124.70, 126.77, 127.34, 130.83, 152.62, 153.41, 172.76. Anal. ($C_{21}H_{27}NO_3$) C, H, N.

***N*-[2-(8-Methoxyacenaphthen-1-yl)ethyl]acetamide (22a).** It was obtained from the nitrile **9e** and acetic anhydride (yield 54%) as a white solid: mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 1.77−2.00 (m, 1H), 1.94 (s, 3H), 2.12−2.29 (m, 1H), 3.06−3.32 (m, 2H), 3.39−3.64 (m, 2H), 3.77−3.89 (m, 1H), 3.95 (s, 3H), 5.57 (s, 1H), 7.18−7.34 (m, 3H, H_{ar}), 7.54 (d, 1H, J = 8.2 Hz, H_{ar}), 7.64 (d, 1H, J = 8.8 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 23.39, 34.46, 37.61, 37.90, 39.69, 56.19, 115.18, 119.56, 122.22, 125.17, 125.81, 126.94, 130.97, 139.98, 143.27, 152.08, 170.02. Anal. ($C_{17}H_{19}NO_2$). C, H, N.

***N*-[2-(8-Methoxyacenaphthen-1-yl)ethyl]propanamide (22b).** It was obtained from the nitrile **9e** and propionic anhydride (yield 76%) as a white solid: mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.5 Hz), 1.74−1.93 (m, 1H), 2.07−2.24 (m, 3H), 3.01−3.12 (dd, J = 3.0 Hz, J = 17.2 Hz), 3.16−3.60 (m, 3H), 3.70−3.85 (m, 1H), 3.92 (s, 3H), 5.57 (s, 1H), 7.15−7.31 (m, 3H, H_{Ar}), 7.51 (d, 1H, J = 7.9 Hz, H_{Ar}), 7.61 (d, 1H, J = 9.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 9.91, 29.82, 34.57, 37.66, 37.72, 39.67, 56.21, 115.20, 119.57, 122.20, 125.16, 125.82, 126.95, 130.96, 139.93, 143.28, 145.31, 173.64. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***N*-[2-(8-Methoxyacenaphthen-1-yl)ethyl]butanamide (22c).** It was obtained from the nitrile **9e** and butyric anhydride (yield 63%) as a white solid: mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.59 (m, 2H), 1.73−1.94 (m, 1H), 2.05−2.28 (m, 3H), 3.07−3.15 (dd, J = 2.3 Hz, J = 17.2 Hz), 3.20−3.34 (m, 1H), 3.40−3.64 (m, 2H), 3.72−3.90 (m, 1H), 3.95 (s, 3H), 5.59 (s, 1H), 7.18−7.34 (m, 3H, H_{Ar}), 7.54 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.64 (d, 1H, J = 8,8 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.81, 19.21, 34.62, 37.63, 37.70, 38.83, 39.69, 56.20, 115.22, 119.56, 122.20, 125.14, 125.81, 126.94, 131.05, 139.99, 143.30, 152.07, 172.92. Anal. ($C_{19}H_{23}NO_2$).

***N*-[2-(Acenaphthen-1-yl)ethyl]acetamide (23a).** It was obtained from the nitrile **9f** and acetic anhydride (yield 76%) as a white solid: mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 1.75−2.22 (m, 2H), 1.95 (s, 3H), 3.06−3.14 (m, 1H), 3.31−3.73 (m, 4H), 5.55 (brs, 1H), 7.25−7.29 (m, 2H, H_{Ar}), 7.42−7.49 (m, 2H, H_{Ar}), 7.59−7.64 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.93, 36.81, 37.98, 38.47, 41.62, 119.45, 119.99, 123.02, 123.54, 128.41, 132.11, 139.07, 144.76, 149.11, 170.84. Anal. ($C_{16}H_{17}NO$) C, H, N.

***N*-[2-(Acenaphthen-1-yl)ethyl]propanamide (23b).** It was obtained from the nitrile **9f** and propionic anhydride (yield 81%) as a white solid: mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.6 Hz), 1.76−1.94 (m, 1H), 2.06−2.23 (m, 3H), 3.07−3.15 (m, 1H), 3.32−3.73 (m, 4H), 5.44 (brs, 1H), 7.26−7.29 (m, 2H, H_{Ar}), 7.41−7.49 (m, 2H, H_{Ar}), 7.60−7.64 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 10.52, 30.36, 36.91, 38.00, 38.32, 41.67, 119.47, 120.00, 123.03, 123.55, 128.42, 128.62, 132.15, 139.11, 144.80, 149.17, 174.46. Anal. ($C_{17}H_{19}NO$) C, H, N.

***N*-[2-(Acenaphthen-1-yl)ethyl]butanamide (23c).** It was obtained from the nitrile **9f** and butyric anhydride (yield 81%) as a white solid: mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 7.4 Hz), 1.54 (m, 2H), 1.65−1.85 (m, 1H), 1.98−2.07 (m, 3H), 2.97−3.05 (m, 1H), 3.25−3.60 (m, 4H), 5.37 (s, 1H), 7.16−7.19

(m, 2H, H_{Ar}), 7.31−7.39 (m, 2H, H_{Ar}), 7.48−7.54 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 14.73, 20.11, 37.30, 38.33, 38.60, 39.71, 41.97, 119.79, 120.33, 123.36, 123.88, 128.74, 128.94, 132.46, 142.56, 145.11, 149.46, 173.92. Anal. ($C_{18}H_{21}NO$) C, H, N.

***N*-[(2,3-Dihydrophenalen-1-yl)methyl]acetamide (16a).** It was obtained by the reduction of 1-cyano-2,3-dihydrophenalene[26](0.3 g, 1.25 mmol) and acetic anhydride (178 μL, 1.88 mmol) in anhydrous ethanol (10 mL) under a atmosphere of hydrogen in the presence of a catalytic amount of PtO_2. The mixture was stirred at room temperature for 20 h. The solution was treated by 4 mL of 20% NH_4OH solution, filtered through Celite and evaporated under reduced pressure. The organic material was diluted in CH_2Cl_2, washed with water, a saturated $NaHCO_3$ solution, brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The amido derivative was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 99/2) and crystallized in diethyl ether to give a white solid: yield 85%; mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.12 (m, 2H), 3.25 (m, 4H), 3.64 (m, 1H), 6.02 (brs, 1H), 7.31 (m, 2H, H_{Ar}), 7.4 (m, 2H, H_{Ar}), 7.72 (t, 2H, J = 6.06 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 23.28, 25.25, 26.8, 39.16, 43.42, 124.09, 124.43, 125.32, 125.57, 126.09, 126.9, 133.91, 135.14, 136.37, 170.42, 175.42. Anal. ($C_{16}H_{17}NO$).

***N*-[(2,3-Dihydrophenalen-1-yl)methyl]butanamide (16c).** It was prepared according to the process described above from 1-cyano-2,3-dihydrophenalene and butyric anhydride (yield 72%). It was obtained as colorless oil: ^{1}H NMR ($CDCl_3$) δ 1 (t, 3H, J = 6.06 Hz), 1.73 (m, 2H), 2.18 (m, 4H), 3.23 (m, 4H), 3.72 (m, 1H), 5.57 (brs, 1H), 7.31 (m, 2H, H_{Ar}), 7.45 (m, 2H, H_{Ar}), 0.7.76 (t, 2H, J = 7.88 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ, 14.7, 19.2, 25.8, 26.7, 27.2, 39, 42.9, 124.16, 124.31, 125.34, 125.62, 126.11, 126.85, 133.94, 135.19, 136.24, 170.39, 174.96. Anal. ($C_{18}H_{21}NO$).

Separation of the Enantiomers of Derivatives 13c, 15c, and 20c. A direct chromatographic method using a semipreparative chiral HPLC column (Chirose Bond C1) 10 μm−250 × 10 mm (Chiralsep, Parc d'activités de la Boissière, La Frenaye 76170, France) gave the pure enantiomers of **13c**, **15c** and **20c**. The conditions for the semipreparative separations were estimated by analytical runs using 20 μL of a 0.5 mg/mL solution on an analytical chiral HPLC Chirose Bond C1 column (5 μm−250 × 4.6 mm). A 500 μL loop was used to introduce the samples which were filtered through HV filters (pore size 0.45 μm) (Millipore Corp., Bedford). The concentrations chosen varied between 4 and 12 mg/mL in a mixture of ethanol/heptane 1/3, depending on the resolution of the compound. The mobile phase consisted of heptane/ethanol 9/1 (compound **15c**), heptane/EtOAc/ethanol 90/20/2 (compound **20c**) or heptane/EtOAc/ethanol 90/12/2 (compound **13c**) 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 recorded using a Varian 4270 integrator.

The enantiomers of **13c**, **15c**, and **20c** were separated on a milligram scale and their purity was controlled by analytical HPLC (>99%). They were obtained as yellow oils, and optical rotations α_D were measured on a Polartronic C-Schimdt-Haensch for each enantiomer at 5 mg/mL in chloroform at 589 nm, uncorrected. The following optical rotations were obtained: **13c**, $[\alpha]^{20}_D = -120 \pm 2, +126 \pm 2$; **15c**, $[\alpha]^{20}_D = -22 \pm 2, +20 \pm 2$; **20c**, $[\alpha]^{20}_D = -20 \pm 2, +18 \pm 2$.

Melatonin Receptor Binding Assay in Chicken Brain. Chickens (*Redbrook*, male or female, 4 months, 3−4 kg; Cellubio, France) were decapitated at 12 a.m. The brains were quickly removed and stored at −80 °C. The brains were homogenized (Polytron) in 10 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4) and washed twice by centrifugation (44000*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 of protein/mL as determined by the method of Lowry.[35] 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 fiber filters (GF/B Whatman strips) presoaked in 0.1% poly(ethylenimine) using a Brandel cell harvester. The filters were washed (3 × 4 mL) with buffer, dried, and counted on a γ-counter (Crystal-Packard). Nonspecific binding was defined with 10 μM 2-iodomelatonin and represented 10% of the total binding. K_i values were determined using the Cheng−Prussof equation

Melatonin Receptor Binding Assay with mt_1 and MT_2 Receptors. Competitive inhibition curves displacements were performed according to the methods already described[19,31] with the receptors expressed in HEK-293 cells with [^{125}I]iodomelatonin as the radioligand. Membranes obtained from HEK-293 cells expressing hmt_1 or hMT_2 receptors were incubated in Tris-HCl buffer (50 mM, pH 7.4) with 0.025 or 0.2 nM 2-[^{125}I]-iodomelatonin, respectively, and seven concentrations of the compound under test. Each binding assay was performed in triplicate. The incubation (37 °C, 2 h) was stopped by immediate vacuum filtration through glass fiber filters (GF/B Unifilters) using a Packard cell harvester as above. The filters were washed, dried, and counted in a Packard β-counter (TopCount). Nonspecific binding was defined with 10 μM melatonin. K_i values were calculated as above.

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. 18 h before the bioassay, tadpoles of uniform stage, size, and color 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. They were illuminated 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.[29] 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. EC_{50} values for the compounds were determined from the concentration−response curves obtained with 5 concentrations in the range of 0.1 to 100 × the K_i values for chicken brain receptors. The mean of the data control (animals treated with vehicle) represented 100%. The results (n = 2) were calculated using the PRISM program (Graphpad).

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