Design and Synthesis of New Naphthalenic Derivatives as Ligands for 2-[^{125}I]Iodomelatonin Binding Sites

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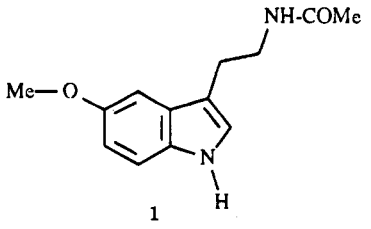
New melatonin-like agents were designed from the frameworks of 2,5-dimethoxyphenethylamine, an important structural moiety for the 5-HT receptor, and (2-methoxynaphthyl)ethylamine. The compounds were synthesized by classical methods and evaluated in binding assays with chicken brain membranes using 2-[^{125}I]iodomelatonin as the radioligand. Preliminary studies on the series of *N*-acyl-disubstituted phenethylamines showed the favorable role of the methoxy group in the ortho position of the side chain on the affinity for the receptor (K_i = 8 ± 0.2 nM) for *N*-[2-(2-methoxy-5-bromophenyl)ethyl]propionamide (**3o**). This effect was confirmed in a series of the naphthalene derivatives, a bioisosteric moiety of the indole ring, and several potent ligands for melatonin binding sites were prepared such as *N*-[2-(2-methoxynaphthyl)ethyl]propionamide (**4b**) (K_i = 0.67 ± 0.05 nM) and *N*-[2-(2,7-dimethoxynaphthyl)ethyl]cyclopropylformamide (K_i = 0.05 ± 0.004 nM) (**4k**). Structure–activity relationships are discussed with regard to melatonin and bioisosteric naphthalenic compound **2**. The K_i value for **4b** was affected to a similar extent to that of melatonin by GTP-γ-S or Mn^{2+} in competition experiments, suggesting an agonist profile for this compound.

Introduction

There is no longer any doubt that melatonin (**1**) is a pineal hormone which modulates a variety of endocrinological, neurophysiological, and behavioral functions in vertebrates.[1] It regulates reproduction in photoperiodic species[2] but is also implicated in circadian rhythms and plays a key role in a number of disorders such as anxiety, seasonal depression, and delayed sleep phase syndrome.[3,4] More recently, the antitumoral properties of melatonin and its implication in immune system responsiveness have been described.[5] Furthermore, the hydroxyl radical scavenger properties of melatonin have been demonstrated, and a role for this hormone in the aging process has been suggested.[6] The synthesis of melatonin, which follows a circadian rhythm, occurs in the pinealocytes of the pineal gland and in the retina, and the maximum level is reached during the night.[7] However, the pattern of the nocturnal rise depends upon the animal species. Therefore, melatonin has been described as "the chemical expression of darkness".[8] It



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is synthesized from serotonin (5-HT) in two enzymatic steps: 5-HT is N-acetylated by *N*-acetyltransferase (NAT) to produce *N*-acetylserotonin and subsequently O-methylated to give melatonin.[9] Melatonin is highly lipophilic, can diffuse out of the pineal gland, and is then released into the blood. Its effects seem to be mediated through membrane receptors[10] located in different regions of the brain, particularly in the suprachiasmatic nucleus (SCN) and the pars tuberalis where it regulates reproductive function[11] in photoperiodic species. However, the distribution of melatonin receptors varies greatly among mammals, and contradictory data have been reported.[12] The receptor is doubtless G-protein-coupled since several experiments have demonstrated inhibition of the high-affinity specific binding of 2-[^{125}I]-iodomelatonin by guanine nucleotides in cerebral tissues of several species and a dose-dependent inhibition of forskolin-stimulated cAMP formation by melatonin.[13]

The design and availability of potent, specific agonists or antagonists for melatonin receptors are important to elucidate totally its role in the physiological events in which it is implicated. These compounds could find therapeutic applications in a number of disorders such as jet lag,[14] anxiety,[15] depression, or disturbances of the circadian rhythms.[16]

Several indolic analogues of melatonin have been synthesized as agonists,[17] and structure–activity studies have shown the favorable role of 2-halogeno substitution and enabled the development of 2-[^{125}I]iodomelatonin as a radioligand for binding studies and autoradiography.[18] Recently, several papers reported the synthesis and agonist properties of several nonindolic compounds. One group[19] designed compounds such as **2** using the bioisosteric properties of naphthalene with regard to the indole ring, while another group[20] used the analogy between 2-amido-8-methoxytetralin and the pharmacophore groups of the melatonin moiety.

We present here our initial results on the design of new nonindolic melatonin-like compounds, emphasizing particularly the importance of the presence of the methoxy group in the ortho position of the ethylaceta-

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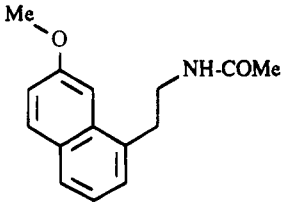

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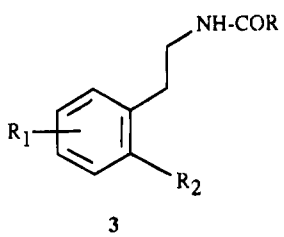
mido chain to obtain a compound with marked affinity for melatonin receptors. They were designed from the framework of serotoninergic agonists because of the structural analogy between melatonin and serotonin. The recent demonstration of 2-amido-8-methoxytetralin[20] as a melatonin agonist derived from 8-OH-DPAT, a potent 5-HT_{1A} agonist, agrees with this hypothesis.

As a preliminary approach, we used 2,5-dimethoxyphenethylamine, an important structural base for 5-HT_2 receptor agonists,[21] to prepare amido derivatives **3** (R_1 = 5-MeO, R_2 = MeO). They were evaluated in binding assays (Table 1) with 2-[125I]iodomelatonin radioligand using chicken brain membranes according to the method already reported for pigeon brain,[22] and their affinities were compared to those of several *N*-acetyl-monosubstituted phenethylamines **3** (R_2 = H). The favorable role of the (2-methoxyphenethyl)amido moiety having been demonstrated by these preliminary structure–activity studies, we then investigated the preparation of the corresponding naphthalene derivatives **4**, a more suitable aromatic system for the design of indolic bioisosteres.



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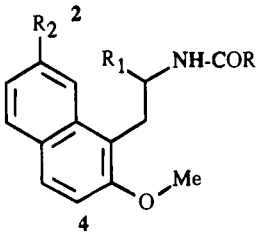

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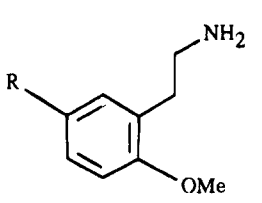
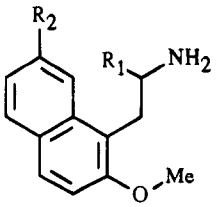
Chemistry

Compounds **3** and **4** (Tables 1 and 2) were obtained by acylation reactions of the corresponding amines which were commercially available or synthesized by classical methods. The amines were prepared according to the routes shown in Scheme 1. **14** and **16–18** were prepared by $LiAlH_4$ reduction of the nitroethylene derivatives **9–12** obtained through the Knoevenagel condensation of the corresponding formyl derivatives with nitromethane or nitroethane (method A).[17b,23] Amines **13** and **15** were synthesized through the cyano derivatives **7** and **8** which were hydrogenated in the presence of Raney Ni (method B). 5-Ethylanisaldehyde (**5**) and 2,7-dimethoxy-1-naphthaldehyde (**6**), the intermediates for the synthesis of **14** and **18**, respectively, were prepared by a formylation reaction with dichloromethyl methyl ether[24] in the presence of $TiCl_4$, and the cyano derivatives **7** and **8** were synthesized routinely from 2-methoxy-5-methylbenzyl alcohol and 2-methoxy-5-bromobenzyl alcohol which were transformed into the corresponding chlorides to react with KCN in DMSO.

The amides **3a–o** and **4a–e,g,i–k** (Tables 1 and 2) were prepared by reaction of the amines with the acyl chlorides in CH_2Cl_2 in the presence of Et_3N (method C) or reaction of the acetic anhydride under Schotten–Baumann conditions (method D), while the trifluoroacetyl derivatives **4f,h,l** were synthesized directly with trifluoroacetic anhydride in CH_2Cl_2 in the presence of pyridine (method E).



13 R = Me
14 R = Et
15 R = Br



16 R_1 = H R_2 = H
17 R_1 = Me R_2 = H
18 R_1 = H R_2 = OMe

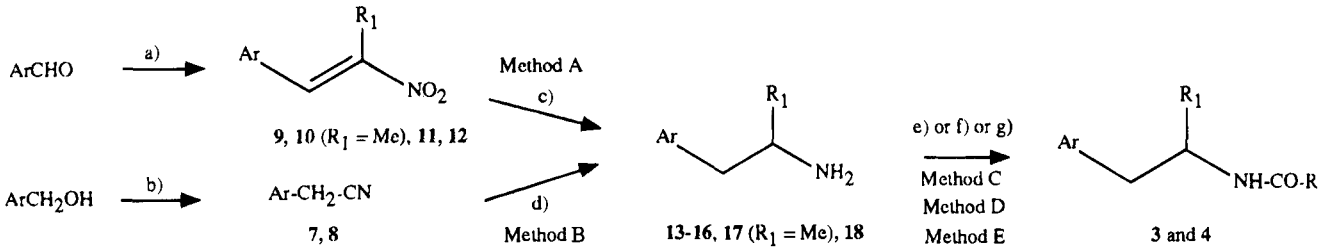
Biochemistry

The affinities values (K_i) of the amido derivatives **3** and **4** for melatonin binding sites are shown in Tables 1 and 2, respectively. They were evaluated *in vitro* by binding assays[22] using 2-[125I]iodomelatonin and chicken brain membranes. Specific binding of the ligand was stable, saturable, and of high affinity (K_d = 0.05 nM), and nonspecific binding was less than 10% of the total binding. Scatchard analyses gave linear plots, and the values of the Hill coefficients were close to 1, suggesting a single class of binding sites for the ligand. B_{max} values for specific 2-[125I]iodomelatonin binding sites in preparations from chickens killed at 12 a.m. and 6 p.m. were about 20% higher than the number of binding sites at 12 p.m. (Figure 1). However, no significant variations in the binding affinities were observed at the different time points. These data suggest that the *in vivo* rhythm of the melatoninergic system is regulated by variations in the number of binding sites available rather than by an increase in their affinity.[25] In the inhibition studies with the new compounds described above, brain homogenates from the chicken killed at 12 a.m. were used and incubated at 25 °C for 60 min with the compounds under investigation. The affinity of melatonin was assessed in this preparation by competition experiments and agreed (K_i = 0.64 nM) with the value already reported.[20]

Discussion

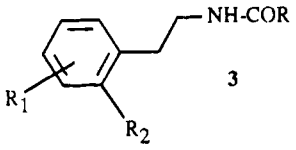
The preliminary approach, which consisted of using the hypothetical analogy between the structural elements of the receptor binding sites of serotonin and melatonin, prompted us to prepare amido derivatives of 2,5-dimethoxyphenethylamine, an important framework in the serotoninergic field. The relatively good affinity of compound **3h** (K_i = 69.9 nM), obtained in competition studies with 2-[125I]iodomelatonin, confirmed the soundness of this hypothesis. In our hands, this derivative was more potent than 2-acetamido-8-methoxytetralin (K_i = 206 nM), another template used recently by Copinga[20] to design new melatoninergic ligands. Structural variations of the amido group of compound **3h** brought about a clear increase in the affinity of the propionyl derivative **3i**, but a marked drop was observed with cyclopropyl and butyl substitutions (compounds **3j,k**). These results differed from those obtained by Guardiola[19] in a series of naphthalenic derivatives where the optimum binding affinity was attained with propyl, butyl, or cyclopropyl chains in

Scheme 1[a]



[a] (a) $MeNO_2$ or $EtNO_2$, $AcONH_4$; (b) $SOCl_2$, pyridine, toluene, KCN, DMSO, rt; (c) $LiAlH_4$, THF, 40 °C, 24 h; (d) NH_4OH, H_2, Ra Ni, EtOH; (e) RCOCl, CH_2Cl_2, Et_3N; (f) $(Ac)_2O$, AcONa, H_2O; (g) $(CF_3CO)_2O$, CH_2Cl_2, pyridine.

Table 1. Displacement of 2-[^{125}I]Iodomelatonin Binding from Melatonin Receptors in Chicken Brain Membranes by the Compounds **3**



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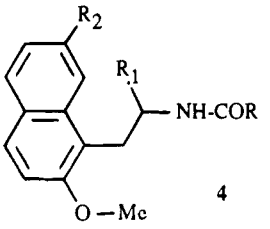
compd	R_1	R_2	R	$K_i \pm$ SEM, nM[a]
3a	4-Cl	H	CH_3	>1000
3b	3-Cl	H	CH_3	>1000
3c	2-Cl	H	CH_3	>1000
3d	3-F	H	CH_3	>1000
3e	4-MeO	H	CH_3	>1000
3f	3-MeO	H	CH_3	253 ± 57
3g	H	MeO	CH_3	213 ± 23
3h	5-MeO	MeO	CH_3	69.9 ± 5.1
3i	5-MeO	MeO	C_2H_5	17.5 ± 3.2
3j	5-MeO	MeO	c-C_3H_5	386 ± 28
3k	5-MeO	MeO	n-C_4H_9	>1000
3l	5-CH_3	MeO	CH_3	192 ± 23
3m	5-C_2H_5	MeO	CH_3	217 ± 23
3n	5-Br	MeO	CH_3	42 ± 2.8
3o	5-Br	MeO	C_2H_5	8 ± 0.2
melatonin				0.67 ± 0.04
2-acetamido-8-methoxytetralin				206 ± 20

[a] K_i values are expressed in nM ± the standard error of the mean (SEM) and were calculated using the Cheng–Prussof equation from IC_{50} values obtained from competition curves; the data are the results of one or two separate determinations.

Table 2. Displacement of 2-[^{125}I]Iodomelatonin Binding from Melatonin Receptors in Chicken Brain Membranes by the Compounds **4**



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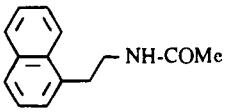
compd	R_1	R_2	R	$K_i \pm$ SEM, nM[a]
4a	H	H	CH_3	2.68 ± 0.3
4b	H	H	C_2H_5	0.67 ± 0.05
4c	H	H	n-C_3H_7	1.37 ± 0.22
4d	H	H	c-C_3H_5	19.4 ± 2.7
4e	H	H	n-C_4H_9	237 ± 50
4f	H	H	CF_3	0.54 ± 0.05
4g	CH_3	H	CH_3	421 ± 48
4h	CH_3	H	CF_3	>1000
4i	H	OMe	CH_3	0.1 ± 0.04
4j	H	OMe	C_2H_5	0.07 ± 0.004
4k	H	OMe	c-C_3H_7	0.05 ± 0.004
4l	H	OMe	CF_3	0.4 ± 0.04
19				321 ± 33
2[b]				0.54 ± 0.03

[a] K_i values are expressed and were calculated as described in Table 1; the data are the results of one or two separate determinations. [b] $K_i = 0.1 \pm 0.03$ nM determined in a receptor binding assay using ovine pars tuberalis membranes; see ref 19.

binding assays using the ovine pars tuberalis. In particular, the affinity of the latter substituent was increased by 2 orders of magnitude with regard to the parent compound. The influence of the position of the methoxy group on the phenyl ring was evaluated with the simple derivatives **3e–g** which emphasized the prevalence of the meta or ortho positions over the para position, and these results agree with a recent report.[20] Although these data concern compounds with a moderate level of activity, they illustrate, compared to the results obtained for the other monosubstituted compounds (**3a–d**), the superiority of the methoxy substitution for recognition by the melatonin receptor site. At this stage of the study, it was postulated that the relatively good affinity of compound **3i** for melatonin receptors was due to the melatonin-like position of the 5-methoxy group of this compound, while the 2-methoxy group could mimic the pyrrole ring of the indole. The contribution of the 5-methoxy group to the improved affinity of compound **3i** for melatonin receptors, and in particular that of the oxygen atom, was clearly demonstrated by the weak activity seen with the deoxy compounds **3l,m**. These data could suggest that, as with serotoninergic receptors, a hydrogen bond[26] may be implicated in the binding of the ligand to the receptor.

However, a significant increase in the affinity was obtained with the substitution of a bromine atom for the 5-methoxy group, and the *N*-propionyl derivative **3o** showed a marked affinity (K_i = 8 nM) for 2-[^{125}I]-iodomelatonin binding sites, being only 12-fold less active than melatonin itself (K_i = 0.67 nM). These data suggested that the presence of both methoxy groups is not necessary to obtain compounds with potent affinity, but moreover, they emphasized the essential role of the methoxy group in the ortho position which could give rise to productive interactions with the melatonin receptor site. Therefore, we prepared and evaluated in binding assays compounds such as **4a** (Table 2) where the phenyl ring was substituted by a naphthalene moiety, a well-known bioisosteric group of the indole.[27] Compound **4a** had nanomolar affinity for 2-[^{125}I]iodomelatonin binding sites, and comparison of its affinity to that of the unsubstituted derivative **19** demonstrated the efficient role of substitution in the ortho position of the side chain. These results are different from those reported previously in the naphthalene series[19] with

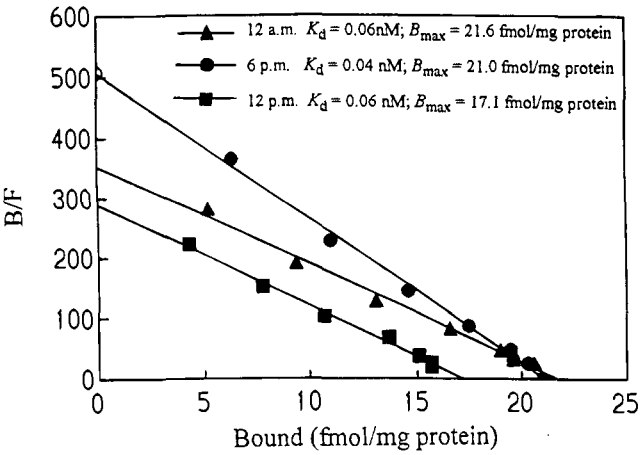


Figure 1. Scatchard plots of the saturation curves of the specific binding of 2-[^{125}I]iodomelatonin (0.02–0.8 nM) in brain membranes from chickens killed by decapitation at 12 a.m., 6 p.m., and 12 p.m., respectively. The data were analyzed by linear regression and are the results of one or two separate determinations.

compounds derived from **2** and indole derivatives where the methoxy group needed to be located in the same position as in melatonin to provide potent compounds.

We investigated the influence of the length of the acyl chain with compounds **4b–e**, and as described above for compound **3h**, only the propionyl group increased the affinity (compound **4b**, K_i = 0.67 nM) to be equipotent to melatonin. We demonstrated again the failure of the cyclopropyl substituent (compound **4d**, K_i = 19.4 nM) to enhance the activity, and the favorable effect of the trifluoroacetyl group (**4f**) to maintain the affinity was also noted. On the other hand, introduction of a methyl group in the α position of the acetamido function resulted in a dramatic drop in the activity of compounds **4g,h**. The different results obtained with the variations of the acyl chain on the affinity of compounds derived from **4a** and **2** for melatonin receptors could be explained by a different positioning of the molecules in the receptor site. This could be due to an interaction with one or other methoxy groups, involving a better or worse fit with the putative lipophilic pocket located near the amido function. However, it is also possible that the steric hindrance of the ortho methoxy group in **4a** brings about, with regard to **2**, some important modifications in the conformation of the flexible side chain and consequently alters the parameters of the pharmacophore implicated in interactions with the receptor site. Nevertheless, the role of the methoxy groups in the 2 or 7 position of the naphthalene ring as anchorage points on the receptor site was demonstrated by the important drop in the affinity observed with the unsubstituted naphthalene acetamido derivative **19** (K_i = 321 ± 33 nM). However, it is possible that compound **4a** could be superimposed with melatonin in two ways corresponding to the different positions of the methoxy group in the receptor site (Figure 2). In position A, the orientation of the side chain of **4a** would be the mirror image of that of melatonin or the bioisosteric derivative **2**, and the different methoxy groups would be superimposed. In this overlay, although the acetamido groups would be located in the same spatial positions in the receptor, the alkyl chain of the acyl group would interact with a different part of the receptor. Consequently, this interaction could explain the difference in affinity observed with the propyl and cyclopropyl substituents of compounds **4c,d**, respectively, with regard to those of the corresponding derivatives of **2**. On the other hand, superimposition with melatonin or compound **2** according to position B implicates a similar orientation of the side chains for the different compounds and suggests the existence of productive interactions between the methoxy group of **4a** and a region of the receptor located in the neighborhood of the side chain capable of interacting with an ortho substituent. The existence of this additional binding site agrees with earlier structure–activity relationship (SAR) studies[28] which demonstrated the favorable role on the affinity values of 2-halogen substitution in melatonin and, particularly, the very high affinity of the 2-iodo derivative. However, the present data reported for **4a** do not indicate which of the two superimpositions with melatonin is correct; further structural variations on the 2 and 7 positions of the naphthalene ring are required to draw definite conclusions. Nevertheless, the existence of the accessory binding site was confirmed in the present study by the enhancement by 1 order of magnitude of the affinity of the 2,7-dimethoxy derivatives (compounds **4i–l**) with regard to the monomethoxy compounds **4a** and **2**. Thus, compounds **4j,k** (K_i = 0.07 and 0.05 nM, respectively) were equipotent to 2-iodomelatonin. Moreover, in contrast to the results with the 2-methoxy derivatives, we did not observe a drop in the affinity with the cyclopropyl substitution which provided compound **4k** with high affinity for melatonin binding sites. Consequently, it seems clear that, for these compounds, the 7-methoxy group mimics the methoxy group of melatonin and the 2-methoxy group complements the site occupied by the iodine atom in 2-iodomelatonin.

This study has confirmed the suitable bioisosteric properties of the naphthalene ring for recognition by the melatonin receptor and the existence of an additional binding site capable of giving productive interactions. However, the structural parameters of the melatoninergic pharmacophore and, particularly, the relative spatial position of the aromatic system and the amido function in the active conformer are still unclear. The previously reported[29] conformational analysis of melatonin demonstrated, as expected for such molecules, a large number of conformers in a relatively small energy range. It is essential to design a potent, conformationally restricted ligand in order to obtain a good insight into the structural parameters of the melatoninergic pharmacophore. The structure of the rigid 2-amido-8-methoxytetralin reported recently[20] does not seem to be a useful starting framework because of the weak activity, and this point was confirmed recently by the data reported by Garrat[30] on a series of the tricyclic indole derivatives related to melatonin, demonstrating the superiority of the compounds with the cis configuration of the ethyl chain equipotent to melatonin while the structurally, closely related tetralin derivatives were markedly less potent.

In the course of this work, it seemed to us worthwhile to evaluate the potential agonist or antagonist properties of the synthesized compounds. Therefore, as a preliminary approach, the influence of guanine nucleotides and cations on the affinity values of melatonin and compound **4b** for the melatonin receptor site was

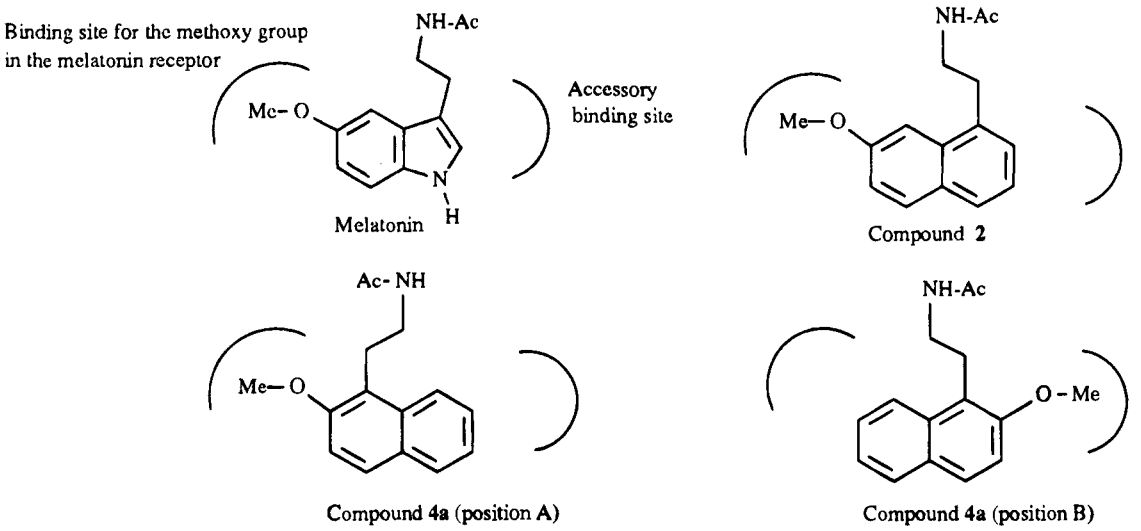


Figure 2. Putative positions of the compound **4a** in the melatonin receptor. In position A, the 2-methoxy group mimics the melatoninergic methoxy; in position B, it interacts with an accessory binding site.

Table 3. Effects of GTP-γ-S and Mn^{2+} on the Affinities of Melatonin and Compound **4b** for Chicken Brain Receptors

		K_i	
compd	K_i[a]	+ 3 × 10^{-5}/ M GTP-γ-S[b]	+ 1 mM $MnCl_2$[b]
melatonin	0.31 ± 0.04	1.08 ± 0.5	0.176 ± 0.048
4b	0.68 ± 0.04	2.86 ± 0.48	0.297 ± 0.04

[a] K_i values are expressed and were calculated as described in Table 1. [b] The experimental conditions were similar to those reported in the Experimental Section, but the assays were carried out in the presence of GTP-γ-S or $MnCl_2$.

studied. There is evidence that this receptor is linked to a G-protein[31] and the addition of GTP or a stable analogue, such as GTP-γ-S, to a membrane preparation decreases the number of high-affinity binding sites available to agonists, giving a shift to the right of the competition curve. In contrast, antagonists bind equally well to the G-protein-coupled or uncoupled receptors, and no shift in the competition curve is seen. Alternatively, Hamon[32] reported that divalent cations such as Mn^{2+} increase the apparent affinity of agonists for their binding sites, whereas the affinity of antagonists is unaffected. A simple binding assay for identifying new agonists and antagonists was carried out by evaluating the ratio of the K_i values in the presence of GTP or Mn^{2+}. An agonist should have a ratio close to 10, whereas it would not differ from unity for an antagonist.[33] In the present study, the K_i values for melatonin and compound **4b** were measured in the presence of GTP-γ-S (30 μM) and compared to the values in the presence of Mn^{2+} (1 mM), and the results are shown in Table 3. The affinity of **4b** was affected by both GTP-γ-S and Mn^{2+} to a similar extent to that of melatonin with a ratio close to 10, suggesting an agonist profile for this compound. The marked affinity of compound **4b** for melatonin receptors was confirmed in another binding assay using ovine pars tuberalis membranes[34,35] (K_i = 0.61 nM (n = 3)). Furthermore, the agonist profile of compound **4b** was evaluated by measuring its influence on the cAMP synthesis. It is well-known that melatonin inhibits forskolin-stimulated cAMP synthesis[13] and the agonist or antagonist activity of new compounds can be evaluated by this method. An assay has been developed using cultured ovine pars tuberalis cells, and the cAMP index was calculated according to the method recently reported by Depreux et al.[19b] Compound **4b** displayed an activity index of 1.02 and fully mimicked the activity of melatonin, indicating that it can be considered as a full agonist for melatonin receptors.

Conclusion

These data confirm the interest of the new naphthalene derivatives **4** as nonindolic, melatoninergic agents, the agonist profile of which should be demonstrated in further pharmacological studies. They also emphasize the important role played by the substituent located on the ortho position of the amido chain on the value of the affinity of the compound for melatonin receptors. On the other hand, these derivatives did not provide complete structural information on the melatoninergic pharmacophore, and for this purpose, the development of high-affinity, conformationally locked compounds is essential. Further studies are in progress to evaluate the pharmacological potential of compound **4b** as a nonindolic, melatoninergic agent.

Experimental Section

Chemistry. Melting points were determined on a Mettler FP 61 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 and 50 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard, and signals are quoted as s (singlet), ds (dedoubled singlet), d (doublet), dd (dedoubled doublet), t (triplet), dt (dedoubled triplet), q (quartet), br s (broad singlet), or m (multiplet). Elemental analyses were performed at the CNRS's analysis services in Vernaison or Gif sur Yvette (France) and are within 0.4% of the theoretical values.

Materials. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. The column chromatography was performed on Merck silica gel 60 (70/230 mesh). 2-(4-Chlorophenyl)ethylamine, 2-(3-chlorophenyl)ethylamine, 2-(2-chlorophenyl)ethylamine, 2-(3-fluorophenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 2-(3-methoxyphenyl)ethylamine, 2-(2-methoxyphenyl)ethylamine, 2-(2,5-dimethoxyphenyl)ethylamine, 4-ethylphenol, 5-bromoanisaldehyde, 5-methylsalicylic acid, 2-methoxy-1-naphthaldehyde, and 2,7-dimethoxynaphthalene were purchased from Aldrich (France).

Synthesis of Formyl Compounds 5 and 6. The method is described for the synthesis of 5-ethylanisaldehyde (**5**). To

a stirred solution of 4-ethylphenol (3.06 g, 25.05 mmol) and K_2CO_3 (7.78 g, 56.29 mmol) in anhydrous acetone (100 mL) under an Ar atmosphere was added dropwise dimethyl sulfate (2.32 mL, 24.56 mmol). After the addition, the reaction mixture was refluxed for 24 h. Excess of $(CH_3O)_2SO_2$ was decomposed by dropwise addition of water (1.4 mL). The solids were removed by filtration and washed with CH_2Cl_2. The organic layers were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2) to yield 2.64 g (19.36 mmol, 77%) of 4-ethylanisole as a colorless liquid: bp 90 °C (13 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, CH_3, J = 7.6 Hz), 2.66 (q, 2H, CH_2, J = 7.6 Hz), 3.84 (s, 3H, MeO), 6.89 (d, 2H, H_2 and H_6, J = 8.6 Hz), 7.17 (d, 2H, H_3 and H_5, J = 8.6 Hz). To 4-ethylanisol (2.35 g, 17.26 mmol) in anhydrous CH_2Cl_2 (50 mL) under an inert atmosphere and at 0 °C were added dropwise $TiCl_4$ (99.9%, 2.65 mL, 24.17 mmol) and dichloromethyl methyl ether (2.35 mL, 25.98 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. The mixture was poured into 1 N HCl (50 mL) while stirring, and the two phases were separated. The H_2O layer was washed with CH_2Cl_2. The CH_2Cl_2 layers were washed with H_2O (20 mL) and a saturated $NaHCO_3$ solution (2 × 20 mL) and then dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude liquid was purified by column chromatography (silica gel, CH_2Cl_2) to yield 1.76 g (10.72 mmol, 62%) of **5** as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3, J = 7.6 Hz), 2.61 (q, 2H, CH_2, J = 7.6 Hz), 3.90 (s, 3H, MeO), 6.90 (d, 1H, H_3, J = 8.6 Hz), 7.38 (dd, 1 H, H_4, J = 2.3, 8.6 Hz), 7.65 (ds, 1H, H_6, J = 2.3 Hz), 10.44 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 15.47 (CH_3), 27.66 (CH_2), 55.62 (MeO), 110.60 (C_3), 124.47 (C_1), 127.25 (C_6), 135.46 (C_4), 136.38 (C_5), 160.08 (C_2), 189.94 (CHO).

2,7-Dimethoxy-1-naphthaldehyde (6). This compound was obtained from 2,7-dimethoxynaphthalene. The product was purified by recrystallization from EtOH to yield pure **6** as a yellow crystalline solid: yield 72%; mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H, MeO), 4.00 (s, 3H, MeO), 7.01–7.08 (m, 2H, H_3 and H_6), 7.62 (d, 1H, H_4 or H_5, J = 9 Hz), 7.92 (d, 1H, H_4 or H_5, J = 9 Hz), 8.82 (ds, 1H, H_8, J = 2.4 Hz), 10.86 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.10 (MeO), 56.05 (MeO), 103.13 (C_8), 109.10 (C_3), 115.31 (C_1), 117.05 (C_6), 123.67 (C_{10}), 129.42 (C_5), 133.16 (C_9), 137.04 (C_4), 161.17 (C_7), 164.51 (C_2), 191.73 (CHO).

Synthesis of Benzyl Cyanides 7 and 8. The method is described for the synthesis of 1-(cyanomethyl)-2-methoxy-5-methylbenzene (**7**). It was prepared from 5-methylsalicylic acid according to the following process: to a stirred solution of 5-methylsalicylic acid (5.07 g, 33.32 mmol) and K_2CO_3 (anhydrous, 22.33 g, 161.6 mmol) in anhydrous acetone (175 mL) under an Ar atmosphere was added dropwise dimethyl sulfate (7.25 mL, 76.62 mmol). After the addition, the reaction mixture was refluxed for 6 h. Water (5 mL) was added dropwise to destroy the excess $(CH_3O)_2SO_2$. After the usual workup, the crude product was purified by chromatography (silica gel, CH_2Cl_2) to yield 5.47 g (30.36 mmol, 91%) of methyl 2-methoxy-5-methylbenzoate: bp 130 °C (12 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 3.84 (s, 3H, MeO), 3.85 (s, 3H, MeO), 6.86 (d, 1H, H_3, J = 8.4 Hz), 7.25 (dd, 1H, H_4, J = 2.4, 8.4 Hz), 7.59 (sd, 1H, H_6, J = 2.4 Hz).

The previous compound (4.99 g, 27.69 mmol) in THF (150 mL) was added to a stirred suspension of $LiAlH_4$ (1.56 g, 41.08 mmol) in THF (100 mL) under an Ar atmosphere. After the addition, the reaction mixture was refluxed for 20 h. After cooling at 0 °C, water (1.3 mL), NaOH (15%, 1.3 mL), ether (40 mL), and water (5 mL) were added dropwise successively to destroy the excess hydride. The mixture was filtered, and the filtrate was dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude alcohol was purified by distillation to yield 3.68 g (24.18 mmol, 87%) of 2-methoxy-5-methylbenzyl alcohol: bp 131 °C (12 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3), 2.40 (br s, 1H, OH), 3.84 (s, 3H, MeO), 4.65 (s, 2H, CH_2), 6.78 (d, 1H, H_3, J = 8.6 Hz), 7.07 (d, 1H, H_4, J = 8.6 Hz), 7.09 (s, 1H, H_6).

To a stirred solution of 2-methoxy-5-methylbenzyl alcohol (3.23 g, 21.22 mmol) in anhydrous toluene (50 mL) under an Ar atmosphere and at 0 °C were added dropwise pyridine (1.7 mL, 21.10 mmol) and then thionyl chloride (3.5 mL, 47.98 mmol). The reaction mixture was allowed to stand at room temperature for 24 h. The mixture was poured into an ice bath and stirred for 1 h. After the usual workup, the crude product was purified by distillation to yield 2.5 g (14.65 mmol, 69%) of 2-methoxy-5-methylbenzyl chloride: bp 118 °C (13 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 3.86 (s, 3H, MeO), 4.64 (s, 2H, CH_2), 6.80 (d, 1H, H_3, J = 8.7 Hz), 7.11 (dd, 1H, H_4, J = 1.9, 8.7 Hz), 7.17 (sd, 1H, H_6).

To a stirred mixture of 2-methoxy-5-methylbenzyl chloride (2.44 g, 14.30 mmol) in anhydrous DMSO (50 mL) were added KCN (1.85 g, 28.41 mmol) and a catalytic amount of KI, and the reaction mixture was stirred at room temperature for 20 h. After evaporation of the DMSO under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL) and water (20 mL). The two phases were separated and the aqueous portion was washed with CH_2Cl_2 (20 mL). The combined organic extracts were washed with water (20 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by distillation to yield 2.11 g (13.09 mmol, 91%) of **7**: bp 138 °C (16 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 3.83 (s, 3H, MeO), 6.77 (d, 1H, H_3, J = 8.3 Hz), 7.10 (d, 1H, H_4, J = 8.3 Hz), 7.17 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 18.33 (CH_2), 20.21 (CH_3), 55.37 (OCH_3), 110.23 (C_3), 118.04, 118.14 (C_1 and CN), 129.54, 129.64, 129.96 (C_4, C_5, and C_6), 154.5 (C_2).

1-(Cyanomethyl)-2-methoxy-5-bromobenzene (8). It was prepared from 5-bromo-*o*-anisaldehyde which was reduced by $LiAlH_4$ in 5-bromo-2-methoxybenzyl alcohol which gave 5-bromo-2-methoxybenzyl chloride according to the process used previously for 5-methyl-2-methoxybenzyl alcohol. It was obtained after purification by chromatography (silica gel, ether–pentane, 3:7); ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H, MeO), 4.51 (s, 2H, CH_2), 6.69 (d, 1H, H_3, J = 8.6 Hz), 7.24–7.41 (m, 2H, H_4 and H_6).

The cyano derivative **8** was obtained according to the above procedure described for **7**. The product was purified by chromatography (silica gel, ether–pentane, 8:2) and then by recrystallization from hexane/AcOEt to yield the pure compound as a yellow crystalline solid: yield 35%; mp 61 °C; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 2H, CH_2), 3.78 (s, 3H, MeO), 6.70 (d, 1H, H_3, J = 8.7 Hz), 7.34 (dd, 1H, H_4, J = 2.3, 8.7 Hz), 7.41 (ds, 1H, H_6, J = 2.3 Hz). Anal. (C_9H_8NOBr).

Synthesis of the Nitro Compounds 9–12. The method is described for the synthesis of 1-nitro-2-(2-methoxynaphthyl)-ethylene (**9**). A solution of 2-methoxy-1-naphthaldehyde (1.52 g, 8.16 mmol) and ammonium acetate (0.4 g, 5.19 mmol) in nitromethane (20 mL) was refluxed for 2 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (30 mL) and H_2O (30 mL) was added. The aqueous portion was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with H_2O (20 mL). The CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford 1.77 g (7.73 mmol, 95%) of **9** as a yellow crystalline solid: mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H, MeO), 7.25 (d, 1H, ArH, J = 9.7 Hz), 7.37 (dt, 1H, ArH, J = 7.2 Hz), 7.56 (dt, 1H, ArH, J = 7.2 Hz), 7.76 (d, 1H, ArH, J = 8 Hz), 7.92 (d, 1H, ArH, J = 9.2 Hz), 8.12 (d, 1H, ArH, J = 8.6 Hz), 8.09 (d, 1H, $CHNO_2$, J = 13.4 Hz), 8.79 (d, 1H, ArCH, J = 13.4 Hz).

2-Nitro-1-(2-methoxynaphthyl)propene (10). The reaction was carried out with 2-methoxynaphthaldehyde in nitroethane as described in the above procedure. Two isomers, *Z* and *E*, were obtained (2/1): yield 95%; mp 72 °C; ^{1}H NMR *Z* component ($CDCl_3$) δ 2.1 (s, 3H, CH_3), 3.97 (s, 3H, MeO), 7.23–7.96 (m, 6H, ArH), 8.33 (s, 1H, ArCH); ^{1}H NMR *E* component ($CDCl_3$) δ 2.52 (s, 3H, CH_3), 3.89 (s, 3H, MeO), 6.92 (s, 1H, CH=C-NO_2), 7.23–7.96 (m, 6H, ArH).

1-Nitro-2-(2-methoxy-5-ethylphenyl)ethylene (11). The reaction was carried out with 5-ethylanisaldehyde (**5**) in nitromethane as described in the above procedure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to afford 11 as a yellow liquid: yield 82%; bp 155 °C (0.9 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, J = 7.6 Hz), 2.61 (q, 2H, CH_2, J = 7.6 Hz), 3.92 (s, 3H, MeO), 6.89 (d, 1H,

H_3, J = 8.6 Hz), 7.26 (s, 1H, H_6), 7.28 (d, 1H, H_4, J = 8.6 Hz), 7.88 (d, 1H, $CHNO_2$, J = 13.6 Hz), 8.13 (d, 1H, ArCH, J = 13.6 Hz); ^{13}C NMR ($CDCl_3$) δ 15.50 (CH_3), 27.61 (CH_2), 55.64 (OMe), 111.32 (C_3), 118.85 (C_1), 131.51 (C_6), 132.83 (C_4), 136.80 (C_5), 135.57, 138.06 (ArCH and $CHNO_2$), 157.67 (C_2).

1-Nitro-2-(2,7-dimethoxynaphthyl)ethylene (12). The reaction was carried out with 2,7-dimethoxy-1-naphthaldehyde (**6**) in nitromethane as described in the above procedure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to afford **12** as a yellow crystalline solid: yield 95%; mp 140 °C; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H, MeO), 4.02 (s, 3H, MeO), 7.04 (dd, 1H, H_6, J = 2.4, 8.9 Hz), 7.06 (d, 1H, H_3, J = 9.1 Hz), 7.24 (ds, 1H, H_8, J = 2.4 Hz), 7.66 (d, 1H, H_4 or H_5, J = 8.9 Hz), 7.82 (d, 1H, H_4 or H_5, J = 9.1 Hz), 8.07 (d, 1H, $CHNO_2$, J = 13.2 Hz), 8.62 (d, 1H, ArCH, J = 13.2 Hz); ^{13}C NMR ($CDCl_3$) δ 55.51 (OMe), 56.21 (OMe), 101.52 (C_8), 109.53 (C_3 or C_6), 110.68 (C_1), 116.72 (C_3 or C_6), 124.41 (C_9 or C_{10}), 130.76, 131.03, 134.24 (ArCH, C_4, and C_5), 135.28 (C_9 or C_{10}), 139.69 ($CHNO_2$), 159.9 (C_2 and C_7).

Synthesis of Amines 14 and 16–18. Method A. The method is described for the synthesis of 2-(2-methoxynaphthyl)ethylamine (**16**). To a stirred suspension of $LiAlH_4$ (1.74 g, 45.82 mmol) in anhydrous THF (50 mL) under an Ar atmosphere and at 0 °C was added dropwise a solution of 1-nitro-2-(2-methoxynaphthyl)ethylene (**9**) (2.05 g, 8.94 mmol) in THF (75 mL). After the addition, the reaction mixture was heated at 40 °C for 24 h. After cooling at 0 °C, water (1.6 mL), 15% NaOH solution (1.6 mL), ether (37 mL), and water (4.7 mL) were added. The mixture was filtered, and the filtrate was dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude oil was purified by column chromatography (silica gel, AcOEt–MeOH–Et_3N, 15:3:2) to yield 1.42 g (7.06 mmol, 79%) of **16** as an orange oil: ^1H NMR ($CDCl_3$) δ 1.71 (br s, 2H, NH_2), 2.98 (t, 2H, $ArCH_2$, J = 7.1 Hz), 3.26 (t, 2H, CH_2NH_2, J = 7.1 Hz), 3.94 (s, 3H, MeO), 7.27 (d, 1H, H_1, J = 9.1 Hz), 7.34 (dt, 1H, ArH, J = 7.8 Hz), 7.48 (dt, 1H, ArH, J = 1.2, J = 7.8 Hz), 7.75 (d, 1H, ArH, J = 9.1 Hz), 7.79 (d, 1H, ArH, J = 8.5 Hz), 7.98 (d, 1H, ArH, J = 8.5 Hz).

The oil was dissolved in ether (10 mL), and 2 equiv of a solution of 4 N chlorhydric ether was added. After evaporation of the solvent under reduced pressure, the solid was recrystallized from ethanol/ether to afford the pure HCl salt of the amine **16**: yield 100%; mp >220 °C. Anal. ($C_{13}H_{16}NOCl$).

1-(2-Methoxynaphthyl)-2-aminopropane (17). The reaction was carried out with 2-nitro-1-(2-methoxynaphthyl)-propene (**10**) as described in the above procedure. The crude oil was purified by chromatography (silica gel, AcOEt and then AcOEt–MeOH–Et_3N, 15:3:2) to afford **17** as an orange oil: yield 59%; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, CH_3, J = 6.7 Hz), 1.44 (br s, 2H, NH_2), 3.14 (d, 2H, CH_2, J = 6.7 Hz), 3.28 (m, 1H, CH, J = 6.7 Hz), 3.94 (s, 3H, MeO), 7.28 (d, 1H, ArH, J = 8.8 Hz), 7.34 (dt, 1H, ArH, J = 1.2, 7.8 Hz), 7.47 (dt, 1H, ArH, J = 1.2, 7.8 Hz), 7.76 (d, 1H, ArH, J = 8.8 Hz), 7.79 (d, 1H, ArH, J = 7 Hz), 7.99 (d, 1H, ArH, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.83 (CH_3), 35.23 ($ArCH_2$), 47.85 (CHN), 56.25 (OMe), 113.08 (C_3), 121.04 (C_1), 123.11, 123.45 (C_8 and C_6), 126.15, 127.91, 128.44 (C_5, C_7, and C_4), 129.13 (C_{10}), 133.37 (C_9), 154.92 (C_2).

2-(2-Methoxy-5-ethylphenyl)ethylamine (14). The reaction was carried out with 1-nitro-2-(2-methoxy-5-ethylphenyl)-ethylene (**11**) as described in the above procedure. The crude compound was dissolved in ether (10 mL), and 2 equiv of a solution of 4 N chlorhydric ether was added. After evaporation of the solvent under reduced pressure, the solid was recrystallized from ethanol/ether to afford the pure HCl salt of the amine **14**: yield 28%; mp 173 °C; ^1H NMR (CD_3OD) δ 1.19 (t, 3H, CH_3, J = 7.6 Hz), 2.56 (q, 2H, $ArCH_2$, J = 7.6 Hz), 2.92 (t, 2H, $ArCH_2$, J = 7.6 Hz), 3.11 (t, 2H, CH_2N, J = 7.6 Hz), 3.82 (s, 3H, MeO), 6.89 (d, 1H, H_3, J = 8.3 Hz), 7.02 (ds, 1H, H_6, J = 2.1 Hz), 7.10 (dd, 1H, H_4, J = 2.1, 8.3 Hz); ^{13}C NMR (CD_3OD) δ 16.40 (CH_3), 28.86 ($ArCH_2$), 29.97 ($ArCH_2$), 40.87 (CH_2N), 59.81 (MeO), 111.68 (C_3), 125.61 (C_1), 128.80 (C_6), 131.14 (C_4), 137.40 (C_5), 157.01 (C_2). Anal. ($C_{11}H_{18}NOCl$).

2-(2,7-Dimethoxynaphthyl)ethylamine (18). The reaction was carried out with 1-nitro-2-(2,7-dimethoxynaphthyl)-ethylene (**12**) as described in the above procedure. The crude compound was dissolved in ether (10 mL), and 2 equiv of a solution of 4 N chlorhydric ether was added. After evaporation of the solvent under reduced pressure, the solid was recrystallized from ethanol/ether to afford the pure HCl salt of the amine **18**: yield 63%; mp >222 °C dec; ^1H NMR (CD_3OD) δ 3.14 (t, 2H, $ArCH_2$, J = 7.8 Hz), 3.41 (t, 2H, CH_2N, J = 7.8 Hz), 3.94 (s, 3H, MeO), 3.97 (s, 3H, MeO), 7.02 (dd, 1H, H_6, J = 2.4, 8.9 Hz), 7.23 (ds, 1H, H_8, J = 2.4 Hz), 7.24 (d, 1H, H_3, J = 9 Hz), 7.72 (d, 1H, H_4 or H_5, J = 8.8 Hz), 7.76 (d, 1H, H_4 or H_5, J = 8.6 Hz); ^{13}C NMR (CD_3OD) δ 24.16 ($ArCH_2$), 40.27 (CH_2N), 55.88 (MeO), 56.58 (MeO), 101.84 (C_8), 103.62, 111.22 (C_3 and C_6), 121.45 (C_1), 126.21 (C_{10}), 130.17, 131.50 (C_4 and C_5), 135.39 (C_9), 157.04 (C_7), 160.39 (C_2). Anal. ($C_{14}H_{18}NO_2Cl$).

Synthesis of Amines 13 and 15. Method B. The method is described for the synthesis of 2-(2-methoxy-5-methylphenyl)-ethylamine (**13**). Ammoniaque (3.8 mL) was added to a vigorously stirred solution of **7** (1.7 g, 10.54 mmol) in ethanol (38 mL). A catalytic amount of Raney Ni was added to the mixture, and the reaction mixture was heated at 40–50 °C for 48 h under a H_2 atmosphere. After cooling, the mixture was filtered on Celite, and the solid was washed with ethanol. After evaporation of the solvent under reduced pressure, the residue was dissolved in ether (30 mL) and dried over $MgSO_4$, and the solvent was evaporated. To a solution of the crude amine **13** in ether (10 mL) was added a solution of 4 N chlorhydric ether. After evaporation of the solvent under reduced pressure, the solid was recrystallized from a mixture of ethanol/ether to afford 1.07 g (5.31 mmol, yield 50%) of the pure HCl salt of the amine **13**: mp 170 °C; ^1H NMR (CD_3OD) δ 2.25 (s, 3H, CH_3), 2.91 (t, 2H, $ArCH_2$, J = 7.4 Hz), 3.11 (t, 2H, CH_2N, J = 7.4 Hz), 3.81 (s, 3H, MeO), 6.85 (d, 1H, H_3, J = 8.3 Hz), 7.01 (ds, 1H, H_6), 7.06 (dd, 1H, H_4, J = 1.7, 8.3 Hz); ^{13}C NMR (CD_3OD) δ 20.49 (CH_3), 29.83 ($ArCH_2$), 40.91 (CH_2N), 55.89 (MeO), 111.69 (C_3), 125.56 (C_1), 130.06 (C_6), 131.13 (C_4), 132.29 (C_5), 156.90 (C_2). Anal. ($C_{10}H_{16}NOCl$).

2-(2-Methoxy-5-bromophenyl)ethylamine (15). The reaction was carried out with **8** as described in the above procedure. The crude amine was used directly in the next reaction without further purification: ^1H NMR ($CDCl_3$) δ 1.39 (br s, 2H, NH_2), 2.66 (m, 2H, $ArCH_2$), 2.83 (m, 2H, CH_2N), 3.71 (s, 3H, MeO), 6.64 (d, 1H, ArH, J = 8.5 Hz), 7.16–7.23 (m, 2H, ArH).

Synthesis of Amides 3a–k,n,o, 4a–e,g,j,k. Method C. The method is described for the synthesis of *N*-[2-(2-methoxynaphthyl)ethyl]propionamide (**4b**). To a stirred solution of **16** (1.40 g, 6.96 mmol) in anhydrous CH_2Cl_2 (20 mL) under an Ar atmosphere and at 0 °C were added dropwise Et_3N (1.5 mL, 10.4 mmol) and then propionyl chloride (0.7 mL, 8.06 mmol). After these additions, the reaction mixture was stirred at room temperature 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 crude solid was recrystallized from pentane/AcOEt to yield 0.70 g (2.72 mmol, 39%) of **4b** as a white crystalline solid: mp 103 °C; ^1H NMR ($CDCl_3$) δ 1.08 (t, 3H, CH_3, J = 7.2 Hz), 2.11 (q, 2H, $COCH_2$, J = 7.2 Hz), 3.33 (t, 2H, $ArCH_2$, J = 6.7 Hz), 3.53 (t, 2H, CH_2N, J = 6.7 Hz), 3.96 (s, 3H, CH_3O), 5.82 (br s, 1H, NH), 7.28 (d, 1H, ArH, J = 8.7 Hz), 7.34 (dt, 1H, ArH, J = 1.3, 7.8 Hz), 7.49 (dt, 1H, ArH, J = 1.3, 7.8 Hz), 7.76 (d, 1H, ArH, J = 9.0 Hz), 7.78 (d, 1H, ArH, J = 7.5 Hz), 8.02 (d, 1H, ArH, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 9.63 (CH_3), 24.46 ($ArCH_2$), 29.67 ($COCH_2$), 39.85 (CH_2N), 56.41 (MeO), 112.89 (C_3), 120.26 (C_1), 123.10, 123.47 (C_6 and C_8), 126.69, 128.35, 128.47 (C_4, C_5, and C_7), 129.22 (C_{10}), 133.24 (C_9), 154.58 (C_2), 173.82 (CO). Anal. ($C_{16}H_{19}NO_2$).

***N*-[2-(4-Chlorophenyl)ethylacetamide (3a).** Acylation of 2-(4-chlorophenyl)ethylamine with acetyl chloride in the above procedure produced **3a** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 84%; mp 96 °C; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3H, CH_3), 2.61 (t, 2H, $ArCH_2$, J = 7.0 Hz), 3.29 (q, 2H, CH_2N, J = 6.6 Hz), 5.66 (br s, 1H, NH), 6.93 (d, 2H, H_2 and H_6, J = 8.4 Hz), 7.09 (d, 2H, H_3 and H_5, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.17 (CH_3), 35.02 ($ArCH_2$),

40.68 (CH_2NH), 128.78 (C_3 and C_5), 130.11 (C_2 and C_6), 132.41 (C_4), 137.34 (C_1), 170.32 (CO). Anal. ($C_{10}H_{12}NOCl$).

***N*-[2-(3-Chlorophenyl)ethyl]acetamide (3b).** Acylation of 2-(3-chlorophenyl)ethylamine with acetyl chloride in the above procedure produced **3b** as a yellow oil purified by column chromatography (silica gel, $CHCl_3$–MeOH, 95:5): yield 89%; ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3), 2.72 (t, 2H, $ArCH_2$, J = 7.0 Hz), 3.41 (q, 2H, CH_2N, J = 6.7 Hz), 5.66 (br s, 1H, NH), 6.99–7.03 (dd, 1H, H_6, J = 8.1 Hz), 7.11–7.20 (m, 3H, H_2, H_4, and H_5). Anal. ($C_{10}H_{12}NOCl$).

***N*-[2-(2-Chlorophenyl)ethyl]acetamide (3c).** Acylation of 2-(2-chlorophenyl)ethylamine with acetyl chloride in the above procedure produced **3c** as an oil purified by column chromatography (silica gel, $CHCl_3$–MeOH, 95:5): yield 61%; ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3), 2.88 (t, 2H, $ArCH_2$, J = 7.0 Hz), 3.44 (q, 2H, CH_2N, J = 6.6 Hz), 5.77 (br s, 1H, NH), 7.06–7.16 (m, 3H, H_4, H_5, and H_6), 7.27 (d, 1H, H_3, J = 8.2 Hz). Anal. ($C_{10}H_{12}NOCl$).

***N*-[2-(3-Fluorophenyl)ethyl]acetamide (3d).** Acylation of 2-(3-fluorophenyl)ethylamine with acetyl chloride in the above procedure produced **3d** as an oil purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5): yield 58%; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, CH_3), 2.73 (t, 2H, $ArCH_2$, J = 7.1 Hz), 3.40 (q, 2H, CH_2N, J = 6.6 Hz), 5.86 (br s, 1H, NH), 6.78–6.90 (m, 3H, H_2, H_4, and H_6), 7.16 (t, 1H, H_5, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 23.23 (CH_3), 35.49 ($ArCH_2$), 40.62 (CH_2NH), 113.48 (d, 1C, C_4, J = 21 Hz), 115.66 (d, 1C, C_2, J = 21 Hz), 124.52 (C_6), 130.16 (d, 1C, C_5, J = 8 Hz), 141.66 (d, 1C, C_1, J = 7 Hz), 160.62, 165.51 (d, 1C, C_3, J = 250 Hz), 170.47 (CO). Anal. ($C_{10}H_{12}NOF$).

***N*-[2-(4-Methoxyphenyl)ethyl]acetamide (3e).** Acylation of 2-(4-methoxyphenyl)ethylamine with acetyl chloride in the above procedure produced **3e** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 41%; mp 86 °C; ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H, CH_3), 2.67 (t, 2H, $ArCH_2$, J = 6.9 Hz), 3.39 (q, 2H, CH_2N, J = 6.8 Hz), 3.71 (s, 3H, MeO), 5.58 (br s, 1H, NH), 6.76 (d, 2H, H_3 and H_5, J = 8.6 Hz), 7.02 (d, 2H, H_2 and H_6, J = 8.5 Hz). Anal. ($C_{11}H_{15}NO_2$).

***N*-[2-(3-Methoxyphenyl)ethyl]acetamide (3f).** Acylation of 2-(3-methoxyphenyl)ethylamine with acetyl chloride in the above procedure produced **3f** as an oil purified by column chromatography (silica gel; $CHCl_3$–MeOH, 9:1): yield 60%; ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H, CH_3), 2.69 (t, 2H, $ArCH_2$, J = 7.0 Hz), 3.40 (q, 2H, CH_2N, J = 6.6 Hz), 3.69 (s, 3H, OCH_3), 5.74 (br s, 1H, NH), 6.64–6.70 (m, 2H, H_4 and H_6), 7.12 (t, 1H, H_5, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.26 (CH_3), 35.68 ($ArCH_2$), 40.68 (CH_2NH), 55.25 (OMe), 111.91 (C_4), 114.56 (C_2), 121.12 (C_6), 129.70 (C_5), 140.54 (C_1), 159.92 (C_3), 170.35 (CO). Anal. ($C_{11}H_{15}NO_2$).

***N*-[2-(2-Methoxyphenyl)ethyl]acetamide (3g).** Acylation of 2-(2-methoxyphenyl)ethylamine with acetyl chloride in the above procedure produced **3g** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 53%; mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, $COCH_3$), 2.78 (t, 2H, $ArCH_2$, J = 6.9 Hz), 3.53 (t, 2H, CH_2N, J = 6.9 Hz), 3.72 (s, 3H, MeO), 6.36 (br s, 1H, NH), 6.65–6.76 (m, 3H, ArH), 7.18 (t, 1H, ArH, J = 7.9 Hz). Anal. ($C_{11}H_{15}NO_2$).

***N*-[2-(2,5-Dimethoxyphenyl)ethyl]acetamide (3h).** Acylation of 2-(2,5-dimethoxyphenyl)ethylamine with acetyl chloride in the above procedure produced **3h** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 69%; mp 96 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, $COCH_3$), 2.73 (t, 2H, $ArCH_2$, J = 6.6 Hz), 3.40 (t, 2H, CH_2N, J = 6.6 Hz), 3.69 (s, 3H, MeO), 3.73 (s, 3H, MeO), 5.64 (br s, 1H, NH), 6.64–6.76 (m, 3H, ArH). Anal. ($C_{12}H_{17}NO_2$).

***N*-[2-(2,5-Dimethoxyphenyl)ethyl]propionamide (3i).** Acylation of 2-(2,5-dimethoxyphenyl)ethylamine with propionyl chloride in the above procedure produced **3i** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 81%; mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, CH_3, J = 7.6 Hz), 2.08 (q, 2H, $COCH_2$), 2.73 (t, 2H, $ArCH_2$, J = 6.6 Hz), 3.40 (m, 2H, CH_2N), 3.69 (s, 3H, MeO), 3.73 (s, 3H, MeO), 5.69 (br s, 1H, NH), 6.64–6.76 (m, 3H, ArH). Anal. ($C_{13}H_{19}NO_2$).

***N*-[2-(2,5-Dimethoxyphenyl)ethyl]cyclopropylformamide (3j).** Acylation of 2-(2,5-dimethoxyphenyl)ethylamine with cyclopropanecarbonyl chloride in the above procedure produced **3j** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 84%; mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 0.56–0.65 (m, 2H, cyclopropyl), 0.87–0.94 (m, 2H, cyclopropyl), 1.13–1.23 (m, 1H, cyclopropyl), 2.75 (t, 2H, $ArCH_2$, J = 6.7 Hz), 3.42 (m, 2H, CH_2N), 3.69 (s, 3H, MeO), 3.74 (s, 3H, MeO), 5.79 (br s, 1H, NH), 6.66–6.76 (m, 3H, ArH). Anal. ($C_{14}H_{19}NO_2$).

***N*-[2-(2,5-Dimethoxyphenyl)ethyl]-*n*-valeramide (3k).** Acylation of 2-(2,5-dimethoxyphenyl)ethylamine with *n*-valeryl chloride in the above procedure produced **3k** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 68%; mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, CH_3, J = 7.2 Hz), 1.10–1.32 (m, 2H, CH_2), 1.42–1.47 (m, 2H, CH_2), 2.05 (t, 2H, $COCH_2$, J = 7.2 Hz), 2.73 (t, 2H, $ArCH_2$, J = 6.6 Hz), 3.40 (m, 2H, CH_2N), 3.69 (s, 3H, MeO), 3.73 (s, 3H, MeO), 5.66 (br s, 1H, NH), 6.64–6.75 (m, 3H, ArH). Anal. ($C_{15}H_{23}NO_2$).

***N*-[2-(2-Methoxy-5-bromophenyl)ethyl]acetamide (3n).** Acylation of the crude amine **15** with acetyl chloride in the above procedure produced **3n** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 39%; mp 103 °C; ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, $COCH_3$), 2.71 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.34–3.44 (m, 2H, CH_2N), 3.75 (s, 3H, MeO), 5.53 (br s, 1H, NH), 6.67 (d, 1H, ArH, J = 8.6 Hz), 7.17–7.27 (m, 2H, ArH). Anal. ($C_{11}H_{14}NO_2Br$).

***N*-[2-(2-Methoxy-5-bromophenyl)ethyl]propionamide (3o).** Acylation of the crude amine **15** with propionyl chloride in the above procedure produced **3o** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 30%; mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, CH_3, J = 7.6 Hz), 2.09 (q, 2H, CH_2, J = 7.6 Hz), 2.72 (t, 2H, $ArCH_2$, J = 7.6 Hz), 3.34–3.44 (m, 2H, CH_2N), 3.75 (s, 3H, MeO), 5.55 (br s, 1H, NH), 6.66 (d, 1H, ArH, J = 8.7 Hz), 7.15–7.27 (m, 2H, ArH). Anal. ($C_{12}H_{16}NO_2Br$).

***N*-[2-(2-Methoxynaphthyl)ethyl]acetamide (4a).** Acylation of **16** with acetyl chloride in the above procedure produced **4a** as a white crystalline solid purified by recrystallization from hexane/ethyl acetate: yield 77%; mp 139 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H, $COCH_3$), 3.25 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.48 (t, 2H, CH_2N, J = 6.8 Hz), 3.90 (s, 3H, CH_3O), 5.69 (br s, 1H, NH), 7.19–7.31 (m, 2H, ArH), 7.39–7.47 (m, 1H, ArH), 7.68–7.74 (m, 2H, ArH), 7.94 (d, 1H, ArH, J = 8.6 Hz). Anal. ($C_{15}H_{17}NO_2$).

***N*-[2-(2-Methoxynaphthyl)ethyl]-*n*-butyramide (4c).** Acylation of **16** with butyryl chloride in the above procedure produced **4c** as a white crystalline solid purified by recrystallization from pentane/AcOEt: yield 48%; mp 76 °C; ^{1}H NMR δ 0.86 (t, 3H, CH_3, J = 7.5 Hz), 1.57 (m, 2H, CH_2, J = 7.5 Hz), 2.03 (t, 2H, $COCH_2$, J = 7.5 Hz), 3.30 (t, 2H, $ArCH_2$, J = 6.5 Hz), 3.52 (t, 2H, CH_2N, J = 6.5 Hz), 3.95 (s, 3H, CH_3O), 5.74 (br s, 1H, NH), 7.26 (d, 1H, ArH, J = 9.4 Hz), 7.33 (dt, 1H, ArH, J = 7.4 Hz), 7.48 (dt, 1H, ArH, J = 1.0, 7.4 Hz), 7.76 (d, 1H, ArH, J = 9.0 Hz), 7.77 (d, 1H, ArH, J = 7.5 hz), 8.03 (d, 1H, ArH, J = 8.5 Hz). Anal. ($C_{17}H_{21}NO_2$).

***N*-[2-(2-Methoxynaphthyl)ethyl]cyclopropylformamide (4d).** Acylation of **16** with cyclopropanecarbonyl chloride in the above procedure produced **4d** as a beige crystalline solid purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 99.8:0.2) followed by recrystallization from hexane/AcOEt: yield 39%; mp 127.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.56–0.65 (m, 2H, cyclopropyl), 0.85–0.92 (m, 2H, cyclopropyl), 1.08–1.18 (m, 2H, cyclopropyl), 3.24 (t, 2H, $ArCH_2$, J = 6.3 Hz), 3.49 (t, 2H, CH_2N, J = 6.3 Hz), 3.90 (s, 3H, CH_3O), 5.86 (br s, 1H, NH), 7.21 (d, 1H, ArH, J = 8.8 Hz), 7.30 (dt, 1H, ArH, J = 1.3, 7.8 Hz), 7.44 (dt, 1H, ArH, J = 1.3, 7.8 Hz), 7.71 (d, 1H, ArH, J = 9.0 Hz), 7.73 (d, 1H, ArH, J = 7.5 Hz), 7.96 (d, 1H, ArH, J = 8.6 Hz). Anal. ($C_{17}H_{19}NO_2$).

***N*-[2-(2-Methoxynaphthyl)ethyl]-*n*-valeramide (4e).** Acylation of **16** with *n*-valeryl chloride in the above procedure produced **4e** as a white crystalline solid purified by recrystallization from pentane/AcOEt: yield 47%; mp 72 °C; ^{1}H NMR δ 0.88 (t, 3H, CH_3, J = 7.3 Hz), 1.27 (m, 2H, CH_2, J = 7.3 Hz), 1.54 (m, 2H, CH_2, J = 7.3 Hz), 2.08 (t, 2H, $COCH_2$, J = 7.6 Hz), 3.33 (t, 2H, $ArCH_2$, J = 6.4 Hz), 3.54 (t, 2H, CH_2N, J = 6.4 Hz), 3.97 (s, 3H, CH_3O), 5.77 (br s, 1H, NH), 7.28 (d, 1H,

ArH, J = 9.3 Hz), 7.33 (t, 1H, ArH, J = 7.7 Hz), 7.50 (dt, 1H, ArH, J = 1.2, 7.7 Hz), 7.77 (d, 1H, ArH, J = 9.1 Hz), 7.79 (d, 1H, ArH, J = 7.8 Hz), 8.03 (d, 1H, ArH, J = 8.6 Hz). Anal. ($C_{18}H_{23}NO_2$).

***N*-[1-Methyl-2-(2-methoxynaphthyl)ethyl]acetamide (4g).** Acylation of **17** with acetyl chloride in the above procedure produced **4g** as a white crystalline solid purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2): yield 90%; mp 151 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3H, CH_3-CH, J = 6.5 Hz), 1.84 (s, 3H, $COCH_3$), 3.13–3.38 (m, 2H, $ArCH_2$, J_{A-B} = 13.7 Hz, J_{A-X} = 6.3 Hz, J_{B-X} = 8 Hz), 3.97 (s, 3H, CH_3O), 4.14–4.34 (m, 1H, CH, J_{A-X} = 6.3 Hz, J_{B-X} = 8 Hz), 6.02 (d, 1H, NH, J = 5.7 Hz), 7.28 (d, 1H, ArH, J = 7.8 Hz), 7.34 (dt, 1H, ArH, J = 7.8 Hz), 7.50 (dt, 1H, ArH, J = 1.2, 7.3 Hz), 7.76 (d, 1H, ArH, J = 9.1 Hz), 7.78 (d, 1H, ArH, J = 8.1 Hz), 8.07 (d, 1H, ArH, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.71 (CH_3CO), 23.45 (CH_3CH), 31.22 ($ArCH_2$), 47.0 (CHN), 56.45 (MeO), 112.92 (C_3), 119.93 (C_1), 123.40, 123.51 (C_6 and C_8), 126.66, 128.43, 128.43 (C_4, C_5, and C_7), 129.32 (C_{10}), 133.3 (C_9), 154.62 (C_2), 169.48 (CO). Anal. ($C_{16}H_{19}NO_2$).

***N*-[2-(2,7-Dimethoxynaphthyl)ethyl]propionamide (4j).** Acylation of the free amine **18** with propionyl chloride in the above procedure produced **4j** as a white crystalline solid purified by recrystallization from CH_2Cl_2/petroleum ether: yield 74%; mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, CH_3, J = 7.6 Hz), 2.04 (q, 2H, $COCH_2$, J = 7.6 Hz), 3.20 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.46 (q, 2H, CH_2N, J = 6.4 Hz), 3.87 (s, 3H, MeO), 3.88 (s, 3H, MeO), 5.78 (br s, 1H, NH), 6.98 (dd, 1H, H_6, J = 2.5, 8.9 Hz), 7.03 (d, 1H, H_3, J = 8.9 Hz), 7.26 (ds, 1H, H_8, J = 2.5 Hz), 7.59 (d, 2H, H_4 and H_5, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 9.64 (CH_3), 24.73 ($ArCH_2$), 29.74 (CH_2), 39.52 (CH_2N), 55.38 (MeO), 56.27 (MeO), 101.65 (C_8), 110.22, 116.31 (C_3 and C_6), 119.04 (C_1), 124.71 (C_{10}), 128.02, 129.97 (C_4 and C_5), 134.65 (C_9), 155.18 (C_7), 158.53 (C_2), 173.84 (CO). Anal. ($C_{17}H_{21}NO_3$).

***N*-[2-(2,7-Dimethoxynaphthyl)ethyl]cyclopropylformamide (4k).** Acylation of the free amine **18** with cyclopropanecarbonyl chloride in the above procedure produced **4k** as a beige crystalline solid purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2): yield 61%; mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 0.62–0.72 (m, 2H, cyclopropyl), 0.89–0.97 (m, 2H, cyclopropyl), 1.15–1.25 (m, 2H, cyclopropyl), 3.28 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.56 (q, 2H, CH_2N, J = 6.3 Hz), 3.94 (s, 3H, MeO), 3.96 (s, 3H, MeO). 5.94 (br s, 1H, NH), 6.91 (dd, 1H, H_6, J = 2.4, 8.9 Hz), 7.12 (d, 1H, H_3, J = 8.9 Hz), 7.30 (ds, 1H, H_8, J = 2.4 Hz), 7.68 (d, 1H, H_4 or H_5, J = 8.9 Hz), 7.69 (d, 1H, H_4 or H_5, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 6.79 (2C, CH_2 cyclopropyl), 14.77 (CH cyclopropyl), 24.92 ($ArCH_2$), 39.74 (CH_2N), 55.34 (MeO), 56.28 (MeO), 101.70 (C_8), 110.28, 116.25 (C_3 and C_6), 119.14 (C_1), 124.70 (C_{10}), 127.99, 129.95 (C_4 and C_5), 134.63 (C_9), 155.24 (C_7), 158.50 (C_2), 173 (CO). Anal. ($C_{18}H_{21}NO_3$).

Synthesis of Acetamides 3l,m and 4i. Method D. The method is described for the synthesis of *N*-[2-(2-methoxy-5-methylphenyl)ethyl]acetamide (**3l**). To a stirred solution of the hydrochloride salt **13** (0.31 g, 1.54 mmol) in water (15 mL) were added successively AcONa (1.6 g, 19.51 mmol) and acetic anhydride (3.6 mL, 38.15 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). This organic extract was washed with a saturated $NaHCO_3$ solution (30 mL) and water (30 mL) and then dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) to yield 0.25 g (1.21 mmol, 79%) of **3l**: mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H, $COCH_3$), 2.25 (s, 3H, CH_3), 2.77 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.44 (q, 2H, CH_2N, J = 6.4 Hz), 3.79 (s, 3H, MeO), 5.95 (br s, 1H, NH), 6.74 (d, 1H, H_3, J = 8.1 Hz), 6.94 (dd, 1H, H_4, J = 1.8, 8.1 Hz), 7.01 (ds, 1H, H_6, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.41 ($ArCH_3$), 23.27 ($COCH_3$), 30.07 ($ArCH_2$), 40.13 (CH_2NH), 55.47 (OCH_3), 110.47 (C_3), 127.25 (C_1), 128.07 (C_6), 129.96 (C_4), 131.37 (C_5), 155.46 (C_2), 170.07 (CO). Anal. ($C_{12}H_{17}NO_2$).

***N*-[2-(2-Methoxy-5-ethylphenyl)ethyl]acetamide (3m).** Acetylation of the chlorhydrate of the amine **14** in the above procedure produced **3m**. The crude amide was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2): yield 87%; mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, CH_3, J = 7.6 Hz), 1.85 (s, 3H, $COCH_3$), 2.50 (q, 2H, C_5CH_2, J = 7.6 Hz), 2.73 (t, 2H, C_1CH_2, J = 6.7 Hz), 3.39 (q, 2H, CH_2N, J = 6.3 Hz), 3.74 (s, 3H, MeO), 5.69 (br s, 1H, NH), 6.72 (d, 1H, H_3, J = 8.3 Hz), 6.90 (ds, 1H, H_6), 6.96 (dd, 1H, H_4, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 15.99 (CH_3), 23.43 ($COCH_3$), 28.07 (CH_2), 30.26 ($ArCH_2$), 40.25 (CH_2NH), 55.59 (OCH_3), 110.60 (C_3), 126.98 (C_6), 127.39 (C_1), 130.37 (C_4), 136.71 (C_5), 155.71 (C_2), 170.10 (CO). Anal. ($C_{13}H_{119}NO_2$).

***N*-[2-(2,7-Dimethoxynaphthyl)ethyl]acetamide (4i).** Acylation of the chlorhydrate of the amine **18** in the above procedure produced **4i**. The crude amide was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2): yield 64%; mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H, $COCH_3$), 3.29 (t, 2H, $ArCH_2$, J = 7 Hz), 3.52 (q, 2H, CH_2N, J = 6.5 Hz), 3.95 (s, 3H, MeO), 3.97 (s, 3H, MeO), 5.79 (br s, 1H, NH), 7.02 (dd, 1H, H_6, J = 2,4, 8.8 Hz), 7.12 (d, 1H, H_3, J = 8.9 Hz), 7.35 (ds, 1H, H_8, J = 2.4 Hz), 7.68 (d, 1H, H_4 or H_5, J = 9 Hz), 7.69 (d, 1H, H_4 or H_5, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.33 (CH_3), 24.79 ($ArCH_2$), 39.68 (CH_2N), 55.39 (MeO), 56.31 (MeO), 101.56 (C_8), 110.25, 116.38 (C_3 and C_6), 118.98 (C_1), 124.69 (C_{10}), 128.02, 129.95 (C_4 and C_5), 134.67 (C_9), 155.19 (C_7), 158.53 (C_2), 170.25 (CO). Anal. ($C_{16}H_{19}NO_3$).

Synthesis of Trifluoroacetamides 4f,h,l. Method E. The method is described for the synthesis of N-[1-methyl-2-(2-methoxynaphthyl)ethyl]trifluoroacetamide (**4h**). To a stirred solution of **17** (0.31 g, 1.44 mmol) in anhydrous CH_2Cl_2 (20 mL) under an Ar atmosphere and at 0 °C were added dropwise pyridine (0.12 mL, 1.44 mmol) and then trifluoroacetic anhydride (0.245 mL, 1.73 mmol). After these additions, the reaction mixture was allowed to stir at room temperature for 30 min. The mixture was poured into water (20 mL), the two phases were separated, and the aqueous portion was washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (40 mL) and water (40 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude solid was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2) and recrystallization from pentane/AcOEt to yield 0.15 g (0.482 mmol, 34%) of **4h** as a white crystalline solid: mp 123 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3H, CH_3, J = 6.4 Hz), 3.22–3.46 (m, 2H, $ArCH_2$, J_{A-B} = 14.3 Hz, J_{A-X} = 4.7 Hz, J_{B-X} = 9.5 Hz), 4.00 (s, 3H, CH_3O), 4.21–4.26 (m, 1H, CH, J_{A-X} = 4.7 Hz, J_{B-X} = 9.5 Hz), 7.30 (d, 1H, ArH, J = 9 Hz), 7.38 (dt, 1H, ArH, J = 7.5 Hz), 7.53 (dt, 1H, ArH, J = 7.5 Hz), 7.82 (d, 2H, ArH, J = 8.8 Hz), 7.92 (d, 1H, ArH, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.40 (CH_3), 30.69 ($ArCH_2$), 48.46 (CHN), 56.10 (MeO), 112.34 (C_3), 118.49 (C_1), 122.64, 123.73 (C_6 and C_8), 127.0, 128.75, 129.09 (C_4, C_5, and C_7), 129.45 (C_{10}), 133.2 (C_9), 154.27 (C_2). Anal. ($C_{16}H_{19}NO_2F_3$).

***N*-[2-(2-Methoxynaphthyl)ethyl]trifluoroacetamide (4f).** Acylation of **16** with trifluoroacetic anhydride in the above procedure produced **4f** as a white crystalline solid purified by recrystallization from hexane/AcOEt: yield 29%; mp 87 °C; ^{1}H NMR ($CDCl_3$) δ 3.34 (t, 2H, $ArCH_2$, J = 6.8 Hz), 3.55–3.64 (m, 2H, CH_2N), 3.91 (s, 3H, CH_3O), 6.97 (br s, 1H, NH), 7.18–7.49 (m, 3H, ArH), 7.72–7.87 (m, 3H, ArH). Anal. ($C_{15}H_{14}NO_2F_3$).

***N*-[2-(2,7-Dimethoxynaphthyl)ethyl]trifluoroacetamide (4l).** Acylation of the free amine **18** with trifluoroacetic anhydride in the above procedure produced **4l** as a white crystalline solid purified by column chromatography (silica gel, CH_2Cl_2): yield 48%; mp 132 °C; ^{1}H NMR ($CDCl_3$) δ 3.29 (t, 2H, $ArCH_2$, J = 6.6 Hz), 3.58 (q, 2H, CH_2N, J = 6.1 Hz), 3.88 (s, 3H, MeO), 3.89 (s, 3H, MeO), 6.96 (br s, 1H, NH), 6.96 (dd, 1H, H_6, J = 2.5, 8.9 Hz), 7.06 (d, 1H, H_3, J = 8.9 Hz), 7.12 (ds, 1H, H_8, J = 2.5 Hz), 7.63 (d, 1H, H_4 or H_5, J = 8.9 Hz), 7.65 (d, 1H, H_4 or H_5, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 23.76 ($ArCH_2$), 40.32 (CH_2N), 55.36 (MeO), 56.09 (MeO), 101.10 (C_8), 109.88, 116.45 (C_3 and C_6), 115.91 (q, 1C, CF_3, J = 288 Hz), 118.77 (C_1), 124.87 (C_{10}), 128.73, 130.34 (C_4 and C_5), 134.28 (C_9), 155.14 (C_7), 157.37 (q, 1C, CO, J = 37 Hz), 158.88 (C_2). Anal. ($C_{16}H_{19}NO_3$).

Melatonin Binding Assays. Chickens (Redbro, 4 months, 3–4 kg; Cellu-bio, France) were decapitated at 12 a.m., 6 p.m.,

and 12 p.m., respectively. The whole brains were stored at −80 °C. They were homogenized with a Polytron homogenizer 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 mg of protein/mL determined by the method of Lowry.[36] The membrane aliquots were stored at −80 °C until subsequent use. The binding assays were performed according to the method of Dubocovich with modifications.[37,22,18] Membrane aliquots (20 μL) were incubated in a total volume of 0.25 mL of Tris-HCl buffer (50 mM, pH 7.4) with eight concentrations (0.02−0.8 nM) of the labeled ligand 2-[^{125}I]iodomelatonin (2000 Ci/mmol; purchased from NEN or amersham) for the saturation experiments; 0.05 nM 2-[^{125}I]iodomelatonin and seven concentrations of the compound under test were used for the competition studies. 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 of 2-iodomelatonin and represented 10% of the total binding. Competition studies with brain homogenates from the chicken killed at 12 a.m., were also performed in the presence of 30 μM GTP-γ-S or 1 mM $MnCl_2$[38] to evaluate the agonist or antagonist profile of the tested compounds.

Data Analysis. Both saturation and competition experiments were analyzed using nonlinear least squares curve fitting or linear regression programs in LOTUS 1.2.3 and GraphPad. K_i values were determined using the Cheng−Prussof equation.[39]

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