Mapping the Melatonin Receptor. 3. Design and Synthesis of Melatonin Agonists and Antagonists Derived from 2-Phenyltryptamines

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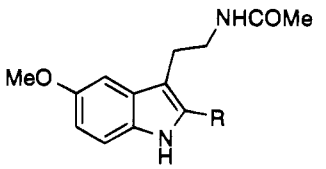
Three series of 2-phenyltryptamides were prepared as melatonin analogues to investigate the nature of the binding site of the melatonin receptor in chicken brain and in *Xenopus laevis* melanophore cells. The 5-methoxy-2-phenyltryptamides (**6a–j**) have high binding affinities for the chicken brain receptor, in some cases (**6a–d**) greater than that for melatonin, confirming and extending the work of Spadoni *et al.*, and act as agonists in the *Xenopus* melanophore assay. Analogues lacking the 5-methoxyl group (**2a–n**) had a considerably lower affinity for the chicken brain receptor. In the *Xenopus* melanophore assay the compounds acylated on nitrogen by an alkyl group (**2a–d**) were agonists whereas the compounds acylated on nitrogen by an alicyclic group (**2f–i**) were antagonists. Introducing a methyl group at N^1 (**7**) led to an increase in binding affinity in the chicken brain assay, whereas introducing an ethyl group (**13**) led to a decrease in binding affinity. A methyl substituent at the β-position of the 3-amidoethane side chain (**8**, **11**) also led to an increase in the binding affinity. The only analogue acylated on nitrogen with an alkyl group (acetyl) which showed antagonist activity was **9**, which has a β-methoxymethyl side chain. In the absence of the 5-methoxyl group the methoxymethyl function may cause the molecule to bind in a different configuration so that it is no longer able to activate the receptor. All of these observations are in agreement with a model of melatonin at the receptor site in which the 3-amidoethane side chain is in a conformation close to the 5-methoxyl group.

Introduction

The pineal hormone melatonin (**1a**), first isolated by Lerner *et al.*[1] in 1958 from bovine pineal tissue, has a central role in the regulation of daily rhythms and seasonal cycles in vertebrates. Quay[2] and Wurtman *et al.*[3] showed that the pineal gland produces and releases melatonin during the hours of darkness, and Hoffman and Reiter[4] found that the endocrine functions of the pineal are governed by changes in the duration of the photoperiod. Many types of seasonal behavior, such as reproduction[5–7] and the accumulation of fat reserves in autumn,[8] in photoperiodic mammals appear to be controlled by the pineal gland. Melatonin has found practical use to induce seasonally breeding animals, such as sheep, to breed out of season.[8,9] In humans it has been suggested that melatonin might have a variety of clinical uses, for example in jet-lag and shift work disturbances,[10] and for circadian rhythm control in the blind. Melatonin has hypnotic properties in animals and humans, and it has been reported to have an oncostatic action and modulate the immune response.[11]

Despite the practical and clinical interest in melatonin, very little is known about its mode of action or of the way in which it interacts with its receptor. High-affinity melatonin binding sites have been identified in central and, more recently, in peripheral tissues,[12] and very recently the receptor in has been cloned from *Xenopus* melanophores, sheep, and humans.[13] Advantage can now be taken of these advances in our knowledge of the receptor characteristics and structure to attempt to model the binding of melatonin to its receptor and to use this model to design melatonin agonists and antagonists.



1a R = H
1b R = I

From experiments with melatonin and tryptamine derivatives on melanophores in patches of frog skin (*Rana pipiens*), Heward and Hadley[14] proposed that the melatonin molecule could be divided into three regions: the indole nucleus, which acts as a spacer, probably with some van der Waals binding affinity, the C-3 amidoethane side chain acting as the major binding site, and the 5-methoxyl group as the biological trigger for the response. Following this model, a number of compounds with improved potency have been obtained[15,16] and some compounds with antagonistic properties have been developed.[12a] It had also been found that 2-iodomelatonin (**1b**) binds to the receptor more strongly than melatonin itself, and this finding has allowed [2-^{125}I]-**1b** to be used in binding studies. Variations of the acyl group on the C-3 side chain had also shown that acetyl was not the optimum group and that replacement by propanoyl or butanoyl effected an improvement in binding affinity.[15,16] As little is known

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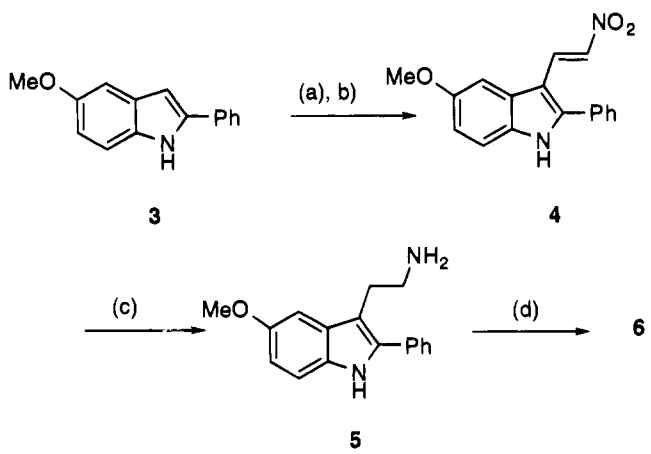
Scheme 1



[a] Reagents: (a) $POCl_3$, DMF, 0 °C to room temperature; (b) CH_3NO_2, NH_4OAc, Δ, 3h; (c) $LiAlH_4$, THF, 4 h; (d) RCOCl, Et_3N, CH_2Cl_2 or $C_nF_{2n+1}CO_2Et$, EtOH, room temperature.

about the factors that are required to bind melatonin to its receptor, we initially decided to incorporate changes at C-2 and in the acyl side chain to investigate the way in which melatonin is bound and then to use these findings to attempt to prepare an antagonist of high potency. We chose to retain the indole nucleus as the spacer group since we wanted to make the smallest number of changes as possible, keeping the compounds closely allied to melatonin. We found that a variety of groups at C-2 increased the binding affinity and discovered that the 5-methoxyl group is not an essential requirement for biological activity,[17] as was originally suggested by Heward and Hadley.[14] The 5-methoxyl group is, however, a major binding site in the attachment of melatonin to its receptor,[17,18] and it appears that the biological response is triggered by inserting the melatonin molecule into the receptor pocket in an orientation controlled by the 5-methoxyl and C-3 amidoethane groups. We found that a phenyl group at C-2 had a similar effect as a halogen at this position[17] and therefore synthesized a range of *N*-acyl-2-phenyltryptamines with different ring substituents and with different acylating groups on the C-3 side chain amine in order to undertake a systematic investigation of their biological properties. The results of this investigation are reported in this paper.

Chemistry

The unsubstituted 2-phenyltryptamine was prepared from 2-phenylindole as previously reported.[17] Mannich reaction gave the dimethylgramine, which was methylated, and the resulting ammonium salt was treated with sodium cyanide to give the nitrile. Hydrogenation of the nitrile then provided the desired 2-phenyltryptamine, which was acylated or fluoroacylated to give the desired amides **2a**–**n**.[19,20]

5-Methoxy-2-phenylindole (**3**) was synthesized by the method Houlihan *et al.*[21] Reaction of indole **3** under the Vilsmeier–Haack conditions followed by a Henry reaction with nitromethane gave the nitroalkene **4**, which was reduced with $LiAlH_4$ to the desired **5** in overall 19% yield.[22] The amine **5** was then acylated or fluoroacylated to give the amides **6a**–**j**[19,20] (see Scheme 1).

The azido derivative **2k** was prepared from the bromide **2l** by treatment with sodium azide in boiling acetone for 48 h. The β-methyl (**8**, **11**) and β-methoxymethyl (**9**, **12**) derivatives were prepared from *N*-methyl-3-(cyanomethyl)-2-phenyltryptamine by treatment with butyllithium and then the appropriate alkyl bromide or iodide.[23] Alkylation of the indole nitrogen was carried out on the corresponding 3-(cyanomethyl)indole by deprotonation and addition of the appropriate alkyl iodide.[24]

Pharmacology

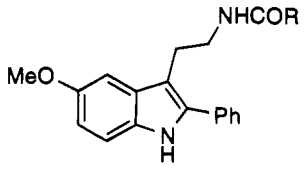
The affinity of the *N*-acyl-2-phenyltryptamine derivatives at the melatonin binding site in chicken brain membranes was determined in a competition radioligand binding assay using [2-^{125}I]-melatonin. This radioligand binding assay was conducted as described previously by Sugden and Chong.[15]

The biological activity of the 2-phenyltryptamine derivatives was examined in a specific *in vitro* model of melatonin action, the pigment aggregation response in *Xenopus laevis* melanophores.[16,25] When these cells are pretreated with α-melanocyte stimulating hormone (30 nM), pigment granules are evenly distributed throughout the cell. Addition of melatonin triggers a rapid redistribution (aggregation) of pigment granules toward the center of the cell. This change in pigment granule distribution can be quantified by computer-assisted image analysis, and concentration–response curves can be constructed.[16,25] In the present study, most compounds were tested at only one concentration, which depended on their binding affinity in the chicken brain membrane assay, and the action is reported at this concentration. In addition, if the pigment in the melanophores is first aggregated with melatonin (10^{-8} M), melatonin receptor antagonists can be detected since these produce pigment granule dispersion. Concentration–response curves can be constructed and IC_{50}'s (concentration of antagonist required to reverse melatonin-induced pigment aggregation by 50%) determined. This was done for compounds showing antagonist activity and having high affinity in the chicken brain radioligand binding assay.

Results and Discussion

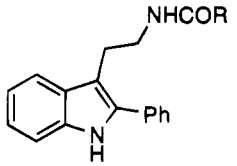
The results of the binding and biological response assays for *N*-acyl-5-methoxy-2-phenyltryptamines are shown in Table 1. Compounds **6a**–**d** all bind to the receptor more strongly than melatonin itself. The substitution of an alicyclic ring for the alkyl side chain of the *N*-acyl group causes a decrease in binding affinity, the cyclopropyl derivative **6e** having a binding affinity 6 times weaker than that for the butanoyl derivative **6c**. An increase in the size of the alicyclic ring led to a progressive loss of binding affinity. All of the derivatives tested (**6a**–**j**) act as agonists in the *Xenopus* melanophore assay. The synthesis of 2-phenylmelatonin (**6a**) and the cyclopropyl derivative **6e** were reported during the course of this study by Spadoni *et al.*,[18] and the affinity constants determined in quail brain membrane binding assays were similar to the K_i values we determined (**6a**, 57 pM; **6e**, 240 pM). Interestingly, these authors found both of these compounds were antagonists in the Syrian hamster gonadal regression model[26] and to have mixed activity, behaving as an antagonist in greater than 60% of tested neurones, in

Table 1. Binding Affinity in Chicken Brain Assay and Response of *Xenopus laevis* Melanophores to 5-Methoxy-2-phenyltryptamine Derivatives



compound	R	receptor binding [K_i], nM	*Xenopus* melanophores action, [conc], M
melatonin		0.59 ± 0.06	agonist, [10^{-8}]
6a	Me	0.0596 ± 0.0074	agonist, [10^{-8}]
6b	Et	0.0466 ± 0.0066	agonist, [10^{-8}]
6c	Prop	0.0558 ± 0.012	agonist, [10^{-8}]
6d	CF_3	0.0190 ± 0.003	agonist, [10^{-8}]
6e	c-C_3H_5	0.3047 ± 0.066	agonist, [10^{-8}]
6f	c-C_4H_7	2.7 ± 0.66	agonist, [10^{-6}]
6g	c-C_5H_9	32.8 ± 7.8	agonist, [10^{-6}]
6h	c-C_6H_{11}	216 ± 31	agonist, [10^{-6}]
6i	1-adamantyl	1100 ± 300	agonist, [10^{-6}]
6j	$(CH_2)_2Ph$	263 ± 40	agonist, [10^{-6}]

Table 2. Binding Affinity in Chicken Brain Assay and Response of *Xenopus laevis* Melanophores to 2-Phenyltryptamine Derivatives



compound	R	receptor binding [K_i], nM	*Xenopus* melanophores action, [conc], M
melatonin		0.59 ± 0.06	agonist, [10^{-8}]
2a	Me	100 ± 12	agonist, [10^{-6}]
2b	Et	70 ± 9	agonist, [10^{-6}]
2c	Pr	112 ± 13	agonist, [10^{-6}]
2d	CF_3	148 ± 37	agonist, [10^{-6}]
2e	C_2F_5	6500 ± 1060	NA, [10^{-5}]
2f	c-C_3H_5	213 ± 46	antagonist[a]
2g	c-C_4H_7	565 ± 126	antagonist[a]
2h	c-C_5H_9	633 ± 113	antagonist[a]
2i	c-C_6H_{11}	1550 ± 240	antagonist[a]
2j	$(CH_2)_2Ph$	7000	NA, [10^{-5}]; NAnt, [10^{-5}]
2k	CH_2N_3	410 ± 79	agonist, [10^{-6}]
2l	CH_2Br	55 ± 12	agonist, [10^{-6}]
2m	CHBrMe	1900 ± 400	NA, [10^{-5}]
2n	1-adamantyl	1100 ± 190	NA, [10^{-5}]; NAnt, [10^{-5}]

[a] See Figure 2 for concentration/response curve and IC_{50}; NA = no agonist response; NAnt = no antagonist response.

the rabbit parietal cortex model.[27] It will clearly be of interest to study these compounds in a number of biological models of melatonin action to compare the activity and potency.

The binding affinities and biological responses of the 2-phenyltryptamine derivatives lacking the 5-methoxyl group are given in Table 2. As entries **2a–2d** clearly illustrate, there is a dramatic loss of binding affinity on removing the 5-methoxyl group, a finding that parallels previous results with melatonin and *N*-acetyltryptamine.[14] The binding affinity of the 2-phenyltryptamine derivatives is, however, much greater than that found for the corresponding tryptamine derivatives lacking the 2-phenyl group.[17] In the *Xenopus* melanophore assay, all of these compounds (**2a–d**) are agonists as we have previously reported.[17] Clearly, although there has been a considerable decrease in binding affinity on removing the 5-methoxyl group (for example, **6a** has a binding affinity 1.7 × 10^3 greater than **2a**), these compounds do invoke a full agonist response. Figure 1 shows the concentration–response curves for **2a**, **2b**, and **2d** in the pigment aggregation model. Although these compounds require higher concentrations to trigger a melanophore response than melatonin, the concentration curves are very similar. Interestingly, unlike **2a** and **2b**, **2d** was much less potent on melanophores than would have been expected from its affinity in the chick brain radioligand binding assay (K_i, 148 nM, binding assay; EC_{50}, 5.1 μM, melanophore assay).

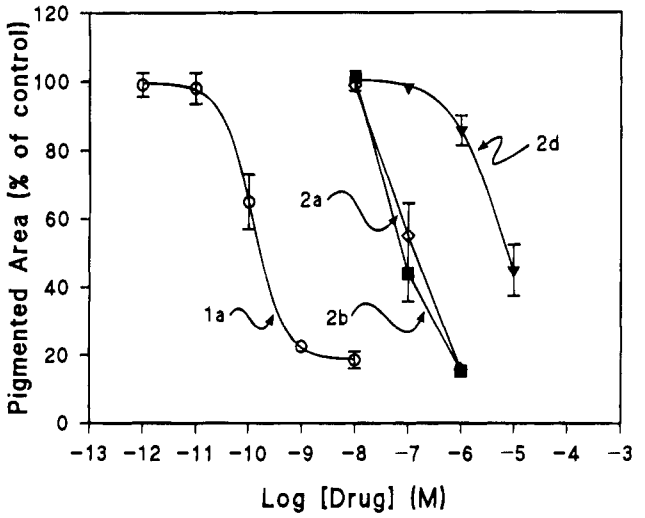


Figure 1. Pigment aggregation in *Xenopus laevis* melanophores in response to melatonin (**1a**) and the analogues **2a**, **2b**, and **2d**. The area occupied by pigment in individual cells was measured on digitized images of cells 15 min after addition of each concentration of drug. Results are expressed as a percentage of the initial area of each cell occupied by pigment granules. Each point is the mean ± SEM of 10–12 cells. Where the error is <2%, no error bars are shown. EC_{50} (concentration of agonist producing 50% of maximal aggregation) **1a**, 123 pM; **2a**, 95 nM; **2c**, 66 nM; **2d**, 5.1 μM.

Substituting an alicyclic ring for the aliphatic chain of the acylating acid leads to a decrease in binding affinity, the cyclopropyl derivative having the highest affinity and the binding decreasing with increasing ring size. The biological response of these derivatives is, however, completely different from the acyclic analogues. Compounds **2f–i** show no agonist activity (data not shown) but act as melatonin antagonists in the *Xenopus* melanophore assay. Figure 2 shows the concentration–response curves for dispersal of pigment in aggregated melanophores. The cyclopropyl derivative **2f** acts at lower concentration than the cyclobutyl derivative **2g** which, in turn, acts at lower concentration than the cyclopentyl **2h** and cyclohexyl **2i** derivatives, which are equivalent. These compounds appear to be full antagonists, giving, at higher concentrations, almost a complete reversal of melatonin-induced pigment aggregation.

The substitution of groups other than the cycloalkanes (**2k–n**) gave compounds that bind poorly. The bromoalkane derivatives **2l,m** almost certainly act as alkylating agents and the binding data is probably unreliable. The azide derivative **2k** was prepared as a

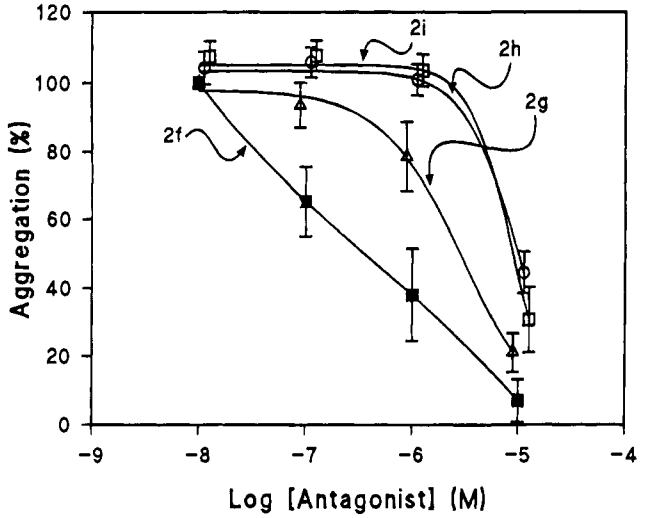
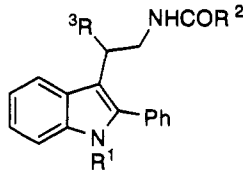


Figure 2. Reversal of melatonin-induced pigment aggregation in Xenopus laevis melanophores. Melanophores were aggregated with melatonin (10 nM, 30 min) and increasing concentrations of the compound under test (**2f**–**i**) were added. Pigment aggregation was remeasured 30 min later. Each point is the mean ± SEM of 9–10 cells. Where the error is <2%, no error bars are shown. IC_{50} (concentration of agonist inhibiting aggregation by 50%) **2f**, 152 nM; **2g**, 3 μM; **2h**, 9.5 μM; **2i**, 8.5 μM.

Table 3. Binding Affinity in Chicken Brain Assay and Response of *Xenopus laevis* Melanophores to N-Alkylated 2-Phenyltryptamine Derivatives



compound	R^1	R^2	R^3	receptor binding [K_i], nM	*Xenopus* melanophores action, [conc], M
melatonin				0.59 ± 0.6	agonist, [10^{-8}]
7	Me	Me	H	63 ± 13	agonist, [10^{-6}]
8	Me	Me	Me	5.9 ± 0.4	agonist, [10^{-7}]
9	Me	Me	CH_2OMe	350 ± 30	NA, [10^{-5}], antagonist, [10^{-5}]
10	Me	c-C_4H_7	H	726 ± 80	antagonist, [10^{-5}]
11	Me	c-C_4H_7	Me	222 ± 22	antagonist, [10^{-5}]
12	Me	c-C_4H_7	CH_2OMe	659 ± 57	antagonist, [10^{-5}]
13	Et	Me	H	154 ± 23	agonist, [10^{-5}]

possible photosensitive compound to allow covalent receptor bonding, but it is poorly photolabile.

Compounds **2k** and **2l** showed agonist activity on pigment granule aggregation, but **2m** and **2n** (the adamantyl derivative) were inactive.

A number of other variations to the 2-phenyltryptamine system were then made (Table 3). Methylation at N^1 gave **7**, which had a slightly greater affinity than its non-methylated analogue **2a**. In contrast, methylation of melatonin to *N*-methylmelatonin resulted in a slight loss of binding affinity.[28] Introducing methyl groups at N^1 and at the β-carbon of the amide side chain in **8** led to a substantial (10-fold) increase in binding affinity compared to **7**. Compound **8** again had a slightly greater binding affinity than its corresponding non-N-methylated analogue (11.6 ± 3.3 nM). Adding a methoxymethyl group at the β-carbon instead of methyl led to a 6-fold decrease in binding affinity, to a value lower than that for **2a**. Compounds **7** and **8** were agonists; compound **9** had no agonist activity even at 10^{-5} M but did show antagonist activity at this concentration.

The same series of substitutions were carried out with the cyclobutanecarbonyl rather than the acetyl amide. All three compounds had lower binding affinities than the corresponding acetyl derivatives, but in contrast to the acetyl derivatives had no agonist activity (10^{-5} M), but were antagonists at this concentration, like **2g**.

Substituting ethyl for methyl on the indole nitrogen leads to a loss in binding affinity (**13** compared to **7**), and the *N*-ethylindole **13** acts as a agonist at high concentrations (10^{-5} M) in the *Xenopus* melanophore assay.

A number of conclusions can be drawn about the nature of the melatonin receptor pocket from the data which we have so far accumulated. The 5-methoxyl group and the 3-amidoethane side chain appear to have a mutual action docking the melatonin molecule onto the receptor. We have proposed that there is a preferred orientation of the 3-amidoethane side chain which is more highly populated when there is a substituent at position C-2, when the side chain is incorporated in a ring,[29] or when there is a β-methyl substituent on the 3-amidoethyl side chain. The region of the receptor in which the 3-amidoethane chain is accommodated is larger than necessary for the acetyl group and increasing the length of the aliphatic side chain initially improves binding, presumably through enhanced van der Waals attractions. Removal of the 5-methoxyl group greatly decreases binding affinity, as was known for the tryptamine analogues,[14] but this decrease in affinity can be partially compensated by substitution at C-2, by substitution at the β-carbon of the amidoethane side chain, and by changing the acylating group. The compounds so produced act as agonists and presumably occupy the active site with the same orientation as melatonin despite the lack of the 5-methoxyl group. One can envisage that these compounds have more stable hydrogen bonds between the receptor and the amide function because of the superior fit, further supported by an increase in van der Waals attractive interactions via the 2-substituent and the acyl side chain.

The introduction of an alicyclic ring in place of the aliphatic side chain decreases the binding affinity but, more interestingly, converts those compounds without a 5-methoxyl group into melatonin antagonists. This small change has surprising consequences, and one must presume that a changed orientation of the molecule in the receptor pocket now cannot evoke transmission of the biological signal but instead impedes the access of melatonin to the receptor site. The C-3 side chain in all these molecules has a number of low-energy conformations, but an inkling of how the alicyclic ring may change the energetic binding requirement comes from an X-ray study of melatonin and its cyclobutyl analogue, the latter having a different hydrogen bonding preference to the former.[30] Although this cyclobutyl derivative is an agonist, it would be expected that in the comparable cyclobutyl derivative without the 5-methoxyl group, the preferred conformational requirements of the C-3 ethanamide side chain will predominate and that the exchange of cyclobutyl for methyl will make a

more significant influence on the arrangement of the molecule in the active site.

The high potency of melatonin, which is biologically active at the picomolar level, suggests that it is bound to the active site by at least three major interactions and the 5-methoxyl group and the 3-ethanamide side chain can clearly provide these, with π-π stacking of the indole ring a fourth, probably less important, interaction. The indole nitrogen appears to be unimportant since it can be substituted or replaced by a C=C moiety with little change.[32,33] These suggestions are consistent with a molecular model of the putative binding site which has recently been proposed on the basis of the predicted amino acid sequence of the cloned *Xenopus* melanophore receptor, estimates of thermodynamic binding parameters, and a quantitative structure–activity analysis of a series of tryptamine analogues of melatonin.[34]

Experimental Section

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Mass spectra were recorded on a VG7070H mass spectrometer with a Finnigan Incos II data system or on a VG ZAB-2F (EI) or VG 12-250 (CI) mass spectrometers. Only molecular ions (M^+), base peaks, and the next two peaks due to ions of maximum abundance are given. IR spectra were recorded on a Perkin-Elmer PE-983 or Perkin-Elmer 1605 FTIR spectrophotometer using KBr pellets unless stated otherwise, and spectral data are reported in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ unless stated otherwise on a Varian VXR-400 spectrometer, and the spectral data are reported in δ. ^{13}C NMR spectra were recorded at 100 MHz on a Varian VXR-400 spectrometer and are reported in δ. Microanalyses were carried out by the microanalytical section, Department of Chemistry, University College London.

Merck Kieselgel 60 F_{254} plates were used for analytical TLC and were visualized with ultraviolet light or developed with *p*-anisaldehyde. Flash column chromatography was performed using Sorbsil C60-A silica (40–60 μm) as the stationary phase.

General Procedure. 2-Phenyltryptamine and 5-methoxy-2-phenyltryptamine were prepared by known methods.[17,21,22] The amines (*ca.* 1–2 mmol) were dissolved in CH_2Cl_2, Et_3N (slight molar excess) was added dropwise with stirring, then the acid chloride (1 molar equiv) in CH_2Cl_2 was added dropwise at room temperature, and the mixture was stirred for 3 h. The mixture was filtered and the filtrate washed successively with H_2O, 10% aqueous HCl, 2 M NaOH, H_2O, and brine. The filtrate was then dried (Na_2SO_4) and the solvent removed under reduced pressure.

***N*-[2-(2-Phenylindol-3-yl)ethyl]acetamide (2a):** colorless oil, 0.45 g, 1.62 mmol, 94%; ^1H NMR δ 8.29 (bs, 1H), 7.62 (d, 1H, J = 7.4 Hz), 7.57–7.54 (m, 2H), 7.47–7.44 (m, 2H), 7.39–7.36 (m, 2H), 7.21 (ddd, 1H, J = 7.5 Hz, J = 1.2 Hz), 7.14 (ddd, 1H, J = 7.5 Hz, J = 1 Hz), 5.45 (bs, 1H), 3.52 (q, 2H, J = 6.55 Hz), 3.11 (t, 2H, J = 6.8 Hz), 1.74 (s, 3H); ^{13}C NMR δ 170.0, 135.8, 135.3, 132.9, 129.0, 129.0, 128.0, 127.9, 122.5, 119.9, 118.9, 110.9, 109.8, 40.1, 24.4, 23.2; IR 3415, 3175, 1879, 1658, 1531, 1491, 1431, 846, 770 cm^{-1}; EIMS 278, 219, 218, 206 (100). Anal. ($C_{18}H_{18}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]propanamide (2b):** colorless oil, 0.40 g, 1.30 mmol, 80%; ^1H NMR δ 8.21 (bs, 1H), 7.64 (d, 1H, J = 7.9 Hz), 7.56 (m, 2H), 7.48–7.34 (m, 4H), 7.21 (ddd, J = 8 Hz, J = 1.1 Hz), 7.14 (ddd, J = 8 Hz, J = 1.1 Hz), 5.44 (bs, 1H), 3.55 (q, 2H, J = 6.5 Hz), 3.12 (t, 2H, J = 6.7 Hz), 1.96 (m, 1H, J = 7.6 Hz, J = 0.9 Hz), 0.99 (m, 1H, J = 7.6 Hz, J = 1.1 Hz); ^{13}C NMR δ 173.6, 135.8, 135.3, 132.9, 129.0, 127.95, 127.9, 122.5, 119.9, 119.0, 110.9, 109.9, 40.0, 29.6, 24.5, 9.65; IR 3415, 3175, 1879, 1658, 1531, 1491, 1431, 846, 770 cm^{-1}; EIMS 293, 292, 220, 206 (100). Anal. ($C_{19}H_{20}N_2O$) C, H, N.

***N*-[2-(Phenylindol-3-yl)ethyl]butanamide (2c):** white foam, 0.45 g, 1.50 mmol, 86%; ^1H NMR δ 8.4 (bs, 1H), 7.63 (d, 1H, J = 8 Hz), 7.55 (m, 2H), 7.46–7.33 (m, 4H), 7.21 (dd, 1H, J = 8 Hz), 7.13 (dd, 1H, J = 7.9 Hz), 5.47 (bs, 1H), 3.54 (q, 2H, J = 6.7 Hz), 3.10 (t, 2H, J = 6.7 Hz), 1.90 (t, 2H, J = 7.6 Hz), 1.48 (m, 2H), 0.82 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 172.9, 135.9, 135.3, 132.9, 129.0, 128.0, 127.8, 122.5, 119.8, 110.9, 109.8, 39.9, 38.6, 24.6, 18.9, 13.7; IR 3415, 3175, 1658, 1531, 1491, 1431, 846, 770 cm^{-1}; EIMS 306, 219, 218, 217, 206 (100). Anal. ($C_{20}H_{22}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]trifluoroacetamide (2d):** white crystalline solid, 0.94 g, 2.80 mmol, 94%; mp 140–141 °C; ^1H NMR δ 8.24 (bs, 1H), 7.63 (d, 1H, J = 8 Hz), 7.55–7.39 (m, 6H), 7.26 (ddd, 1H, J = 7.1 Hz, J = 1.1 Hz), 7.18 (ddd, 1H, J = 7.1 Hz, J = 1.0 Hz), 6.38 (bs, 1H), 3.64 (q, 2H, J = 6.7 Hz), 3.10 (t, 2H, J = 6.9 Hz); ^{13}C NMR δ 157.1 (q, J_{C-F} = 36.7 Hz), 135.8, 135.7, 132.35, 129.1, 128.9, 128.4, 128.3, 128.2, 128.0, 122.7, 122.6, 120.1, 115.6 (q, J_{C-F} = 288.1 Hz), 111.1, 108.4, 40.4, 23.8; IR 3392, 3306, 1698, 1568, 1452, 1192, 1134, 740, 700 cm^{-1}; EIMS 333 (100), 332, 206, 112. Anal. ($C_{18}H_{15}F_3N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]pentafluoropropanamide (2e):** white crystalline solid, 0.29 g, 0.76 mmol, 85%; mp 124–125 °C; ^1H NMR δ 8.18 (bs, 1H), 7.62 (d, 1H, J = 7.9 Hz), 7.53–7.37 (m, 6H), 7.24 (ddd, 1H, J = 8.0, J = 1.0 Hz), 7.17 (dd, 1H, J = 7.9 Hz), 6.45 (bs, 1H), 3.66 (q, 2H, J = 6.5 Hz), 3.18 (t, 2H, J = 6.7 Hz); ^{13}C NMR δ 157.6 (t, J_{C-F} = 25.6 Hz), 135.8, 135.7, 132.4, 129.1, 128.6, 128.2, 128.0, 122.7, 120.15, 119.1 (J_{C-F} = 268.7 Hz, J_{C-F} = 35 Hz), 118.6, 111.1, 108.3, 106.85 (J_{C-F} = 266.5 Hz, J_{C-F} = 38.9 Hz), 40.5, 23.9; IR 3389, 3322, 2944, 1700, 1550, 1433, 1339, 1311, 1227, 1155, 1061, 1000, 744, 700 cm^{-1}; EIMS 382, 207, 206, 204. Anal. ($C_{19}H_{15}F_5N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]cyclopropanecarboxamide (2f):** colorless oil, 0.72 g, 2.37 mmol, 79%; ^1H NMR δ 8.18 (bs, 1H) 7.67–7.12 (m, 9H), 5.65 (bs, 1H), 3.58 (q, 2H, J = 6.6 Hz), 3.11 (t, 2H, J = 6.8 Hz), 1.10–1.06 (m, 1H), 0.91–0.87 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR δ 173.4, 135.8, 135.3, 132.9, 129.1, 129.0, 128.0, 27.9, 122.5, 119.9, 119.15, 110.9, 110.0, 40.3, 24.7, 14.7, 7.0; IR 3043, 3278, 1635, 1525, 1446, 1227, 913, 740, 693 cm^{-1}; EIMS 321, 306, 305 (100), 233. Anal. ($C_{20}H_{20}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]cyclobutanecarboxamide (2g):** white amorphous solid, 0.39 g, 1.22 mmol, 72%; ^1H NMR δ 8.32 (bs, 1H), 7.65 (d, 1H, J = 7.4 Hz), 7.58–7.55 (m, 2H), 7.41–7.37 (m, 2H), 7.23 (ddd, 1H, J = 7.5 Hz, J = 1.2 Hz), 7.15 (ddd, 1H, J = 7.9 Hz, J = 1.1 Hz), 5.41 (bs, 1H), 3.56 (q, 2H, J = 6.7 Hz), 3.12 (t, 2H, J = 6.7 Hz), 2.75 (m, 1H), 2.14–1.7 (m, 4H); ^{13}C NMR δ 174.8, 135.9, 135.3, 132.85, 129.0, 129.0, 127.9, 127.85, 122.5, 119.8, 119.0, 110.9, 109.9, 39.9, 25.2, 24.6, 18.0; IR 3393, 3276, 2930, 1640, 1525, 1452, 743, 700 cm^{-1}; EIMS 318, 220, 219, 218. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]cyclopentanecarboxamide (2h):** pale yellow foam, 0.46 g, 1.40 mmol, 82%; ^1H NMR δ 8.18 (bs, 1H), 7.65 (d, 1H, J = 7.9 Hz), 7.57–7.54 (m, 2H), 7.47–7.44 (m, 2H), 7.39–7.34 (m, 2H), 7.21 (ddd, 1H, J = 7.1 Hz, J = 1.1 Hz), 7.14 (ddd, 1H, J = 7.1 Hz, J = 1.0 Hz), 5.46 (bs, 1H) 2.26–2.22 (m, 1H), 1.69–1.56 (m, 8H); ^{13}C NMR δ 176.1, 135.85, 135.25, 132.85, 129.1, 129.0, 129.0, 128.0, 127.9, 122.5, 119.9, 119.9, 119.1, 110.9, 101.0, 45.9, 39.9, 30.3, 29.95, 25.8, 24.65; IR 3392, 3276, 2930, 2640, 1524, 1452, 743, 700 cm^{-1}; EIMS 256, 144, 130, 143 (100). Anal. ($C_{22}H_{24}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]cyclohexanecarboxamide (2i):** white amorphous foam, 0.52 g, 1.50 mmol, 88%; ^1H NMR δ 8.24 (bs, 1H), 7.65 (d, 1H, J = 7.9 Hz), 7.57–7.54 (m, 2H), 7.47–7.44 (m, 2H), 7.39–7.34 (m, 2H), 7.21 (ddd, 1H, J = 7.1 Hz, J = 1.1 Hz), 7.14 (ddd, 1H, J = 7.1 Hz, J = 1.0 Hz), 5.45 (bs, 1H), 3.54 (q, 2H, J = 6.7 Hz), 3.11 (t, 2H, J = 6.7 Hz), 1.94–1.81 (m, 1H), 1.79–1.07 (m, 10H); ^{13}C NMR δ 176.0, 135.9, 135.2, 132.9, 129.0, 129.0, 128.0, 127.9, 122.5, 119.9, 119.1, 110.9, 109.9, 45.5, 39.7, 29.4, 25.7, 25.7, 25.65, 25.6, 25.5, 25.35, 24.6; IR 3393, 3277, 2930, 1640, 1524, 1452, 743.5, 700 cm^{-1}; EIMS 347 ($M^+ + 1$) 219 (100), 218, 206. Anal. ($C_{23}H_{26}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]-3-phenylpropanoamide (2j):** pale yellow oil, 0.24 g, 0.66 mmol, 77%; ^1H NMR

δ 8.61 (bs, 1H), 7.57 (d, 1H, J = 8.1 Hz), 7.55–7.52 (m, 2H), 7.44–7.10 (m, 11H), 5.49 (bs, 1H), 3.49 (q, 2H, J = 6.8 Hz), 3.06 (t, 2H, J = 6.8 Hz), 2.79 (t, 2H, J = 7.9 Hz), 2.21 (t, 2H, J = 7.9 Hz); ^{13}C NMR δ 172.0, 140.8, 135.9, 132.85, 128.9, 128.35, 128.25, 128.2, 127.9, 127.7, 126.05, 126.0, 122.3, 119.7, 118.8, 111.0, 109.6, 40.0, 38.3, 31.5, 28.4; IR 3393, 3277, 1640, 1525, 1452, 740, 700 cm^{-1}; EIMS 36, 206, 105, 91. Anal. ($C_{25}H_{24}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]azidoacetamide (2k):** white crystalline solid, 0.45 g, 1.40 mmol, 71%; mp 93–95 °C; ^{1}H NMR δ 8.41 (bs, 1H), 7.63 (d, 1H, J = 7.9 Hz), 7.58–7.55 (m, 2H), 7.50–7.46 (m, 2H), 7.41–7.38 (m, 2H), 7.23 (ddd, 1H, J = 7.1 Hz, J = 1.2 Hz), 7.16 (ddd, 1H, J = 7.1 Hz, J = 1.1 Hz), 6.31 (bs, 1H), 3.68 (s, 2H), 3.56 (q, 2H, J = 6.6 Hz), 3.17 (t, 2H, J = 6.6 Hz); ^{13}C NMR δ 166.5, 135.9, 135.4, 132.8, 128.9, 128.75, 128.05, 127.9, 122.5, 119.8, 118.7, 111.0, 109.3, 52.4, 40.0, 30.9, 24.05; IR 3364, 3305, 2929, 2091, 1640, 1539, 744, 700 cm^{-1}; EIMS 320, 219, 207, 205. Anal. ($C_{18}H_{17}N_5O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]bromoacetamide (2l):** gray crystalline solid, 0.45 g, 1.25 mmol, 73%; mp 90–93 °C; ^{1}H NMR δ 8.24 (bs, 1H), 7.63 (d, 1H, J = 7 8 Hz), 7.56 (m, 2H), 7.46 (m, 2H), 7.39–7.35 (m, 2H), 7.22 (ddd, J = 8 Hz, J = 1.1 Hz), 7.15 (dd, J = 7.9 Hz), 6.45 (bs, 1H), 3.61 (s, 2H), 3.56 (q, 2H, J = 6.5 Hz), 3.16 (t, 2H, J = 6.95 Hz); ^{13}C NMR δ 165.4, 135.8, 135.5, 132.7, 129.0, 128.75, 128.1, 128.0, 128.0, 122.6, 119.9, 118.8, 118.8, 111.0, 109.2, 40.7, 29.0, 24.0; IR 3389, 3278, 3044, 2922, 1650, 1528, 1444, 1300, 1206, 739, 689, 539, 500 cm^{-1}; EIMS 358, 356, 219, 206 (100), 204. Anal. ($C_{18}H_{17}BrN_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]-2-bromopropanamide (2m):** tan platelets, 0.50 g, 1.34 mmol, 79%; mp 116–117 °C; ^{1}H NMR δ 8.35 (bs, 1H), 7.64 (d, 1H, J = 7.6 Hz), 7.56 (m, 2H), 7.45 (m, 2H), 7.22 (ddd, 1H, J = 7 Hz, J = 1 Hz), 7.15 (ddd, 1H, J = 7 Hz, J = 1 Hz), 6.41 (bs, 1H), 4.15 (q, 1H, J = 7 Hz), 3.57 (m, 2H), 1.69 (d, 3H); ^{13}C NMR δ 169.2, 135.9, 135.4, 132.7, 128.95, 128.8, 127.9, 122.5, 119.8, 118.9, 111.0, 109.2, 45.1, 40.6, 24.2, 22.9; IR 3387, 3289, 3056, 2922, 1672, 1533, 1489, 1450, 1422, 1256, 1211, 1172, 1067, 739, 700, 639, 556, 533 cm^{-1}; EIMS 372, 370, 219, 218, 206 (100). Anal. ($C_{18}H_{17}N_2O$) C, H, N.

***N*-[2-(2-Phenylindol-3-yl)ethyl]adamantane-1-carboxamide (2n):** white amorphous foam, 0.29 g, 0.73 mmol, 86%; ^{1}H NMR δ 8.39 (bs, 1H), 7.65 (d, 1H, J =7 .9 Hz), 7.58–7.57 (m, 2H), 7.44 (t, 1H), 7.40–7.32 (m, 3H), 7.21 (ddd, 1H, J = 7.1 Hz, J = 1.1 Hz), 7.14 (t, 1H, J = 7.0 Hz), 5.62 (bs, 1H), 3.54 (q, 2H, J = 6.5 Hz), 3.12 (t, 2H, J = 6.5 Hz), 1.90–1.54 (m, 15H); ^{13}C NMR δ 177.0, 135.95, 135.2, 132.9, 129.0, 128.0, 127.9, 127.8, 122.5, 119.75, 119.1, 119.1, 110.95, 109.9, 40.3, 39.8, 39.7, 38.8, 36.4, 28.0, 24.6, 24.5; IR 3393, 3277, 2930, 1640, 1524, 1452, 743.5, 700 cm^{-1}; EIMS 399, 398, 220, 219 (100), 206. Anal. ($C_{27}H_{30}N_2O$) C, H, N.

2-Phenylmelatonin (6a):[18] colorless oil, 0.17 g, 0.54 mmol, 72%; ^{1}H NMR δ 8.40 (bs, 1H), 7.53–7.49 (m, 2H), 7.43–7.40 (m, 2H), 7.34–7.30 (m, 1H), 7.24 (d, 1H, J = 8.7 Hz), 7.06 (d, 1H, J = 2.5 Hz), 6.84 (dd,1 H J = 2.5 Hz, J = 8.7 Hz), 5.55 (bs, 1H), 3.84 (s, 3H), 3.48 (q, 2H, J = 6.7 Hz), 3.06 (t, 2H, J = 6.9 Hz), 1.72 (s, 3H); ^{13}C NMR δ 170.15, 154.2, 136.1, 132.95, 131.0, 129.4, 128.9, 127.8, 127.7, 112.6, 111.8, 109.5, 100.5, 55.9, 55.9, 40.0, 24.4, 23.1; IR 3392, 3279, 2919, 1648, 1528, 1483, 1453, 1303, 1212.5, 1152, 762, 702 cm^{-1}.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]propanamide (6b):** white foam, 0.20 g, 0.61 mmol, 81%; ^{1}H NMR δ 8.30 (bs, 1H), 7.52 (m, 2H), 7.42 (m, 2H), 7.33 (m, 1H), 7.25 (d, 1H, J = 8.9 Hz), 7.06 (d, 1H, J = 2.25 Hz), 6.86 (dd, 1H, J = 2.4 Hz, J = 8.8 Hz), 5.48 (bs, 1H), 3.85 (s, 3H), 3.52 (q, 2H, J = 6.7 Hz), 3.07 (t, 2H, J = 6.7 Hz), 1.96 (q, 2H, J = 7.7 Hz), 0.98 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 173.7, 154.2, 136.1, 132.95, 131.0, 129.4, 128.95, 127.8, 127.8, 112.6, 111.75, 109.6, 100.6, 55.95, 39.8, 29.6, 24.5; IR 3399, 3279, 2919, 1648, 1528, 1483, 1453, 1213, 762, 702 cm^{-1}; EIMS 322, 249, 248, 236 (100); $C_{20}H_{22}O_2N_2$ requires 322.1681, found 322.1688.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]butanamide (6c):** pale yellow gum, 0.17 g, 0.50 mmol, 67%; ^{1}H NMR δ 7.99 (bs, 1H), 7.56–7.54 (m, 2H), 7.48–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.27 (d, 1H, J = 8.7 Hz), 7.08 (d, 1H, J = 2.5 Hz), 6.87 (dd, 1H, J = 8.7 Hz, J = 2.3 Hz), 5.42 (bs, 1H), 3.87 (s, 3H), 3.55 (q, 2H, J = 6.9 Hz), 3.09 (t, 2H J = 6.7 Hz), 1.92 (t, 2H, J = 7.3 Hz), 1.48 (m, 2H, J = 7.5 Hz), 0.82 (t, 3H, J = 7.3 Hz); ^{13}C NMR 173.7, 154.2, 136.1, 133.0, 131.0, 129.4, 129.0, 127.8, 127.8, 112.6, 111.75, 109.6, 100.6, 55.95, 39.8, 29.6, 27.7, 18.9, 13.8; IR 3392, 3279, 2919, 1648, 1528, 1483, 1453, 1213, 762, 702 cm^{-1}; EIMS 336, 322, 248, 236 (100); $C_{21}H_{24}N_2O_2$ requires 336.1838, found 336.1346.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]trifluoroacetamide (6d):** white crystalline sold, 0.13 g, 0.36 mmol, 94%; mp 159–160 °C; ^{1}H NMR δ 8.03 (bs, 1H), 7.52–7.38 (m, 5H), 7.28 (d, 1H, J = 8.7 Hz), 7.04 (d, 1H, J = 2.2 Hz), 6.88 (dd, 1H, J = 8.75 Hz, J = 2.4 Hz), 6.28 (bs, 1H), 3.87 (s, 3H), 3.62 (d, 2H, J = 6.6 Hz), 3.16 (t, 2H, J = 6.64 Hz); ^{13}C NMR 157.2 (q, J = 36.7 Hz), 136.5, 132.5, 131.0, 131.0, 129.7, 128.2, 127.9, 115.6 (q, J = 287.8 Hz), 113.0, 111.9, 108.3, 100.35, 55.9, 40.3, 23.9; IR 3378, 3311, 3089, 2933, 1700, 1556, 1483, 1439, 1361, 1217, 1172, 1022, 694, 622, 522 cm^{-1}; EIMS 363, 362, 237, 236 (100). Anal. $C_{19}H_{17}F_3N_2O_2$ C, H, N.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]cyclopropanecarboxamide (6e):**[18] white foam, 0.21 g, 0.62 mmol, 83%; ^{1}H NMR δ 8.16 (bs, 1H), 7.54–7.51 (m, 2H), 7.45–7.42 (m, 2H), 7.36–7.32 (m, 1H), 7.26 (d, 1H, J = 8.7 Hz), 7.07 (d, 1H, J = 2.4 Hz), 6.86 (dd, 1H, J = 8.7 Hz, J = 2.5 Hz), 5.66 (bs, 1H), 3.86 (s, 3H), 3.56 (q, 2H, J = 6.7 Hz), 3.07 (t, 2H, J = 6.7 Hz), 1.10–1.04 (m, 1H), 0.89–0.85 (m, 2H), 0.63–0.59 (m, 2H); ^{13}C NMR δ 173.4, 154.3, 144.9, 136.2, 132.9, 131.0, 129.5, 129.0, 127.9, 127.8, 121.7, 112.7, 111.7, 109.7, 100.7, 55.95, 55.9, 40.1, 24.65; IR 3399, 3279, 2919, 1648, 1528, 1453, 1303, 1213, 1152, 1032, 912, 762, 702 cm^{-1}; EIMS 334, 249, 248, 236 (100); $C_{21}H_{22}N_2O_2$ requires 334.1681, found 334.1676.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]cyclobutanecarboxamide (6f):** white foam, 0.20 g, 0.57 mmol, 76%; ^{1}H NMR δ 8.27 (bs, 1H), 7.52 (m, 2H), 7.43 (t, 2H), 7.32 (m, 1H), 7.26 (d, 1H, J = 8.7 Hz), 7.05 (d, 1H, J = 2.25 Hz), 6.86 (dd, 1H, J = 8.7 Hz, J = 2.5 Hz), 5.38 (bs, 1H), 3.85 (s, 3H), 3.52 (q, 2H, J = 6.7 Hz), 3.07 (t, 2H, J = 6.7 Hz), 2.73 (m, 1H), 2.13–1.7 (m, 6H); ^{13}C NMR δ 174.9, 154.2, 136.1, 132.9, 131.0, 129.4, 129.1, 129.0, 128.9, 128.1, 128.0, 127.8, 127.8, 112.6, 111.7, 109.6, 100.7, 56.0, 55.95, 39.9, 39.7, 25.2, 24.6; IR 3399, 3279, 2919, 1648, 1528, 1483, 1453, 1303, 1213, 1152, 1032, 912, 762, 702 cm^{-1}; EIMS 348, 250, 249, 248, 236 (100); $C_{22}H_{24}N_2O_2$ requires 348.1838, found 348.1843.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]cyclopentanecarboxamide (6g):** white foam, 0.11 g, 0.32 mmol, 77%; ^{1}H NMR δ 8.21 (bs, 1H), 7.53 (m, 2H), 7.43 (t, 2H), 7.34 (m, 1H), 7.26 (d, 1H, J = 8.7 Hz), 7.06 (d, 1H, J = 2.2 Hz), 6.85 (dd, 1H, J = 8.7 Hz, J = 2.3 Hz), 5.48 (bs, 1H), 3.85 (s, 3H), 3.54 (q, 2H, J = 6.5 Hz), 3.07 (t, 2H, J = 6.7 Hz), 2.22 (m, 1H, J = 7.6 Hz), 1.73–1.53 (m, 8H); ^{13}C NMR δ 176.1, 154.25, 136.1, 132.9, 131.0, 129.4, 129.0, 128.9, 127.9, 127.8, 112.6, 111.7, 109.6, 100.8, 60.0, 45.9, 39.7, 30.2, 25.8, 24.6; IR (KBr) 3392, 3279, 3039, 2949, 1648, 1513, 1483, 1453, 1363, 1303, 1213, 1152, 1062, 1032, 762, 702 cm^{-1}; EIMS 362, 249 (100), 247, 236; $C_{23}H_{26}N_2O_2$ requires 362.1994, found 362.1996.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]cyclohexanecarboxamide (6h):** white foam, 0.13 g, 0.35 mmol, 91%; ^{1}H NMR δ 8.04 (bs, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.27 (d, 1H, J = 8.8 Hz), 6.86 (dd, 1H, J = 8.7 Hz, J = 2.4 Hz), 5.42 (bs, 1H), 3.87 (s, 3H), 3.54 (q, 2H, J = 6.7 Hz), 3.08 (t, 2H, J = 6.7 Hz), 1.78 (m, 1H), 1.66 (m, 5H), 1.17 (m, 5H); ^{13}C NMR δ 154.3, 136.1, 132.95, 131.0, 129.4, 129.05, 127.9, 127.9, 112.7, 111.7, 109.8, 100.8, 56.0, 45.5, 39.5, 29.5, 25.7, 25.7, 24.6; IR 3392, 3279, 3038, 2949, 1648, 1513, 1482, 1453, 762, 702 cm^{-1}; EIMS 377, 376, 249, 236 (100); $C_{24}H_{28}N_2O_2$ requires 376.2150, found 376.2159.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)]adamantane-1-carboxamide (6i):** pale yellow foam, 0.050 g, 0.12 mmol, 96%; ^{1}H NMR δ 8.18 (bs, 1H), 7.59 (m, 2H), 7.47 (m, 2H), 7.29 (d, 1H, J = 8.7 Hz), 7.08 (d, 1H, J = 2.2 Hz), 6.88 (dd, 1H, J = 8.7 Hz, J = 2.4 Hz), 3.55 (q, 2H, J = 6.5 Hz), 3.11 (t, J = 6.6 Hz), 3.55 (q, 2H, J = 6.5 Hz), 3.11 (t, 2H, J = 6.6 Hz), 1.92–1.56 (m, 15H); ^{13}C NMR δ 177.8, 154.25, 136.0, 132.9, 131.1, 129.4, 129.0, 128.8, 127.9, 127.8, 112.6, 111.7, 109.7, 100.9, 56.0, 56.0, 40.35, 39.5, 38.9, 38.8, 38.6, 36.4, 28.0, 27.8, 24.5; IR 3424, 3259, 2907, 2841, 2357, 1634, 1518, 1480, 1447, 1210,

1144, 1072, 767, 689 cm^{-1}; EIMS 429, 420 (M^+), 249 (100), 248, 236; $C_{28}H_{32}N_2O_2$ requires 428.2664, found 428.2675.

***N*-[2-(5-Methoxy-2-phenylindol-3-yl)ethyl]-3-phenylpropionamide (6):** pale yellow oil, 0.12 g, 0.30 mmol, 80%; ^{1}H NMR δ 8.15 (bs, 1H), 7.51 (m, 2H), 7.44 (m, 2H), 7.34 (m, 1H), 7.27–7.13 (m, 5H), 7.08 (d, 1H, J = 6.8 Hz), 7.05 (d, 1H, J = 2.2 Hz), 6.86 (dd, 1H, J = 2.5, 8.7 Hz), 5.39 (bs, 1H), 3.86 (s, 3H), 3.5 (q, 2H, J = 6.6 Hz) 3.04 (t, 2H, J = 6.8 Hz), 2.79 (t, 2H, J = 7.8 Hz), 2.2 (t, 2H, J = 8.1 Hz); ^{13}C NMR 172.0, 154.3, 140.8, 136.05, 132.9, 131.0, 129.4, 129.0, 128.5, 128.4, 128.2, 127.8, 126.1, 112.6, 111.7, 109.5, 100.65, 56.0, 39.8, 38.4, 31.5, 24.45; IR 3441, 3289, 3045, 2922, 2345, 1645, 1522, 1483, 1450, 1300, 1211, 1150, 1072, 1028, 895, 761 cm^{-1}; EIMS 399, 398, 249, 248, 236 (100); $C_{26}H_{26}N_2O_2$ requires 398.1994, found 398.1999.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)ethyl]acetamide (7):** colorless oil, 1.06 g, 3.6 mmol, 90%; ^{1}H NMR δ 7.67 (dd, 1H, J = 7.9 Hz, J = 1.1 Hz), 7.53–7.45 (m, 3H), 7.43–7.36 (m, 3H), 7.28 (ddd, 1H, J = 7.9 Hz, J = 1.1 Hz), 7.18 (ddd, 1H, J = 8 Hz, J = 1.1 Hz), 5.43 (bs, 1H), 3.60 (s, 3H), 3.44 (q, 2H, J = 6.6 Hz), 2.94 (t, 2H, J = 6.6 Hz), 1.78 (s, 3H); ^{13}C NMR 169.8, 138.65, 137.1, 131.7, 130.5, 130.5, 128.6, 128.3, 127.55, 122.0, 119.5, 118.8, 109.9, 109.5, 40.35, 30.8, 24.4, 23.2; EIMS 292, 233, 220 (100) 204. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)-2-methylethyl]acetamide (8):** white foam, 0.22 g, 0.71 mmol, 94%; ^{1}H NMR δ 7.34 (d, 1H, J = 7.9 Hz), 7.50 (m, 3H), 7.36 (d, 1H, J = 8.2 Hz), 7.27 (ddd, 1H, J = 8.2 Hz, J = 1.0 Hz), 7.12 (ddd, 1H, J = 8.0 Hz, J = 1.0 Hz), 5.27 (bs, 1H), 3.83–3.76 (m, 1H), 3.54 (s, 3 H), 3.35–3.28 (m, 1H), 3.09–2.92 (m, 1H), 1.77 (s, 3H), 1.37 (d, 3H); ^{13}C NMR δ 169.6, 137.4, 131.7, 130.6, 130.6, 130.5, 128.6, 128.5, 128.5, 125.7, 121.8, 120.0, 119.3, 114.1, 109.7, 44.75, 31.8, 23.3, 19.1; IR 3411, 3256, 3067, 2967, 2911, 1645, 1550, 1461, 1381, 1300, 1250, 1139, 1089, 1017, 800, 733, 700, 600 cm^{-1}; EIMS 307 (M^+ + 1),236, 235, 218. Anal. ($C_{19}H_{22}N_2O$) C, H, N.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)-2-(methoxymethyl)ethyl]acetamide (9):** white foam, 0.34 g, 1.0 mmol, 82%; ^{1}H NMR δ 7.68 (d, 1H, J = 8.15 Hz), 7.50–7.44 (m, 3H), 7.35–7.33 (m, 3H), 7.25 (t, 1H, J = 7.9 Hz), 5.72 (bs, 1H), 3.85–3.79 (m, 2H), 3.65 (m, 1H), 3.53 (s, 3H), 3.52 (m, 1H), 3.28 (s, 3H), 3.25 (m, 1H), 1.80 (s, 3H); ^{13}C NMR δ 169.6, 139.3, 137.25, 131.5, 130.7, 128.5, 126.1, 121.8, 119.9, 119.4, 110.4, 109.7, 75.6, 75.6, 58.8, 58.8, 42.3, 37.8, 30.8, 30.8, 23.3; IR 3456, 3267, 3078, 2934, 2878, 1645, 1567, 1467, 1367, 1283, 1106, 999, 733, 700 cm^{-1}; EIMS 336, 264, 232, 220. Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)ethyl]cyclobutanecarboxamide (10):** white foam, 0.79 g, 2.36 mmol, 82%; ^{1}H NMR δ 7.69 (dd, 1H, J = 7.8 Hz, J = 1 Hz), 7.51–7.41 (m, 3H), 7.37–7.33 (m, 3H), 7.28 (ddd, 1H, J = 8.0 Hz, J = 1.1 Hz), 7.15 (ddd, 1H, J = 8 Hz, J = 1.1 Hz), 5.32 (bs, 1H), 3.58 (s, 3H), 3.44 (q, 2H, J = 6.6 Hz), 2.91 (t, 2H, J = 6.8 Hz), 2.58 (m, 1H), 2.13 (m, 6H); ^{13}C NMR δ 174.6, 138.6, 137.1, 131.6, 130.5, 128.6, 128.6, 127.5, 128.3, 127.6, 121.6, 119.5, 118.9, 109.9, 109.4, 40.2, 39.9, 30.8, 29.7, 25.2, 24.6, 18.02; IR 3245, 3064, 2938, 2865, 1636, 1557, 1468, 1364.5, 1229, 1196, 748, 698 cm^{-1}; EIMS 332, 233, 221, 220 (100). Anal. ($C_{22}H_{26}N_2O$) C, H, N.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)-2-methylethyl]cyclobutanecarboxamide (11):** white foam, 0.43 g, 1.23 mmol, 81%; ^{1}H NMR δ 7.73 (d, 1H, J = 7.9 Hz), 7.50 (m, 3H), 7.36 (d, 1H, J = 8.2 Hz), 7.27 (ddd, 1H, J = 8 Hz, J = 1.0 Hz), 7.12 (ddd, 1H, J = 8.0 Hz, J = 1.0 Hz), 5.27 (bs, 1H), 3.83–3.76 (m, 1H), 3.53 (s, 3H), 3.35–3.28 (m, 1H), 3.09–2.92 (m, 1H), 2.74 (m, 1H), 2.16–1.75 (m, 6H), 1.37 (d, 3H, J = 7.1 Hz); ^{13}C NMR δ 174.4, 138.6, 137.4, 131.7, 130.6, 130.5, 128.6, 128.5, 128.4, 125.8, 121.7, 120.1, 119.2, 114.2, 109.6, 44.5, 39.9, 33.5, 32.0, 30.8, 25.3, 25.1, 19.1, 18.0; IR 3430, 3251, 3058, 2930, 2874, 1648, 1568, 1463, 1368, 1108, 733, 700 cm^{-1}; EIMS 346, 235, 234 (100), 218; $C_{23}H_{26}N_2O_2$ requires 346.2045, found 346.2045.

***N*-[2-(*N*-Methyl-2-phenylindol-3-yl)-2-(methoxymethyl)ethyl]cyclobutanecarboxamide (12):** white foam, 0.35 g, 0.94 mmol, 77%; ^{1}H NMR δ 7.69 (d, 1H, J = 8.1 Hz), 7.49–7.43 (m, 3H), 7.35–7.33 (m, 3H), 7.25 (ddd, 1H, J = 8 Hz, J = 1 Hz), 5.70 (bs, 1H), 3.85–3.80 (m, 2H), 3.65 (dd, 1H), 3.54 (m, 1H), 3.53 (s, 3H), 3.28 (s, 3H), 3.25 (m, 1H), 2.78 (m, 1H), 2.15–1.82 (m, 6H); ^{13}C NMR δ 174.5, 139.2, 137.3, 131.5, 130.7, 128.6, 128.5, 126.1, 121.8, 120.0, 119.4, 110.5, 109.7, 75.7, 58.8, 58.8, 58.8, 42.2, 39.8, 37.8, 30.8, 30.8, 25.3, 25.2, 18.0; IR 3433, 3255, 3056, 2922, 1633, 1533, 1467, 1367, 1256, 733, 700 cm^{-1}; EIMS 377 (M + 1), 265, 233, 217. Anal. ($C_{23}H_{26}N_2O_2$) C, H, N.

***N*-[2-(*N*-Ethyl-2-phenylindol-3-yl)ethyl]acetamide (13):** colorless oil, 1.10 g, 3.59 mmol, 95%; ^{1}H NMR δ 7.63 (dd, 1H, J = 7.9 Hz), 7.51–7.44 (m, 3H), 7.38–7.35 (m, 3H), 7.25 (ddd, 1H, J = 8.1 Hz, J = 1.1 Hz), 7.15 (ddd, 1H, J = 7.9 Hz, J = 1 Hz), 5.33 (bs, 1H), 4.00 (q, 2H, J = 7.2 Hz), 3.40 (q, 2H, J = 6.7 Hz) 2.94 (t, 2H, J = 6.7 Hz), 1.77 (s, 3H), 1.20 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 169.7, 138.2, 135.8, 131.95, 130.5, 130.4, 128.65, 128.4, 127.8, 121.8, 119.5, 118.85, 110.1, 109.7, 40.3, 38.6, 24.4, 23.3, 15.4; IR 3444, 3256, 3077, 2922, 1633, 1567, 1461, 1367, 1344, 1200, 744,702 cm^{-1}; EIMS 307, 306, 247, 235, 234 (100). Anal. ($C_{20}H_{22}N_2O$) C, H, N.

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Supplementary Material Available: X-ray crystallographic data for *N*-[2-(5-methoxyindol-3-yl)ethyl]cyclobutanecarboxamide and crystal packing diagrams for melatonin (14 pages). Ordering information is given on any current masthead page.

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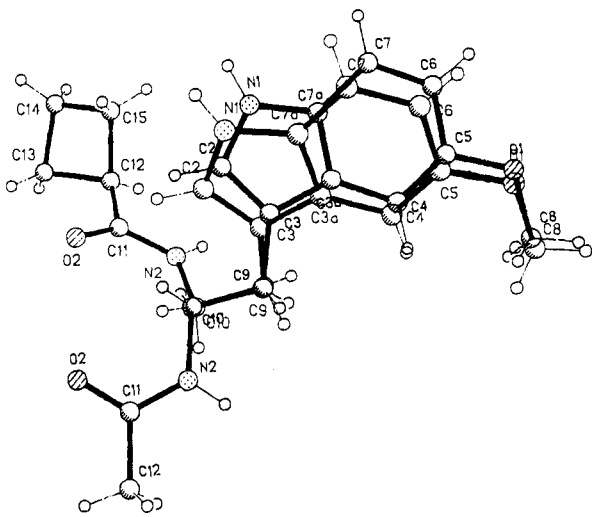
(30) A comparison of the X-ray structure of melatonin[31] and its cyclobutyl analogue, *N*-[2-(5-methoxyindol-3-yl)ethyl]cyclobutanecarboxamide, is shown in the figure. The 3-amidoethane side adopts a very different conformation in the cyclobutyl analogue to its conformation in melatonin. This arises because of the different orientation of the hydrogen bonds in the two crystals: whereas melatonin forms sheets with hydrogen bonds only between molecules in the sheet, the cyclobutyl analogue has hydrogen bonds between molecules in adjacent layers. In the quite polar environment of the crystal, changing from methyl to cyclobutyl has caused a preference for different hydrogen bonds to form, revealing the importance of the change from an alkyl chain to an alicyclic ring in this structure. The X-ray analysis of a derivative showing antagonist properties would be very valuable, but we have not yet been able to obtain suitable crystals.



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