Synthesis of *N*1-Phenethyl Substituted Indole Derivatives as New Melatoninergic Agonists and Antagonists

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The potency of new indolic *N*1-phenethyl substituted melatoninergic ligands with and without methyl groups in the α and β position of the alkanamidoethyl side chain was examined using the pigment aggregation response in a clonal line of *Xenopus laevis* melanophores. The non 5-OMe substituted compounds, 8a—e, are all weak antagonists while introduction of the 5-OMe group, 9a—e, increases both agonist and antagonist activity except for 9c (R=C_3H_7), which is only an agonist and 9e (R=c-C_4H_7), which is only an antagonist. Introduction of an α-methyl group into the 5-OMe derivatives, 14a—e, reduces the agonist potency while introduction of a β-methyl group has only a small effect on either the agonist or antagonist potency. Double β-methyl substitution of the 5-OMe derivatives, 20a—e, generally increases the agonist potential (20c, R=C_3H_7 is the most potent agonist of the compounds described) and decreases the antagonist potency, except for 20a (R=CH_3), which is the most potent antagonist of this series of compounds.

Key words *N*1- substituted indole; synthesis; *Xenopus laevis* melanophore model; melatonin agonist/antagonist

Melatonin (*N*-acetyl-5-methoxytryptamine), Fig. 1, is a vertebrate pineal gland hormone, which is secreted mainly at night.[1)] Melatonin has been shown to have a physiological role in regulating seasonal breeding in photoperiodic species[2)] and can entrain circadian rhythms.[3)] The hormone also increases vascular tone in the rat tail artery[4)] and cerebral vascular bed[5)] and inhibits [^{3}H]dopamine release from rabbit retina.[6)] In addition, a sleep-promoting action of melatonin has been repeatedly observed in animal and human studies.[7)] Melatonin analogs are currently being examined as a therapy for treating circadian rhythm disturbances resulting from various causes (*e.g.* jet-lag, shift-work, blindness) and the use of melatonin as a hypnotic has been advocated.[8)] Molecular cloning data suggest that melatonin exerts all of these effects through a family of specific, high affinity, G-protein coupled cell membrane receptors, MT_1, MT_2, and Mel_{1c},[9)] which have been detected in tissues known to respond to melatonin (*e.g.* in the retina and the suprachiasmatic nuclei of the hypothalamus).

Our understanding of the physiological and pathophysiological role(s) of melatonin in animals and man is hampered by the relatively small number of melatonin receptor agonists and antagonists available. In a series of studies during the last decade we have sought to understand how melatonin binds to and activates its receptor and to use the knowledge gained to design potent receptor agonists and antagonists, which will be useful tools for defining the full physiological and pathophysiological role of this hormone. Thus, several key interactions between ligand and receptor have been identified. The 5-methoxy group and amide moiety, and their relative position, are critical to high affinity.[10—17)] The size of the acyl group is important for the binding of the side chain to the receptor and in some cases (*N*-cyclopropanoyl and *N*-cyclobutanoyl groups) it decreases the intrinsic activity of the corresponding compounds.[18,19)] In naphthalene and indole derivatives the presence of an α-methyl group in the alkanamidoethyl side chain is reported to exert a detrimental effect to agonistic activity.[20,21)] Conversely, the introduction of one or two methyl groups in the β position of the alkanamidoethyl side chain of naphthalene analogs leads to increased potency.[22)]

In order to probe the constraints at the receptor site with regard to the lower *N*1–C2 region of the indole moiety of melatonin, we have recently reported the synthesis and biological activity of a number of 2-phenyltryptamines annulated on the [α] face of the pyrrole moiety by the introduction of 1, 2 or 3 methylene groups, **1**—**3**, Fig. 2.[23)] In the *Xenopus* melanophore pigment aggregation model, compounds **1a**—**j** were found to exhibit agonist activity while their congeners **3a**—**j** were antagonists. Molecules **2a**—**d** were antagonists and **2e**—**h** had agonist activity at low concentrations but antagonised responses at high concentrations, Fig. 2. These findings suggest that the *Xenopus* melatonin receptor can not accommodate an *N*-*n*-alkyl chain attached to a phenyl ring substituent with $n>2$ (Fig. 2, compounds **3a**—**j**) in the required orientation to induce or stabilize the active receptor conformation.

In the present study, we have extended this work to synthesize and evaluate a number of novel *N*-{2-[1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}alkanamides **8a**—**e** and *N*-{2-[5-methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}alkanamides **9a**—**e** (Chart 1). These analogs may probe the constraints at the receptor site with regard to the lower *N*1 region of the in-

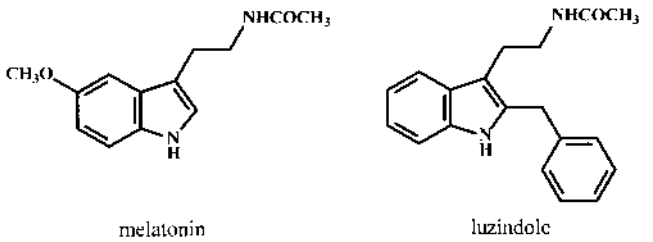

Fig. 1

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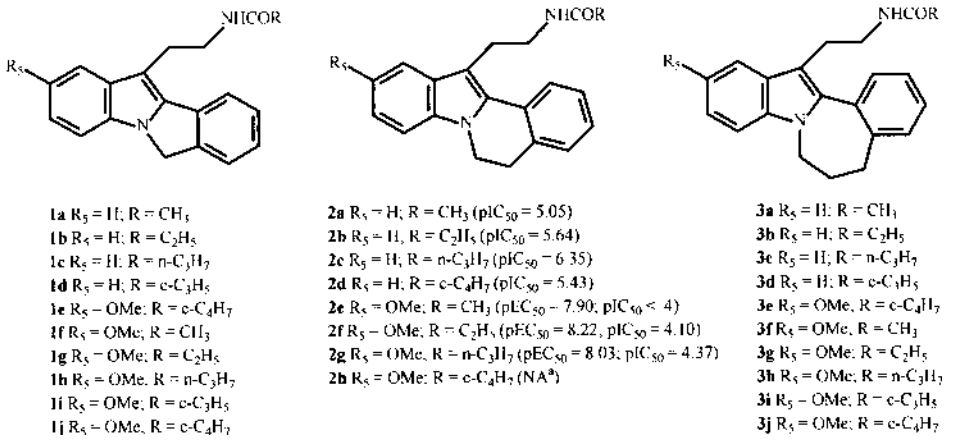
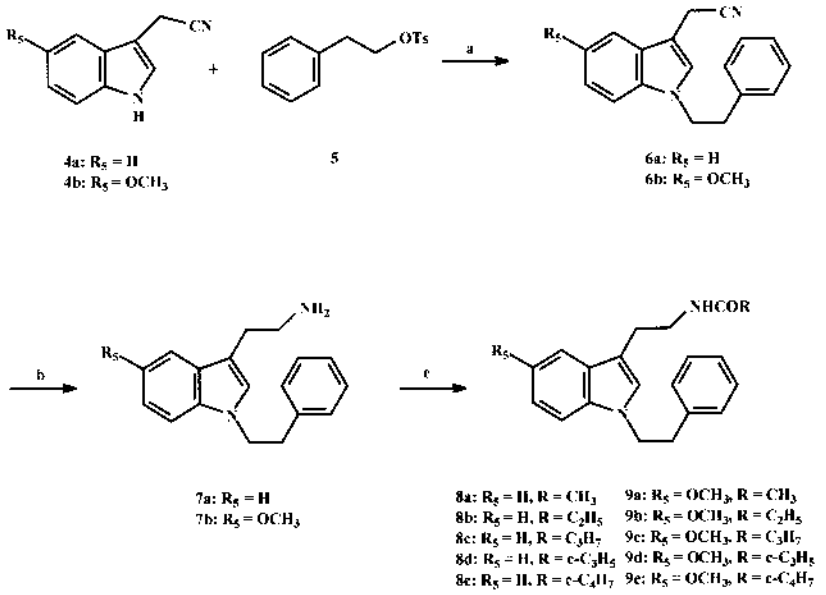


Fig. 2. Structures of Compounds **1**—**3**[23]

[a] NA = No agonist or antagonist effect detected at 100 μM.



(a) KOH, DMF; (b) $LiAlH_4$, diethyl ether, benzene; (c) $(RCO)_2O$ or RCOCl, Et_3N, dichloromethane.

Chart 1

dole moiety in a similar way to compounds **1**—**3** without through linking of the phenyl ring to C-2. In order to explore the possible synergistic influence on potency upon introducing α and β-methyl substituents on the ethyl chain of systems of types **8** and **9**, we also prepared *N*-{2-[5-methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}alkanamides **14a**—**e**, *N*-{2-[5-methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}-alkanamides **17a**—**e** and the analogous β,β'-dimethyl derivatives **20a**—**e** (Charts 2—4).

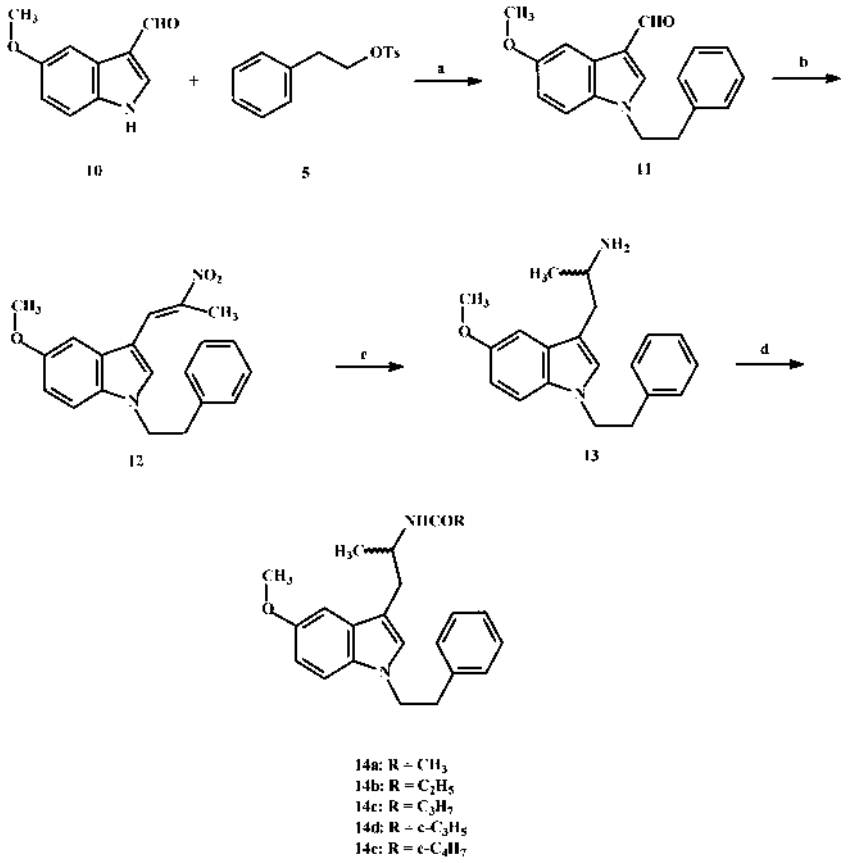
Chemistry

Compounds **8a**—**e** and **9a**—**e** were prepared by the synthetic pathway depicted in Chart 1. 3-Indolylacetonitrile (**4a**) and 5-methoxyindole-3-acetonitrile[24] (**4b**) were separately reacted with the tosylate **5**, prepared from 2-phenylethanol and *p*-toluenesulfonyl chloride (TsCl),[23] to give the *N*-alkylated acetonitriles **6a** and **b**, respectively. These were reduced with lithium aluminun hydride in the presence of diethyl ether and benzene (5 : 1 v/v)[25] to afford the corresponding amines **7a** and **b**, which were not purified but were immediately acylated with the appropriate reagent[23] to give the desired *N*-{2-[1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}alkanamides **8a**—**e** and *N*-{2-[5-methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}alkanamides **9a**—**e**.

The synthesis of analogs **14a**—**e** is shown in Chart 2. 5-Methoxyindole-3-carboxaldehyde (**10**) was condensed with the tosylate **5** to furnish aldehyde **11** and the sequence of the Henry reaction[23] with nitroethane followed by reduction[23] gave the amine **13**, which was acylated with the appropriate reagent[23] to give the desired *N*-{2-[5-methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}alkanamides **14a**—**e**.

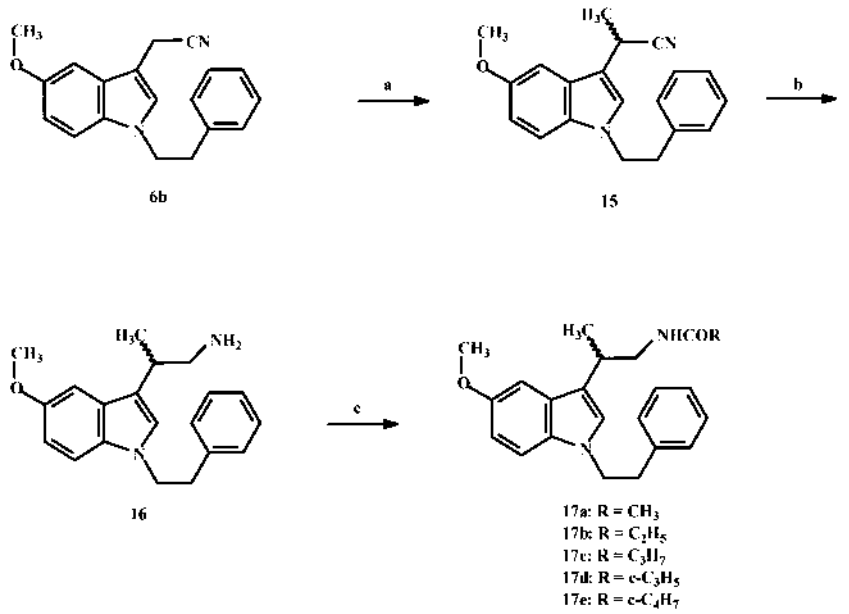
The β-methyl substituted derivatives **17a**—**e** (Chart 3) were obtained by acylation of the amine **16**, which was prepared by the reduction of the α-methyl cyano analog **15**. The latter was derived from acetonitrile **6b** by methylation with methyl iodide in the presence of sodium hydride and *N*,*N*-dimethylformamide (DMF).

The preparation of the β,β'-dimethyl congeners **20a**—**e**



(a) K_2CO_3, acetonitrile; (b) $CH_3CH_2NO_2$, $AcONH_4$; (c) $LiAlH_4$, THF; (d) $(RCO)_2O$ or RCOCl, Et_3N, dichloromethane.

Chart 2



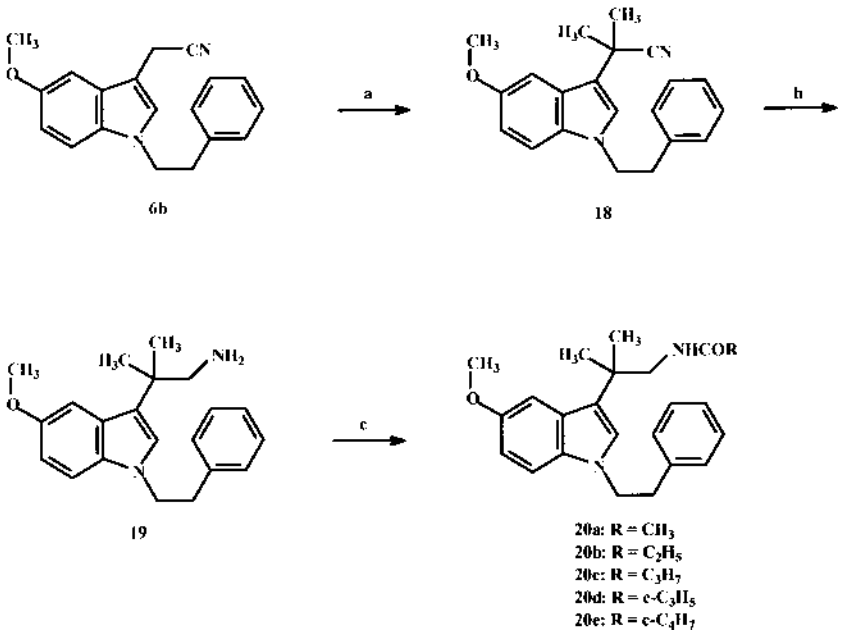
(a) NaH, CH_3I, DMF; (b) $LiAlH_4$, diethyl ether, benzene; (c) $(RCO)_2O$ or RCOCl, Et_3N, dichloromethane.

Chart 3

(Chart 4) was effected by following the procedure described for the synthesis of derivatives **17a**—**e**, with excess methyl iodide.

Results and Discussion

The agonist and antagonist potency of the new compounds was assessed in the *Xenopus laevis* melanophore model. Like luzindole, (Fig. 1), a commonly used melatonin receptor an-



(a) NaH, CH_3I, DMF; (b) $LiAlH_4$, diethyl ether, benzene; (c) $(RCO)_2O$ or RCOCl, Et_3N, dichloromethane.

Chart 4

tagonist (pIC_{50}=5.61), all of the non 5-OMe substituted analogs, **8a**—**e**, are antagonists in the above assay. The size and the nature of the acyl group in the side chain does not seem to play a significant role in their potency, the pIC_{50} values obtained for these molecules being similar (Table 1). These results are in agreement with our earlier findings, which suggest that, in contrast to agonists, antagonist potency varies little with the increase in chain length of the *N*-acylating group.[26] A recent site-directed mutagenesis study has provided strong molecular evidence that agonist and antagonist binding sites are not identical.[27]

Introduction of a methoxyl group at C-5, compounds **9a**—**e**, gave analogs showing varying degrees of agonist activity. Compound **9a** was a moderately potent (pIC_{50}=6.80) partial agonist (maximum effect 33%), while **9b** showed very slight (15% at 10 μM) and **9d** had no agonist action (<10% at 10 μM). The exception was **9c**, which was a full agonist of moderate potency (pIC_{50}=7.16). Compared to the analogous tetracyclic compounds, **2e**—**h**, the present series appears to have less intrinsic agonist activity. Interestingly, **9c**, like **2e**, are full agonists with no antagonist activity whereas **9a** and **b** show some agonist behavior, but are also antagonists. The introduction of the methoxyl group at C-5 did not lead to the expected decrease in the antagonistic activity of molecules **9b**, **d** and **e** (Table 1). This is in contrast to the biological data obtained on the previously reported analogous tetracyclic compounds **2a**—**h**.[23]

The exception observed in the full agonist activity of compound **9c** could be attributed to a synergistic effect caused by the presence of the 5-OMe group and the size of the acyl group (R=C_3H_7). The simultaneous incorporation of both of these moieties to indole analogs is known to drastically enhance melatoninergic agonistic activity.[18]

The α-methyl substituted analogs **14a**—**e** were slightly better antagonists than their congeners **9a**—**e** (Table 2). Furthermore, the introduction of a methyl group at the α-carbon of the amide side chain in **14a**—**e** eliminated the partial agonist potency of analogs **9a** and **b** as well as the full agonistic activity of their counterpart **9c**. One can envisage that α-methyl substitution in the alkanamidoethyl chain of **14a**—**e** comprises an unfavorable steric parameter for recognition by melatonin receptors,[22] which surmounts the contribution to agonistic activity exerted by the 5-OMe group and the acylamido group in analogs **9a**, **b** and **c**, respectively.

The introduction of a β-methyl substituent in the amide side chain of **17a**—**e** does influence in some cases the activation process of the receptor by molecules with agonistic activity. Thus, in this series, analogs **17b** and **d** behave as moderately potent partial agonists (46 and 56% of maximal activity respectively) while their congener **17c** exhibits essentially full agonistic potency (86% of maximum, Table 2). These findings seem to parallel earlier results with other indolic derivatives, which demonstrated that there is a preferred orien-

Table 1. Agonistic and Antagonistic Activity of Compounds **8a**—**e** and **9a**—**e** in the *Xenopus laevis* Melanophore Assay

Compound	R_5	R	Agonist pEC_{50}	Antagonist pIC_{50}
Melatonin			10.07	—
Luzindole			NA	5.61
8a	H	CH_3	NA	4.47
8b	H	C_2H_5	NA	4.51
8c	H	C_3H_7	NA	4.94
8d	H	c-C_3H_5	NA	4.49
8e	H	c-C_4H_7	NA	4.56
9a	OCH_3	CH_3	6.80 (33%)	5.45
9b	OCH_3	C_2H_5	>5 (15%)	5.24
9c	OCH_3	C_3H_7	7.16	NA
9d	OCH_3	c-C_3H_5	>5 (5%)	5.25
9e	OCH_3	c-C_4H_7	NA	4.86

NA=no agonist or antagonist effect detected at 100 μM. Number in brackets indicates the degree of agonist response as a percentage of maximum. Agonist and antagonist data on melanophores are the mean of 3 to 6 experiments.

Table 2. Agonistic and Antagonistic Activity of Compounds **14a**—**e** and **17a**—**e** in the *Xenopus laevis* Melanophore Assay

Compound	R	Agonist pEC_{50}	Antagonist pIC_{50}
Melatonin		10.07	NA
Luzindole		NA	5.61
14a	CH_3	NA	5.85
14b	C_2H_5	NA	5.47
14c	C_3H_7	NA	5.60
14d	c-C_3H_5	NA	5.78
14e	c-C_4H_7	NA	5.85
17a	CH_3	NA	6.26
17b	C_2H_5	6.35 (46%)	4.89
17c	C_3H_7	6.76 (86%)	<4 (19%)
17d	c-C_3H_5	6.74 (56%)	5.02
17e	c-C_4H_7	NA	6.12

NA=no agonist or antagonist effect detected at 100 μM. Number in brackets indicates the degree of agonist response as a percentage of maximum. Agonist and antagonist data on melanophores are the mean of triplicate experiments.

Table 3. Agonistic and Antagonistic Activity of Compounds **20a**—**e** in the *Xenopus laevis* Melanophore Assay

Compound	R	Agonist pEC_{50}	Antagonist pIC_{50}
Melatonin		10.07	NA
Luzindole		NA	5.61
20a	CH_3	NA	6.74
20b	C_2H_5	7.92	4.61
20c	C_3H_7	8.01 (92%)	4.39
20d	c-C_3H_5	NA	4.69
20e	c-C_4H_7	7.02 (65%)	4.79

NA=no agonist or antagonist effect detected at 100 μM. Number in brackets indicates the degree of agonist response as a percentage of maximum. Agonist and antagonist data on melanophores are the mean of triplicate experiments.

tation of the 3-amidoethane side chain, which is more highly populated when there is a methyl group at the β carbon of the 3-amidoethyl moiety.[18] The lack of agonistic activity, particularly of analog **17e**, could be ascribed to the presence of the *N*-cyclobutanoyl group in its side chain, a moiety, which is known to exert a detrimental effect to agonistic potency.[18,28]

The situation is quite different when two methyl groups are present at the β carbon of the 3-amidoethane side chain of molecules **20a**—**e**. Again, as for a single methyl β-substituent, **17a**, the acetamido analog **20a** with two methyl groups has no agonist activity, while the butyramido analogs **17c** and **20c** both retain full agonist activity. Compound **20c** (R=C_3H_7) has full agonist activity (92% of maximum) as does its equivalent analog **17c** with a single β-methyl substituent (86% of maximum). The second methyl substitution appears to increase both agonist and antagonist activity (Table 3).

In conclusion, the biological data presented herein for the five series of analogs suggest that although the structural changes made constitute relatively minor interpositions onto the basic nucleus, the consequences are quite significant. Specifically, methyl substitution on the α-carbon of the acylamido side chain eliminates the ability to activate the melatonin receptor. A single or double methyl substitution on the β-carbon of the side-chain does not drastically impede the access of compounds to the agonist site on the receptor, although varying degrees of full agonistic activity depend on the length of the *N*-acylamido group. One thus must presume that the presence of methyl substituents in the side chain of these molecules contributes to some extent to their disposition in the receptor pocket. However, the lack of annulation of the 2-phenethyl group on the [α] face of the pyrrole moiety seems to reduce their ability to dock onto the receptor.

Continuing the attempts to define the characteristics of melatonin required for ligand binding and receptor activation, we are currently engaged with the synthesis of new series of melatoninergic analogs.

Experimental

Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were taken in $CDCl_3$ and recorded on a Bruker AC200 MHz spectrometer. The spectra are reported in ppm (δ) values and tetramethylsilane was used as internal standard. All the experiments were carried out under an atmosphere of Argon. The solvents used were dried as follows: Benzene using sodium wire, triethylamine over sodium hydroxide, DMF and dichloromethane over molecular sieves (4 Å) and diethyl ether and tetrahydrofuran (THF) over calcium hydride. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with ultraviolet light or developed with iodine or phosphomolybdic acid. Microanalyses were carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation (NHRF). 3-Indolylacetonitrile (**4a**), 5-methoxyindole-3-carboxaldehyde (**10**) and 2-phenylethanol were purchased from Aldrich Chemical Company (Gillingham, Dorset, U.K.).

[1-(2-Phenethyl)-1*H*-indol-3-yl]acetonitrile (6a) Powder potassium hydroxide 85% (0.76 g, 13.57 mmol) was added to a chilled (0 °C) solution of commercially available 3-indolylacetonitrile (**4a**) (0.91 g, 5.86 mmol) in DMF (25 ml). After the suspension had been stirred for 5 min a solution of the tosylate **5** (2.19 g, 7.93 mmol) in DMF (8 ml) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min and then at ambient temperature for 16 h. Upon completion of the reaction (TLC control) the dark suspension was partitioned between AcOEt and water. The organic layer was successively washed with water and brine and then dried over Na_2SO_4. The solvent was removed *in vacuo* to leave an oily residue, which was flash chromatographed eluting with cyclohexane/AcOEt=94 : 6 to give 1.34 g (88%) of **6a** as a viscous oil. ^{1}H-NMR δ: 2.96 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.65 (2H, s, CH_2CN), 4.18 (2H, t, NCH_2, J=7.3 Hz), 6.87 (1H, s, H_2), 6.90—7.02 (4H, m, H_{arom}), 7.15—7.30 (5H, m, H_{arom}); ^{13}C-NMR δ: 14.0 (t), 36.7 (t), 48.2 (t), 99.6 (d), 102.2 (s), 110.4 (d), 112.4 (d), 118.0 (s), 126.5 (d), 126.8 (d), 128.4 (d), 131.2 (s), 136.8 (d), 137.8 (d). *Anal.* Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.72; H, 6.24; N, 10.58.

[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]acetonitrile (6b) Compound **6b** was obtained in the same manner as **6a** in 86% yield as a beige solid after purification by flash chromatography using cyclohexane/AcOEt=94 : 6. mp 88—89 °C (petroleum ether 40—60 °C/ethyl acetate). ^{1}H-NMR δ: 2.99 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.65 (2H, s, CH_2CN), 3.82 (3H, s, OCH_3), 4.18 (2H, t, NCH_2, J=7.3 Hz), 6.82 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.6, 9.5 Hz), 6.94—7.04 (3H, m, H_{arom}), 7.11—7.30 (4H, m, H_{arom}). ^{13}C-NMR δ: 14.0 (t), 36.5 (t), 48.0 (t), 55.6 (q), 99.7 (d), 102.2 (s), 110.4 (d), 112.5 (d), 118.1 (s), 126.5 (d), 126.7 (d), 128.5 (d), 131.2 (s), 138.0 (d), 154.1 (s). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.29; H, 6.30; N, 9.35.

2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethylamine (7a) A solution of **6a** (0.47 g, 1.81 mmol) in benzene (2 ml) was added dropwise to a suspension of lithium aluminum hydride (0.21 g, 5.46 mmol) in dry diethyl ether (10 ml) at 0 °C. The mixture was then refluxed for 1.5 h and upon cooling to 0 °C it was carefully treated with water (5 ml). The resulting suspension was filtered through Celite and the filtrate diluted with diethyl ether. The ether layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 0.46 g (97%) of the crude amine **7a** as a yellow oil, which was used without further purification in the acylation reactions.

2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethylamine (7b) Amine **7b** was prepared according to the procedure described above for **7a**. Yield (95%).

Preparation of the Amides 8a—e and 9a—e Triethylamine (0.07 ml, 0.48 mmol) was added to a solution of the amine **7a** or **b** (0.36 mmol) in dichloromethane (1 ml) at 0 °C. The mixture was stirred at this temperature for 10 min and the appropriate acid anhydride (0.42 mmol in the case of compounds **8a**—**c** and **9a**—**c**) or acid chloride (0.45 mmol in the case of

compounds **8d**, **e** and **9d**, **e**) was then added. After the addition the mixture was left stirring at room temperature for 30 to 60 min before water was added. The resulting mixture was extracted with dichloromethane, washed with water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* to give the crude amides as viscous oils. Unless otherwise indicated the amides were triturated with AcOEt (1 ml) to afford the title compounds as amorphous solids.

N-{2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethyl}acetamide (**8a**): Beige solid, 47%. mp 162—164 °C. ^{1}H-NMR δ: 1.90 (3H, s, $COCH_3$), 2.90 (2H, t, $\underline{CH_2}CH_2NH$, J=6.6 Hz), 3.10 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.52 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 4.32 (2H, t, NCH_2, J=7.3 Hz), 5.43 (1H, br s, NH), 6.73 (1H, s, H_2), 7.03—7.30 (7H, m, H_{arom}), 7.35 (1H, d, H_7, J=8.0 Hz), 7.59 (1H, d, H_4, J=7.7 Hz). ^{13}C-NMR δ: 23.1 (q), 25.2 (t), 36.8 (t), 39.8 (t), 48.5 (t), 106.7 (s), 111.0 (d), 119.6 (d), 120.5 (d), 121.7 (d), 124.1 (d), 126.6 (d), 127.5 (s), 127.7 (d), 128.4 (d), 135.5 (s), 137.5 (s), 170.1 (s). *Anal.* Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.32; H, 7.22; N, 9.20.

N-{2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethyl}propionamide (**8b**): Off-white solid, 28%. mp 124—126 °C. ^{1}H-NMR δ: 1.10 (3H, t, $CH_2\underline{CH_3}$, J=7.3 Hz), 2.11 (2H, q, $\underline{CH_2}CH_3$, J=7.3 Hz), 2.91 (2H, t, $\underline{CH_2}CH_2NH$, J=6.6 Hz), 3.09 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.53 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 4.31 (2H, t, NCH_2, J=7.3 Hz), 5.45 (1H, br s, NH), 6.74 (1H, s, H_2), 7.03—7.29 (7H, m, H_{arom}), 7.34 (1H, d, H_7, J=8.0 Hz), 7.59 (1H, d, H_4, J=7.7 Hz). ^{13}C-NMR δ: 9.8 (q), 25.1 (t), 29.6 (t), 36.7 (t), 39.5 (t), 48.6 (t), 106.8 (s), 111.1 (d), 119.6 (d), 120.5 (d), 121.7 (d), 124.1 (d), 126.6 (d), 127.5 (s), 127.7 (d), 128.5 (d), 135.3 (s), 137.8 (s), 170.0 (s). *Anal.* Calcd for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.67; H, 7.53; N, 8.80.

N-{2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethyl}butyramide (**8c**): Beige solid, 34%. mp 127—129 °C. ^{1}H-NMR δ: 0.91 (3H, t, $CH_2\underline{CH_3}$, J=7.3 Hz), 1.61 (2H, sextet, $CH_2\underline{CH_2}CH_3$, J=7.3 Hz), 2.06 (2H, t, $COCH_2$, J=7.3 Hz), 2.90 (2H, t, $\underline{CH_2}CH_2NH$, J=6.6 Hz), 3.08 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.53 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 4.31 (2H, t, NCH_2, J=7.3 Hz), 5.42 (1H, br s, NH), 6.74 (1H, s, H_2), 7.02—7.30 (7H, m, H_{arom}), 7.34 (1H, d, H_7, J=8.0 Hz), 7.60 (1H, d, H_4, J=8.0 Hz). ^{13}C-NMR δ: 13.6 (q), 19.0 (t), 25.3 (t), 36.7 (t), 38.6 (t), 39.7 (t), 48.5 (t), 106.8 (s), 110.9 (d), 119.6 (d), 120.4 (d), 121.5 (d), 124.1 (d), 126.6 (d), 127.5 (s), 127.8 (d), 128.5 (d), 135.4 (s), 137.9 (s), 170.2 (s). *Anal.* Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 78.85; H, 7.80; N, 8.42.

N-{2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethyl}cyclopropanecarboxamide (**8d**): Pale yellow solid, 40%. mp 149—151 °C. ^{1}H-NMR δ: 0.60—0.75 (2H, m, cycloprop.), 0.87—1.01 (2H, m, cycloprop.), 1.10—1.30 (1H, m, $CO\underline{CH}$ cycloprop.), 2.89 (2H, t, $\underline{CH_2}CH_2NH$, J=6.6 Hz), 3.07 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.52 (2H, dt, $CH_2\underline{CH_2}NH$, J=5.9, 7.0 Hz), 4.29 (2H, t, NCH_2, J=7.3 Hz), 5.77 (1H, br s, NH), 6.73 (1H, s, H_2), 7.00—7.28 (7H, m, H_{arom}), 7.33 (1H, d, H_7, J=8.4 Hz), 7.60 (1H, d, H_4, J=7.7 Hz). ^{13}C-NMR δ: 6.7 (t), 14.5 (d), 25.2 (t), 29.6 (t), 36.6 (t), 39.7 (t), 48.5 (t), 106.7 (s), 110.9 (d), 119.7 (d), 120.5 (d), 121.4 (d), 124.2 (d), 126.5 (d), 127.5 (s), 127.9 (d), 128.4 (d), 135.4 (s), 137.8 (s), 170.1 (s). *Anal.* Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found: C, 79.35; H, 7.25; N, 8.50.

N-{2-[1-(2-Phenethyl)-1*H*-indol-3-yl]ethyl}cyclobutanecarboxamide (**8e**): Beige solid, 23%. mp 112—114 °C. ^{1}H-NMR δ: 1.58—2.38 (6H, m, cyclobut.), 2.75—2.98 (3H, m, $CO\underline{CH}$ cyclobut.+$\underline{CH_2}CH_2NH$), 3.08 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.52 (2H, dt, $CH_2\underline{CH_2}NH$, J=5.9, 7.0 Hz), 4.31 (2H, t, NCH_2, J=7.3 Hz), 5.36 (1H, br s, NH), 6.74 (1H, s, H_2), 7.02—7.30 (7H, m, H_{arom}), 7.34 (1H, d, H_7, J=7.7 Hz), 7.59 (1H, d, H_4, J=8.0 Hz). ^{13}C-NMR δ: 17.9 (t), 25.0 (t), 25.3 (t), 36.7 (t), 39.6 (t), 39.8 (d), 48.7 (t), 106.6 (s), 110.8 (d), 119.6 (d), 120.4 (d), 121.4 (d), 124.1 (d), 126.6 (d), 127.5 (s), 127.8 (d), 128.3 (d), 135.5 (s), 137.7 (s), 170.0 (s). *Anal.* Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.68; H, 7.59; N, 8.12.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}acetamide (**9a**): White solid, 50%. mp 135—137 °C. ^{1}H-NMR δ: 1.91 (3H, s, $COCH_3$), 2.86 (2H, t, $\underline{CH_2}CH_2NH$, J=6.9 Hz), 3.08 (2H, t, $\underline{CH_2}Ph$, J=6.6 Hz), 3.51 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 3.87 (3H, s, OCH_3), 4.28 (2H, t, NCH_2, J=7.3 Hz), 5.40 (1H, br s, NH), 6.70 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.2, 8.8 Hz), 7.00—7.10 (3H, m, H_{arom}), 7.19—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 23.5 (q), 25.1 (t), 36.7 (t), 39.8 (t), 48.2 (t), 55.9 (q), 100.6 (d), 110.3 (d), 110.9 (s), 112.5 (d), 126.5 (d), 126.7 (d), 128.6 (d), 128.8 (s), 131.4 (s), 138.6 (d), 153.9 (s), 169.9 (s). *Anal.* Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.67; H, 7.23; N, 8.24.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}propionamide (**9b**): White solid, 23%. mp 102—104 °C. ^{1}H-NMR δ: 1.11 (3H, t, $CH_2\underline{CH_3}$, J=7.7 Hz), 2.12 (2H, q, $\underline{CH_2}CH_3$, J=7.7 Hz), 2.87 (2H, t, $\underline{CH_2}CH_2NH$, J=6.9 Hz), 3.07 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.52 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 3.87 (3H, s, OCH_3), 4.28 (2H, t, NCH_2, J=7.3 Hz), 5.42 (1H, br s, NH), 6.70 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.2, 9.0 Hz), 7.00—7.12 (3H, m, H_{arom}), 7.19—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 9.7 (q), 25.5 (t), 29.5 (t), 36.5 (t), 39.5 (t), 48.2 (t), 55.7 (q), 100.6 (d), 110.2 (d), 110.8 (s), 112.5 (d), 126.5 (d), 126.7 (d), 128.6 (d), 128.8 (s), 131.5 (s), 138.6 (d), 153.7 (s), 169.8 (s). *Anal.* Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.25; H, 7.55; N, 7.89.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}butyramide (**9c**): White solid, 31%. mp 104—106 °C. ^{1}H-NMR δ: 0.94 (3H, t, $CH_2\underline{CH_3}$, J=7.7 Hz), 1.58 (2H, sextet, $CH_2\underline{CH_2}CH_3$, J=7.5 Hz), 2.09 (2H, t, $COCH_2$, J=7.7 Hz), 2.89 (2H, t, $CH_2\underline{CH_2}NH$, J=6.9 Hz), 3.09 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.54 (2H, dt, $CH_2\underline{CH_2}NH$, J=6.2, 6.8 Hz), 3.89 (3H, s, OCH_3), 4.30 (2H, t, NCH_2, J=7.3 Hz), 5.42 (1H, br s, NH), 6.73 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.3, 8.9 Hz), 7.00—7.12 (3H, m, H_{arom}), 7.19—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 14.5 (q), 20.5 (t), 23.2 (t), 36.5 (t), 39.5 (t), 42.3 (t), 48.2 (t), 55.7 (q), 100.6 (d), 110.2 (d), 110.7 (s), 112.4 (d), 126.5 (d), 126.7 (d), 128.6 (d), 128.8 (s), 131.6 (s), 138.5 (d), 153.6 (s), 169.9 (s). *Anal.* Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 6.89. Found: C, 75.68; H, 7.80; N, 6.81.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}cyclopropanecarboxamide (**9d**): Off-yellow solid, 39%. mp 124—126 °C. ^{1}H-NMR δ: 0.59—0.73 (2H, m, cycloprop.), 0.90—1.00 (2H, m, cycloprop.), 1.10—1.27 (1H, m, $CO\underline{CH}$ cycloprop.), 2.86 (2H, t, $\underline{CH_2}CH_2NH$, J=6.9 Hz), 3.08 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.51 (2H, dt, $CH_2\underline{CH_2}NH$, J=5.9, 7.0 Hz), 3.87 (3H, s, OCH_3), 4.27 (2H, t, NCH_2, J=7.3 Hz), 5.55 (1H, br s, NH), 6.70 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.3, 8.9 Hz), 7.00—7.10 (3H, m, H_{arom}), 7.19—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 6.7 (t), 16.5 (d), 23.2 (t), 36.5 (t), 39.5 (t), 48.2 (t), 55.7 (q), 100.6 (d), 110.2 (d), 110.7 (s), 112.4 (d), 126.5 (s), 126.7 (d), 128.6 (d), 128.8 (s), 131.6 (s), 138.5 (d), 153.6 (s), 169.9 (s). *Anal.* Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.01; H, 7.18; N, 7.78.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]ethyl}cyclobutanecarboxamide (**9e**): Yellowish solid, 32%. mp 95—97 °C. ^{1}H-NMR δ: 1.80—2.30 (6H, m, cyclobut.), 2.71—2.92 (3H, m, $CO\underline{CH}$ cyclobut.+ $\underline{CH_2}CH_2NH$), 3.02 (2H, t, $\underline{CH_2}Ph$, J=7.3 Hz), 3.51 (2H, dt, $CH_2\underline{CH_2}NH$, J=5.9, 7.0 Hz), 3.87 (3H, s, OCH_3), 4.26 (2H, t, NCH_2, J=7.3 Hz), 5.52 (1H, br s, NH), 6.70 (1H, s, H_2), 6.90 (1H, dd, H_6, J=2.6, 8.8 Hz), 7.00—7.10 (3H, m, H_{arom}), 7.19—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 20.1 (t), 23.0 (t), 27.2 (t), 36.6 (t), 39.5 (d), 42.4 (t), 48.2 (t), 55.7 (q), 100.6 (d), 110.2 (d), 110.6 (s), 112.6 (d), 126.5 (s), 126.7 (d), 128.6 (d), 128.9 (s), 131.6 (s), 138.5 (d), 153.5 (s), 169.7 (s). *Anal.* Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.48; H, 7.55; N, 7.38.

5-Methoxy-1-(2-phenethyl)-1*H*-indole-3-carboxaldehyde (11) A solution of the tosylate **5** (4.04 g, 14.64 mmol) in acetonitrile (5 ml) was added dropwise to a refluxing, stirred suspension of 5-methoxyidole-3-carboxaldehyde (**10**) (1.31 g, 7.49 mmol) and potassium carbonate (6.20 g, 44.93 mmol) in acetonitrile (30 ml). The mixture was refluxed for 5 h, cooled to room temperature and then poured into ice-water. The solution was stirred for 30 min, AcOEt was added and the mixture separated. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography using cyclohexane/AcOEt=70 : 30 to give aldehyde **11** as an off-white solid. mp 96—97 °C (hexane/ethyl acetate). ^{1}H-NMR δ: 3.14 (2H, t, $\underline{CH_2}Ph$, J=6.9 Hz), 3.91 (3H, s, OCH_3), 4.37 (2H, t, NCH_2, J=6.9 Hz), 6.93—7.06 (3H, m, H_{arom}), 7.20—7.31 (4H, m, H_{arom}), 7.35 (1H, s, H_2), 7.80 (1H, d, H_{arom}, J=2.4 Hz), 9.85 (1H, s, CHO). ^{13}C-NMR δ: 36.1 (t), 49.0 (t), 55.7 (q), 103.4 (d), 110.7 (d), 114.4 (d), 117.6 (s), 126.1 (s), 127.0 (d), 128.6 (d), 128.7 (d), 131.7 (s), 137.4 (s), 138.7 (d), 156.6 (s), 184.4 (d). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.80; H, 6.21; N, 4.96.

5-Methoxy-3-(2-nitropropen-1-yl)-1-(2-phenethyl)-1*H*-indole (12) A solution of the aldehyde **11** (2.62 g, 9.39 mmol) and ammonium acetate (0.92 g, 11.95 mmol) in nitroethane (33 ml) was refluxed for 4 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in dichloromethane and water was added. The aqueous layer was washed with dichloromethane and the combined organic layers were washed with water and brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a dark orange residue which was triturated with AcOEt. The title compound **12** was obtained as an orange powder. mp 126—127 °C. ^{1}H-NMR δ: 2.30 (3H, s, CH_3), 3.12 (2H, t, $\underline{CH_2}Ph$, J=6.9 Hz), 3.91 (3H, s, OCH_3), 4.40 (2H, t, NCH_2, J=6.9 Hz), 6.94—7.02 (4H, m, H_{arom}), 7.20—7.31 (5H, m, H_{arom}), 8.45 (1H, s, $CH{=}C{-}NO_2$). ^{13}C-NMR δ: 14.7 (q), 36.4 (t), 49.1 (t), 55.9 (q), 100.4 (d), 108.2 (s), 110.9 (d), 114.0 (d), 126.4 (d), 127.0 (d), 128.8 (d), 129.4 (s), 130.8 (s), 131.0 (d), 137.7 (d), 141.1 (s), 155.7 (s). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.30; H, 5.92; N, 8.14.

1-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-propionamine (13) A solution of **12** (0.29 g, 0.86 mmol) in THF (4 ml) was added dropwise at 0 °C to a stirred suspension of lithium aluminum hydride (0.17 g, 4.40 mmol) in THF (5 ml). The mixture was refluxed for 4 h and then allowed to reach ambient temperature. After cooling to 0 °C, water (4 ml) was cautiously added. The resultant mixture was filtered through Celite and the filtrate was taken up in AcOEt. The organic layer was sequentially washed with water and brine and dried over Na_2SO_4. The solvent was removed under vacuum to give 0.25 g (96%) of the amine **13** as a pale yellow oil, which was used in the next step without further purification.

Preparation of the amides 14a—e These were prepared by the same method used for the synthesis of amides **8a**—**e** and **9a**—**e**.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}acetamide (**14a**): Beige amorphous solid, 44%. mp 127—128 °C. ^{1}H-NMR δ: 1.07 (3H, d, CH$\underline{CH_3}$, J=6.9 Hz), 1.89 (3H, s, CH_3CO), 2.83 (2H, d, $\underline{CH_2}$CH, J=5.1 Hz), 3.08 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.88 (3H, s, OCH_3), 4.22—4.40 (3H, m, NCH_2+$\underline{CH}CH_3$), 5.24 (1H, br s, NH), 6.65 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.2, 8.8 Hz), 6.99—7.12 (3H, m, H_{arom}), 7.17—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 20.0 (q), 23.7 (q), 31.4 (d), 36.6 (t), 45.3 (t), 48.2 (t), 55.9 (q), 100.8 (d), 109.5 (d), 110.1 (d), 111.9 (d), 126.6 (s), 127.2 (d), 128.5 (d), 128.8 (s), 129.1 (s), 138.6 (d), 153.9 (s), 169.2 (s). *Anal.* Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.10; H, 7.45; N, 7.68.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}propionamide (**14b**): Beige amorphous solid, 25%. mp 112—113 °C. ^{1}H-NMR δ: 1.08 (3H, d, CH$\underline{CH_3}$, J=7.7 Hz), 1.10 (3H, t, CH2$\underline{CH_3}$, J=7.7 Hz), 2.10 (2H, q, $\underline{CH_2}CH_3$, J=7.7 Hz), 2.83 (2H, d, $\underline{CH_2}$CH, J=4.8 Hz), 3.08 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.85 (3H, s, OCH_3), 4.21—4.37 (3H, m, NCH_2+$\underline{CH}CH_3$), 5.23 (1H, br s, NH), 6.67 (1H, s, H_2), 6.87 (1H, dd, H_6, J=2.6, 9.1 Hz), 7.01—7.09 (3H, m, H_{arom}), 7.18—7.30 (4H, m, H_{arom}). ^{13}C-NMR δ: 9.7 (q), 20.0 (q), 29.6 (t), 31.4 (d), 36.5 (t), 45.0 (t), 48.0 (t), 55.8 (q), 101.0 (d), 109.4 (d), 110.1 (d), 112.0 (d), 126.5 (s), 127.5 (d), 128.5 (d), 128.8 (s), 129.0 (s), 138.6 (d), 154.0 (s), 169.0 (s). *Anal.* Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.59; H, 7.68; N, 7.31.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}butyramide (**14c**): Beige amorphous solid, 29%. mp 116—117 °C. ^{1}H-NMR δ: 0.91 (3H, t, $CH_2\underline{CH_3}$, J=7.3 Hz), 1.09 (3H, d, CH$\underline{CH_3}$, J=6.6 Hz), 1.62 (2H, sextet, $CH_2\underline{CH_2}CH_3$, J=7.3 Hz), 2.05 (2H, t, $COCH_2$, J=7.3 Hz), 2.80—2.87 (2H, m, $\underline{CH_2}$CH), 3.08 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.88 (3H, s, OCH_3), 4.22—4.37 (3H, m, NCH_2+$\underline{CH}CH_3$), 5.27 (1H, br s, NH), 6.68 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.2, 8.8 Hz), 7.03—7.09 (3H, m, H_{arom}), 7.20—7.29 (4H, m, H_{arom}). ^{13}C-NMR δ: 13.6 (q), 19.0 (q), 20.0 (t), 31.4 (d), 36.8 (t), 45.4 (t), 48.4 (t), 56.0 (q), 100.8 (d), 109.7 (d), 110.2 (d), 112.0 (d), 126.6 (s), 127.0 (d), 128.7 (d), 128.9 (s), 130.0 (s), 138.4 (d), 153.7 (s), 169.4 (s). *Anal.* Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 8.00; N, 7.40. Found: C, 75.77; H, 8.02; N, 7.14.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}cyclopropanecarboxamide (**14d**): Beige amorphous solid, 33%. mp 119—120 °C. ^{1}H-NMR δ: 0.66—0.72 (2H, m, cycloprop.), 0.91—1.02 (2H, m, cycloprop.), 1.08 (3H, d, CH$\underline{CH_3}$, J=7.0 Hz), 1.13—1.20 (1H, m, CO$\underline{CH}$ cycloprop.), 2.85 (2H, d, $\underline{CH_2}$CH, J=5.5 Hz), 3.08 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.88 (3H, s, OCH_3), 4.23—4.38 (3H, m, NCH_2+$\underline{CH}CH_3$), 5.43 (1H, br s, NH), 6.69 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.6, 9.2 Hz), 7.02—7.09 (3H, m, H_{arom}), 7.19—7.30 (4H, m, H_{arom}). ^{13}C-NMR δ: 6.7 (t), 14.5 (d), 20.0 (q), 31.4 (d), 36.7 (t), 45.3 (t), 48.2 (t), 55.8 (q), 100.7 (d), 109.5 (d), 110.1 (d), 111.8 (d), 126.6 (s), 127.2 (d), 128.5 (d), 128.8 (s), 129.1 (s), 138.6 (d), 153.9 (s), 169.2 (s). *Anal.* Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.46; H, 7.55; N, 7.24.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-1-methylethyl}cyclobutanecarboxamide (**14e**): Beige amorphous solid, 22%. mp 116—117 °C. ^{1}H-NMR δ: 1.07 (3H, d, CH$\underline{CH_3}$, J=6.9 Hz), 1.74—2.37 (6H, m, cyclobut.), 2.71—2.92 (3H, m, $\underline{CH_2}$CH+CO$\underline{CH}$ cyclobut.), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.87 (3H, s, OCH_3), 4.14—4.37 (3H, m, NCH_2+$\underline{CH}CH_3$), 5.20 (1H, br s, NH), 6.67 (1H, s, H_2), 6.87 (1H, dd, H_6, J=2.6, 8.8 Hz), 6.99—7.09 (3H, m, H_{arom}), 7.16—7.31 (4H, m, H_{arom}). ^{13}C-NMR δ: 18.1 (t), 20.0 (q), 25.3 (t), 31.4 (d), 36.7 (t), 39.8 (d), 45.2 (t), 48.1 (t), 56.0 (q), 101.0 (d), 109.4 (d), 110.1 (d), 112.2 (d), 126.5 (s), 127.2 (d), 128.5 (d), 128.8 (d), 129.1 (d), 138.9 (d), 153.9 (s), 169.0 (s). *Anal.* Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.69; H, 7.76; N, 6.82.

2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propionitrile (15) A solution of the acetonitrile **6b** (0.54 g, 1.86 mmol) in DMF (6 ml) was added dropwise at 0 °C to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.05 g, 1.88 mmol) in DMF (7 ml). The reaction mixture was then treated with methyl iodide (0.15 ml, 2.10 mmol) and left stirring at 0 °C for 30 min before it was allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was treated with saturated NH_4Cl (5 ml) and extracted with AcOEt. The extract was washed with water and brine, dried over Na_2SO_4 and the solvent removed *in vacuo.* The crude product formed was flash chromatographed eluting with cyclohexane/AcOEt=97 : 3 to give 0.40 g (71%) of **15** as an off white solid. mp 67—68 °C. ^{1}H-NMR δ: 1.61 (3H, d, CH$\underline{CH_3}$, J=6.9 Hz), 2.97 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.82 (3H, s, OCH_3), 3.99 (1H, q, $\underline{CH}CH_3$, J=6.9 Hz), 4.17 (2H, t, NCH_2, J=7.3 Hz), 6.78 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.2, 8.8 Hz), 6.93—7.07 (3H, m, H_{arom}), 7.10—7.28 (4H, m, H_{arom}). ^{13}C-NMR δ: 19.7 (q), 22.7 (d), 36.7 (t), 48.4 (t), 55.9 (q), 101.8 (d), 110.6 (d), 112.3 (d), 114.6 (s), 124.5 (s), 124.8 (s), 125.5 (s), 126.7 (d), 128.6 (d), 128.7 (s), 131.9 (s), 138.2 (d), 153.9 (s). *Anal.* Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.75; H, 6.49; N, 8.81.

2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propionamine (16) This amine was prepared by the method described for **7a**. Yellow oil, 98%.

Preparation of the amides 17a—e These were prepared by the same method used for the synthesis of amides **8a**—**e** and **9a**—**e**.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}acetamide (**17a**): Beige amorphous solid, 42%. mp 101—103 °C. ^{1}H-NMR δ: 1.26 (3H, d, CH$\underline{CH_3}$, J=6.6 Hz), 1.86 (3H, s, $COCH_3$), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.12—3.38 (1H, m, $\underline{CH}CH_3$), 3.48—3.67 (2H, m, $\underline{CH_2}$NH), 3.86 (3H, s, OCH_3), 4.27 (2H, t, NCH_2, J=7.3 Hz), 5.30 (1H, br s, NH), 6.63 (1H, s, H_2), 6.88 (1H, dd, H_6, J=2.2, 8.4 Hz), 6.97—7.08 (3H, m, H_{arom}), 7.14—7.28 (4H, m, H_{arom}). ^{13}C-NMR δ: 18.4 (q), 22.6 (q), 30.5 (d), 36.8 (t), 45.5 (t), 48.4 (t), 55.4 (q), 101.0 (d), 110.2 (d), 111.9 (d), 116.6 (s), 125.1 (d), 126.6 (s), 127.6 (d), 128.5 (d), 128.7 (s), 131.4 (s), 138.5 (d), 153.7 (s), 172.8 (s). *Anal.* Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.25; H, 7.48; N, 7.62.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}propionamide (**17b**): Beige amorphous solid, 39%. mp 103—104 °C. ^{1}H-NMR δ: 1.07 (3H, t, $CH_2\underline{CH_3}$, J=7.7 Hz), 1.28 (3H, d, CH$\underline{CH_3}$, J=6.6 Hz), 2.09 (2H, q, $\underline{CH_2}CH_3$, J=7.7 Hz), 3.07 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.14—3.40 (1H, m, $\underline{CH}CH_3$), 3.54—3.69 (2H, m, $\underline{CH_2}$NH), 3.87 (3H, s, OCH_3), 4.28 (2H, t, NCH_2, J=7.3 Hz), 5.33 (1H, br s, NH), 6.65 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.2, 8.8 Hz), 7.00—7.09 (3H, m, H_{arom}), 7.20—7.32 (4H, m, H_{arom}). ^{13}C-NMR δ: 9.7 (q), 18.7 (q), 29.5 (t), 30.8 (d), 36.5 (t), 45.7 (t), 48.5 (t), 55.3 (q), 101.2 (d), 110.0 (d), 112.0 (d), 116.5 (s), 125.1 (d), 126.5 (s), 127.6 (d), 128.5 (d), 128.7 (s), 131.3 (s), 138.5 (d), 153.5 (s), 173.0 (s). *Anal.* Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.65; H, 7.84; N, 7.47.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}butyramide (**17c**): Beige amorphous solid, 77%. mp 116—118 °C. ^{1}H-NMR δ: 0.89 (3H, t, $CH_2\underline{CH_3}$, J=7.3 Hz), 1.29 (3H, d, CH$\underline{CH_3}$, J=6.6 Hz), 1.50—1.70 (2H, m, $\underline{CH_2}CH_3$), 2.03 (2H, t, CO$\underline{CH_2}$, J=6.9 Hz), 3.07 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.15—3.44 (1H, m, $\underline{CH}CH_3$), 3.51—3.68 (2H, m, $\underline{CH_2}$NH), 3.87 (3H, s, OCH_3), 4.28 (2H, t, NCH_2, J=7.3 Hz), 5.36 (1H, br s, NH), 6.65 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.6, 8.8 Hz), 7.00—7.13 (3H, m, H_{arom}), 7.19—7.34 (4H, m, H_{arom}). ^{13}C-NMR δ: 13.6 (q), 18.4 (q), 20.6 (t), 29.5 (t), 30.5 (d), 36.7 (t), 45.3 (t), 48.2 (t), 55.5 (q), 100.9 (d), 110.2 (d), 112.2 (d), 116.8 (s), 125.1 (d), 126.6 (s), 127.8 (d), 128.5 (d), 128.7 (s), 131.0 (s), 138.7 (d), 153.6 (s), 172.8 (s). *Anal.* Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 8.00; N, 7.40. Found: C, 76.06; H, 8.03; N, 7.07.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}cyclopropanecarboxamide (**17d**): Beige amorphous solid, 80%. mp 186—188 °C. ^{1}H-NMR δ: 0.61—0.72 (2H, m, cycloprop.), 0.87—1.00 (2H, m, cycloprop.), 1.09—1.21 (1H, m, CO$\underline{CH}$ cycloprop.), 1.29 (3H, d, CH$\underline{CH_3}$, J=6.6 Hz), 3.08 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.14—3.38 (1H, m, $\underline{CH}CH_3$), 3.58—3.74 (2H, m, $\underline{CH_2}$NH), 3.87 (3H, s, OCH_3), 4.29 (2H, t, NCH_2, J=7.3 Hz), 5.53 (1H, br s, NH), 6.68 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.6, 9.1 Hz), 7.00—7.11 (3H, m, H_{arom}), 7.19—7.29 (4H, m, H_{arom}). ^{13}C-NMR δ: 6.7 (t), 14.5 (d), 18.4 (q), 30.5 (d), 36.8 (t), 45.5 (t), 48.4 (t), 55.4 (q), 101.3 (d), 110.4 (d), 111.9 (d), 116.4 (s), 125.1 (d), 126.6 (s), 127.3 (d), 128.5 (d), 128.7 (s), 131.3 (s), 138.6 (d), 153.4 (s), 172.8 (s). *Anal.* Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.50; H, 7.83; N, 7.04.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]propyl}cyclobutanecarboxamide (**17e**): Beige amorphous solid, 30%. mp 123—125 °C. ^{1}H-NMR δ: 1.28 (3H, d, CH$\underline{CH_3}$, J=7.0 Hz), 1.74—2.29 (6H, m, cyclobut.), 2.76—2.91 (1H, m, CO$\underline{CH}$ cyclobut.), 3.01 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.15—3.39 (1H, m, $\underline{CH}CH_3$), 3.50—3.71 (2H, m, $\underline{CH_2}$NH), 3.87 (3H, s, OCH_3), 4.28 (2H, t, NCH_2, J=7.3 Hz), 5.24 (1H, br s, NH), 6.67 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.6, 9.1 Hz), 7.01—7.14 (3H, m, H_{arom}), 7.20—7.37 (4H, m, H_{arom}). ^{13}C-NMR δ: 18.1 (t), 18.4 (q), 25.3 (t), 30.5 (d), 36.7 (t), 39.8 (d), 45.5 (t), 48.2 (t), 55.2 (q), 101.0 (d), 110.2 (d), 111.8 (d), 116.6 (s), 125.1 (d), 126.6 (s), 127.5 (d), 128.5 (d), 128.6 (d), 131.6 (s), 138.4 (d), 153.7 (s), 173.0 (s). *Anal.* Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C,

76.70; H, 7.72; N, 7.27.

2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropionitrile (18) A solution of the acetonitrile **6b** (0.21 g, 0.73 mmol) and methyl iodide (0.10 ml, 1.82 mmol) in DMF (1.5 ml) was added dropwise at 0 °C to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.04 g, 1.82 mmol) in DMF (1.5 ml). The reaction mixture was then allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was treated with saturated NH_4Cl (5 ml) and extracted with AcOEt. The extract was washed with water and brine, dried over Na_2SO_4 and the solvent removed *in vacuo.* The crude product formed was flash chromatographed eluting with cyclohexane/AcOEt=90 : 10 to give 0.20 g (85%) of **18** as a beige solid. mp 72—73 °C (hexane/ethyl acetate). ^{1}H-NMR δ: 1.77 (6H, s, C($\underline{CH_3}$)$_2$), 3.03 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.90 (3H, s, OCH_3), 4.23 (2H, t, NCH_2, J=7.3 Hz), 6.72 (1H, s, H_2), 6.92–7.05 (4H, m, H_{arom}), 7.23—7.35 (4H, m, H_{arom}). ^{13}C-NMR δ: 27.8 (q), 29.7 (s), 36.6 (t), 48.4 (t), 56.0 (q), 101.8 (d), 110.6 (d), 112.3 (d), 114.6 (s), 124.5 (s), 124.9 (s), 125.5 (s), 126.7, (d) 128.6 (d), 128.7 (s), 131.9 (s), 138.2 (d), 153.9 (s). *Anal.* Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 78.95; H, 6.59; N, 8.61.

2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropionamine (19) This amine was prepared by the method described for **7a**. Yellow oil, 95%.

Preparation of the amides 20a—e These were prepared by the same method used for the synthesis of amides **8a**—**e** and **9a**—**e**.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropyl}acetamide (**20a**): Viscous yellow oil (flash chromatography using cyclohexane/AcOEt=70 : 30), 45%. ^{1}H-NMR δ: 1.32 (6H, s, C($\underline{CH_3}$)$_2$), 1.83 (3H, s, $COCH_3$), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.56 (2H, d, $\underline{CH_2}$NH, J=5.9 Hz), 3.85 (3H, s, OCH_3), 4.26 (2H, t, N$\underline{CH_2}CH_2$, J=7.3 Hz), 5.07 (1H, br s, NH), 6.58 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.6, 8.8 Hz), 6.99—7.08 (3H, m, H_{arom}), 7.14—7.31 (4H, m, H_{arom}). ^{13}C-NMR δ: 23.4 (q), 26.5 (q), 35.7 (s), 36.8 (t), 45.3 (t), 48.9 (t), 56.0 (q), 101.0 (d), 110.2 (d), 111.9 (d), 116.6 (s), 125.1 (s), 126.6 (d), 127.6 (d), 128.5 (d), 128.7 (s), 131.4 (s), 138.5 (d), 153.7 (s), 172.8 (s). *Anal.* Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.55; H, 7.48; N, 7.52.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropyl}propionamide (**20b**): Viscous yellow oil (flash chromatography using cyclohexane/AcOEt=70 : 30), 40%. ^{1}H-NMR δ: 1.04 (3H, t, $CH_2\underline{CH_3}$, J=7.7 Hz), 1.32 (6H, s, C($\underline{CH_3}$)$_2$), 2.03 (2H, q, $\underline{CH_2}CH_3$, J=7.7 Hz), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.57 (2H, d, $\underline{CH_2}$NH, J=5.8 Hz), 3.85 (3H, s, OCH_3), 4.26 (2H, t, N$\underline{CH_2}CH_2$, J=7.3 Hz), 5.05 (1H, br s, NH), 6.60 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.2, 8.4 Hz), 7.00—7.07 (3H, m, H_{arom}), 7.15—7.28 (4H, m, H_{arom}). ^{13}C-NMR δ: 10.0 (q), 26.6 (q), 29.9 (t), 35.9 (s), 36.7 (t), 45.4 (t), 48.7 (t), 56.1 (q), 101.2 (d), 110.0 (d), 112.0 (d), 116.5 (s), 125.1 (s), 126.5 (d), 127.6 (d), 128.5 (d), 128.7 (s), 131.3 (s), 138.5 (d), 153.5 (s), 173.0 (s). *Anal.* Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.95; H, 7.90; N, 7.28.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropyl}butyramide (**20c**): Viscous yellow oil (flash chromatography using cyclohexane/AcOEt=75 : 25), 43%. ^{1}H-NMR δ: 0.85 (3H, t, $CH_2\underline{CH_3}$, J=7.3 Hz), 1.32 (6H, s, C($\underline{CH_3}$)$_2$), 1.47—1.57 (2H, m, $\underline{CH_2}CH_3$), 1.98 (2H, t, CO$\underline{CH_2}$, J=7.3 Hz), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.57 (2H, d, $\underline{CH_2}$NH, J=5.8 Hz), 3.85 (3H, s, OCH_3), 4.26 (2H, t, N$\underline{CH_2}CH_2$, J=7.3 Hz), 5.05 (1H, br s, NH), 6.60 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.2, 8.8 Hz), 6.99—7.08 (3H, m, H_{arom}), 7.14—7.28 (4H, m, H_{arom}). ^{13}C-NMR δ: 13.7 (q), 19.2 (t), 26.5 (q), 35.7 (t), 36.9 (t), 38.8 (s), 45.8 (t), 48.6 (t), 56.1 (q), 100.9 (d), 110.2 (d), 112.2 (d), 116.8 (s), 125.1 (s), 126.6 (d), 127.8 (d), 128.5 (d), 128.7 (s), 131.0 (s), 138.7 (d), 153.6 (s), 172.8 (s). *Anal.* Calcd for $C_{25}H_{32}N_2O_2$: C, 76.50; H, 8.22; N, 7.14. Found: C, 76.35; H, 8.18; N, 7.07.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropyl}cyclopropanecarboxamide (**20d**): Viscous yellow oil (flash chromatography using cyclohexane/AcOEt=75 : 25), 38%. ^{1}H-NMR δ: 0.60—0.65 (2H, m, cycloprop.), 0.87—0.92 (2H, m, cycloprop.), 1.06—1.12 (1H, m, CO$\underline{CH}$ cycloprop.), 1.33 (6H, s, C($\underline{CH_3}$)$_2$), 3.06 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.58 (2H, d, $\underline{CH_2}$NH, J=5.8 Hz), 3.85 (3H, s, OCH_3), 4.26 (2H, t, N$\underline{CH_2}CH_2$, J=7.3 Hz), 5.25 (1H, br s, NH), 6.61 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.5, 8.7 Hz), 7.02—7.06 (3H, m, H_{arom}), 7.18—7.27 (4H, m, H_{arom}). ^{13}C-NMR δ: 6.7 (t), 14.5 (d), 26.5 (q), 35.8 (s), 36.7 (t), 45.6 (t), 48.5 (t), 56.2 (q), 101.3 (d), 110.4 (d), 111.9 (d), 116.4 (s), 125.1 (s), 126.6 (d), 127.3 (d), 128.5 (d), 128.7 (s), 131.3 (s), 138.6 (d), 153.4 (s), 172.8 (s). *Anal.* Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.70; H, 7.69; N, 7.09.

N-{2-[5-Methoxy-1-(2-phenethyl)-1*H*-indol-3-yl]-2-methylpropyl}cyclobutanecarboxamide (**20e**): Viscous yellow oil (flash chromatography using cyclohexane/AcOEt=80 : 20), 35%. ^{1}H-NMR δ: 1.32 (6H, s, C($\underline{CH_3}$)$_2$), 1.76—2.23 (6H, m, cyclobut.), 2.71—2.86 (1H, m, CO$\underline{CH}$ cyclobut.), 3.05 (2H, t, $\underline{CH_2}$Ph, J=7.3 Hz), 3.56 (2H, d, $\underline{CH_2}$NH, J=5.8 Hz), 3.85 (3H, s, OCH_3), 4.26 (2H, t, N$\underline{CH_2}CH_2$, J=7.3 Hz), 5.00 (1H, br s, NH), 6.61 (1H, s, H_2), 6.89 (1H, dd, H_6, J=2.5, 9.1 Hz), 7.00—7.10 (3H, m, H_{arom}), 7.16—7.31 (4H, m, H_{arom}). ^{13}C-NMR δ: 18.1 (t), 25.3 (t), 26.5 (q), 35.8 (s), 36.6 (t), 39.8 (d), 45.7 (t), 48.5 (t), 56.2 (q), 101.0 (d), 110.2 (d), 111.8 (d), 116.6 (s), 125.1 (s), 126.6 (d), 127.5 (d), 128.5 (d), 128.6 (s), 131.6 (s), 138.4 (d), 153.7 (s), 173.0 (s). *Anal.* Calcd for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.52. Found: C, 76.98; H, 7.92; N, 6.48.

Xenopus Melanophore Model for the Evaluation of Agonist and Antagonist Activity Melanophore cells were grown in 96-well tissue culture plates, and growth medium[29,30] was replaced with 0.7×L-15 culture medium 18 h before analogs were tested. Initial absorbance of cells (*Ai*, 630 nm) was measured in each well using a Bio-Tek microtiter plate reader (model EL3115, Anachem, U.K.), then cells were treated with the concentrations of the analogs indicated. All experiments used triplicate wells at six concentrations of analog. The final absorbance (*Af*) was measured after 60 min, and the fractional change in absorbance ($1-Af/Ai$) was calculated. Vehicle did not alter pigment granule distribution itself or inhibit responses to melatonin. The concentration of analog producing 50% of the maximum agonist response (EC_{50}) was determined from concentration–response curves. For evaluation of antagonist potency, cells were treated with vehicle (1% dimethyl sulfoxide or methanol) or varying concentrations (10^{-4}—10^{-9} M) of the analogs for 60 min before melatonin (10^{-9} M) was added. The concentration of analog reducing melatonin-induced pigment aggregation by 50% (IC_{50}) was determined.

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