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7-Substituted-melatonin and 7-substituted-1-methylmelatonin analogues: Effect of substituents on potency and binding affinity

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Abstract—A series of 7-substituted melatonin and 1-methylmelatonin analogues were prepared and tested against human and amphibian melatonin receptors. 7-Substituents reduced the agonist potency of all the analogues in the *Xenopus laevis* melanophore assay, 7-bromomelatonin (**5d**) and *N*-butanoyl 7-bromo-5-methoxytryptamine (**5f**) being the most active compounds, but both were 42-fold less potent than melatonin (**1**). Whereas all the analogues bind with lower affinity at the human MT_1 receptor than melatonin, **5d**, **5f** and *N*-propanoyl 7-bromo-5-methoxytryptamine (**5e**) show a similar binding affinity to melatonin at the MT_2 receptor and consequently show some MT_2 selectivity. These results suggest that the receptor pocket around C-7 favours binding by an electronegative group, suggesting an electropositive region in this area of the receptor.

1. Introduction

Melatonin (*N*-acetyl 5-methoxytryptamine, **1a**), the hormone secreted by the pineal gland, is a major component in the control of circadian rhythms in humans and other animals.[1,2] Since the identification of three distinct melatonin receptor subtypes[3–7] there have been numerous studies in an attempt to find analogues of melatonin that can distinguish between them.[8–15] Such selective agents would allow both the assignment of the different functions of melatonin to specific receptors and provide models for the synthesis of compounds to target receptor subtypes. It has been found that the human MT_2 receptor subtype is much more tolerant to modification of the melatonin structure than the MT_1 receptor and a number of MT_2 selective compounds have been identified. Some progress has been made towards finding MT_1 selective compounds, but highly selective compounds have not yet been prepared.[16] It has recently been suggested that melatonin receptor heterodimers may be biologically significant which, while providing another potential target as an MT_1, MT_2 combination, may render the interpretation of in vivo findings more difficult.[17]

As part of our examination of the melatonin binding sites by preparing analogues of melatonin that have been altered at defined regions of the molecule, we have synthesised a variety of tryptamine derivatives substituted at position seven. It has been suggested from CoMFA model studies that there will be a low steric tolerance to substituents at positions 1, 6 and 7 of melatonin[18] but few 7-substituted derivatives are known. 7-Methoxymelatonin (**1b**)[19] and 7-nitromelatonin (**1c**)[20] have been prepared, the latter binding with 400-fold less affinity than melatonin at the MT_1 and 94-fold less at the MT_2 receptor. Because of our previous findings that the behaviour of β-substituted tryptamines was substantially modified by methyl substitution at *N*-1,[21] we also prepared a similar series of 7-substituted-1-methyl compounds. The binding affinity of these compounds at the human MT_1 and MT_2 receptors was determined and their biological activity examined by the pigment aggregation response using a clonal *Xenopus laevis* melanophore cell line.

Keywords: Melatonin; Human melatonin receptors; Melanophores; Suzuki coupling reaction.
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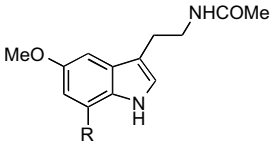


1a R = H
1b R = OMe
1c R = NO_2

2. Results and discussion

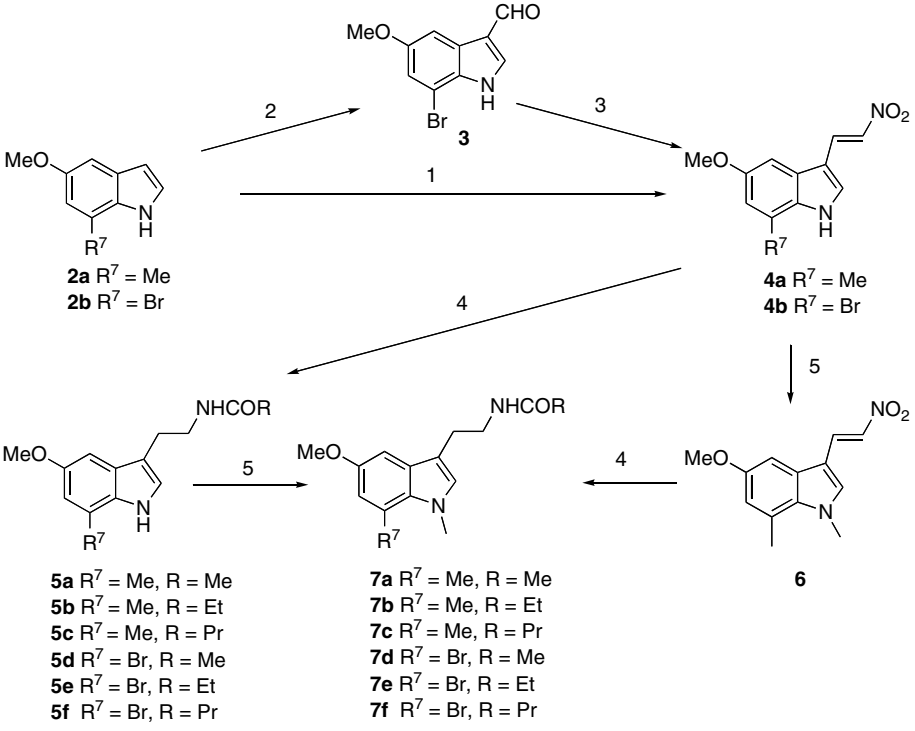
2.1. Chemistry

7-Methylmelatonin (**5a**), 7-bromomelatonin (**5d**),[22] 1,7-dimethylmelatonin (**7a**), 7-bromo-1-methylmelatonin (**7d**) and their analogues were prepared as shown in Scheme 1. 5-Methoxy-7-methylindole (**2a**) was treated with 1-dimethylamino-2-nitroethylene by the method of Büchi and Mak[23] to give **4a** in 65% yield. The nitrovinyl derivative **4a** was then reduced to the saturated amine with $LiAlH_4$ and this was then directly converted to the amides **5a**–**c** by reaction with the appropriate acid chloride. This route proved less satisfactory with the 7-bromo derivatives and the two-step Vilsmeier–Henry procedure was found to be preferable. 7-Bromo-5-methoxyindole (**2b**)[24] was converted to the aldehyde **3** with $POCl_3$ and DMF and reaction of **3** with nitromethane and NH_4OAc gave **4b** in 50% overall yield. The nitrovinyl **4b** was then treated as for **4a** to give after reaction with the appropriate acid anhydride the amides **5d**–**f**. The 1,7-dimethyl derivatives **7a**–**c** were synthesised by methylation of **4a** with iodomethane and NaH to give **6**, which was then reduced and acylated by the same procedure used with **4a**. Attempts to methylate **4b** by the same procedure gave a mixture of the desired 7-bromo-5-methoxy-1-methyl-3-(2-nitrovinyl)indole and the corresponding debrominated derivative, so the amides **7d**–**f** were prepared by methylation of the amides **5d**–**f**.

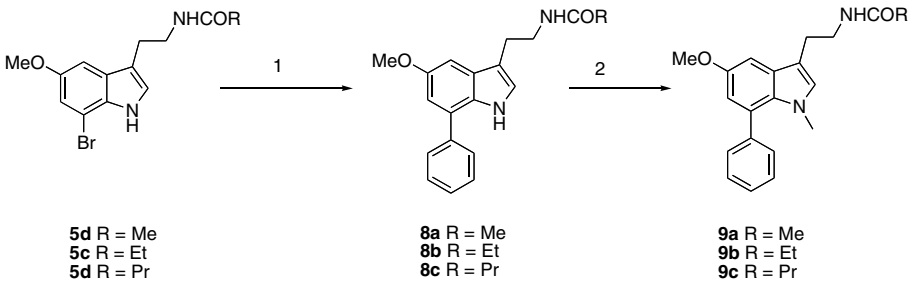
7-Bromo-5-methoxyindole (**2b**) and the acyl 7-bromotryptamines **5** and **7** are valuable intermediates for the synthesis of both 7-substituted indoles and related polycyclic systems. Treatment of 7-bromomelatonin (**5d**) with phenylboronic acid in a Suzuki coupling reaction[25] gave 7-phenylmelatonin (**8a**) in 17% yield, and treatment of **8a** with sodium hydride and MeI gave 1-methyl-7-phenylmelatonin (**9a**) in 14% yield. Similarly, **5e** and **5f** gave **8b** and **8c**, which could be converted to **9b** and **9c**, respectively (Scheme 2). 7-Phenylmelatonin (**8a**) was also prepared in similar overall yield from 7-bromo-5-methoxyindole by Suzuki coupling with phenylboronic acid followed by elaboration of the *N*-acetyl 3-ethylamino side chain.

2.2. Pharmacology

Table 1 shows the pK_i values for the binding affinity of melatonin and the 7-substituted and 7-substituted-1-methyl analogues on human MT_1 and MT_2 receptors and their potency (EC_{50}) on *Xenopus* melanophores.



Scheme 1. Reagents: (1) $Me_2NCHCHNO_2$, TFA; (2) a—$POCl_3$, DMF, CH_2Cl_2; b—NaOAc; (3) CH_3NO_2, THF, NH_4OAc; (4) $LiAlH_4$, THF, then RCOCl, Et_3N; (5) NaH, MeI, DMF.



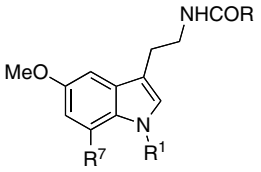
5d R = Me
5c R = Et
5d R = Pr

8a R = Me
8b R = Et
8c R = Pr

9a R = Me
9b R = Et
9c R = Pr

Scheme 2. Reagents: (1) $C_6H_5B(OH)_2$, $Pd(PPh_3)_2Cl_2$, K_2CO_3; (2) NaH, MeI, DMF.

Table 1.



Compound	R_1	R_7	R	Melanophores pEC_{50}	MT_1 pK_i	MT_2 pK_i	MT_2/MT_1
1a melatonin	H	H	Me	10.10 ± 0.03	9.58 ± 0.04	9.47 ± 0.01	0.8
5a	H	Me	Me	7.34 ± 0.02	8.57 ± 0.05	8.76 ± 0.01	1.5
5b	H	Me	Et	7.50 ± 0.02	8.75 ± 0.09	8.96 ± 0.09	1.6
5c	H	Me	Pr	7.90 ± 0.01	8.54 ± 0.06	9.17 ± 0.07	4.3
7a	Me	Me	Me	8.01 ± 0.01	8.06 ± 0.05	8.81 ± 0.08	5.6
7b	Me	Me	Et	7.80 ± 0.03	7.80 ± 0.09	8.58 ± 0.08	6
7c	Me	Me	Pr	7.78 ± 0.04	7.71 ± 0.03	8.87 ± 0.04	14.5
5d	H	Br	Me	8.48 ± 0.02	8.45 ± 0.10	9.17 ± 0.05	5.2
5e	H	Br	Et	7.94 ± 0.01	8.38 ± 0.04	9.27 ± 0.02	7.8
5f	H	Br	Pr	8.46 ± 0.02	8.29 ± 0.02	9.45 ± 0.03	14.5
7d	Me	Br	Me	7.61 ± 0.05	7.98 ± 0.13	8.88 ± 0.02	7.9
7e	Me	Br	Et	7.19 ± 0.01	7.85 ± 0.04	8.64 ± 0.02	6.2
7f	Me	Br	Pr	7.28 ± 0.04	7.48 ± 0.09	8.67 ± 0.04	15.5
8a	H	Ph	Me	6.92 ± 0.01	4.89 ± 0.54	5.52 ± 0.26	4
8b	H	Ph	Et	6.81 ± 0.07	6.21 ± 0.02	6.21 ± 0.02	1
8c	H	Ph	Pr	7.34 ± 0.03	6.02 ± 0.08	6.06 ± 0.12	1
9a	Me	Ph	Me	6.47 ± 0.02	5.90 ± 0.02	6.34 ± 0.10	2.8
9b	Me	Ph	Et	NA	5.23 ± 0.01	6.17 ± 0.02	8.7
9c	Me	Ph	Pr	NA	5.27 ± 0.02	6.07 ± 0.04	6.3

MT_1 and MT_2 receptor binding data are means ± SEM of quadruplicate determinations. Agonist data on melanophores are means ± SEM of triplicate experiments. NA, no agonist effect detected at 10 μM.

NA, no agonist effect detected at 10 μM.

2.3. Discussion

The effects of introducing a methyl, bromine or phenyl group at 7 are shown in the Table 1. In the case of melanophores, the introduction of any of these substituents drastically reduces the potency, with **5d** and **5f** the most potent compounds and **9a** the least, **9b** and **9c** showing no activity. 7-Methylmelatonin (**5a**) is 575 times, 7-bromomelatonin (**5d**) 42 times and 7-phenylmelatonin (**8a**) 1500 times less potent than melatonin. The greater potency of the 7-bromo compounds over their 7-methyl analogues suggests that there may be an electrostatic binding effect from the bromine atom. The 7-phenyl derivatives are the least active, probably because of the greater steric interaction of the phenyl group than that of methyl or bromine. The considerable decrease in potency of the 7-substituted derivatives is in striking contrast to their binding affinity to the human MT_2 receptor. All three 7-bromo analogues have high binding affinities at MT_2, increasing with increasing size of the *N*-acyl group, whereas they show a somewhat lower affinity for the MT_1 receptor and the affinity decreases with increasing alkyl group size. Thus, *N*-butanoyl 7-bromo-5-methoxytryptamine (**5f**) has the same binding affinity at the MT_2 receptor as melatonin, although it binds much more weakly at the MT_1 receptor (MT_2/MT_1 ratio 14:5). 7-Methylmelatonin (**5a**) binds only 5 times less strongly to MT_2 than melatonin, although it is 575 times less active on melanophores, and the difference in binding between MT_1 and MT_2 is not large (MT_2/MT_1 ratio 1:5). The previously reported 7-nitromelatonin (**1c**)[18] has reported binding affinities more closely resembling those of the 7-bromo derivatives, with an MT_2/MT_1 selectivity of 4, but binds significantly less strongly to MT_2 than does **5a** (Fig. 1).

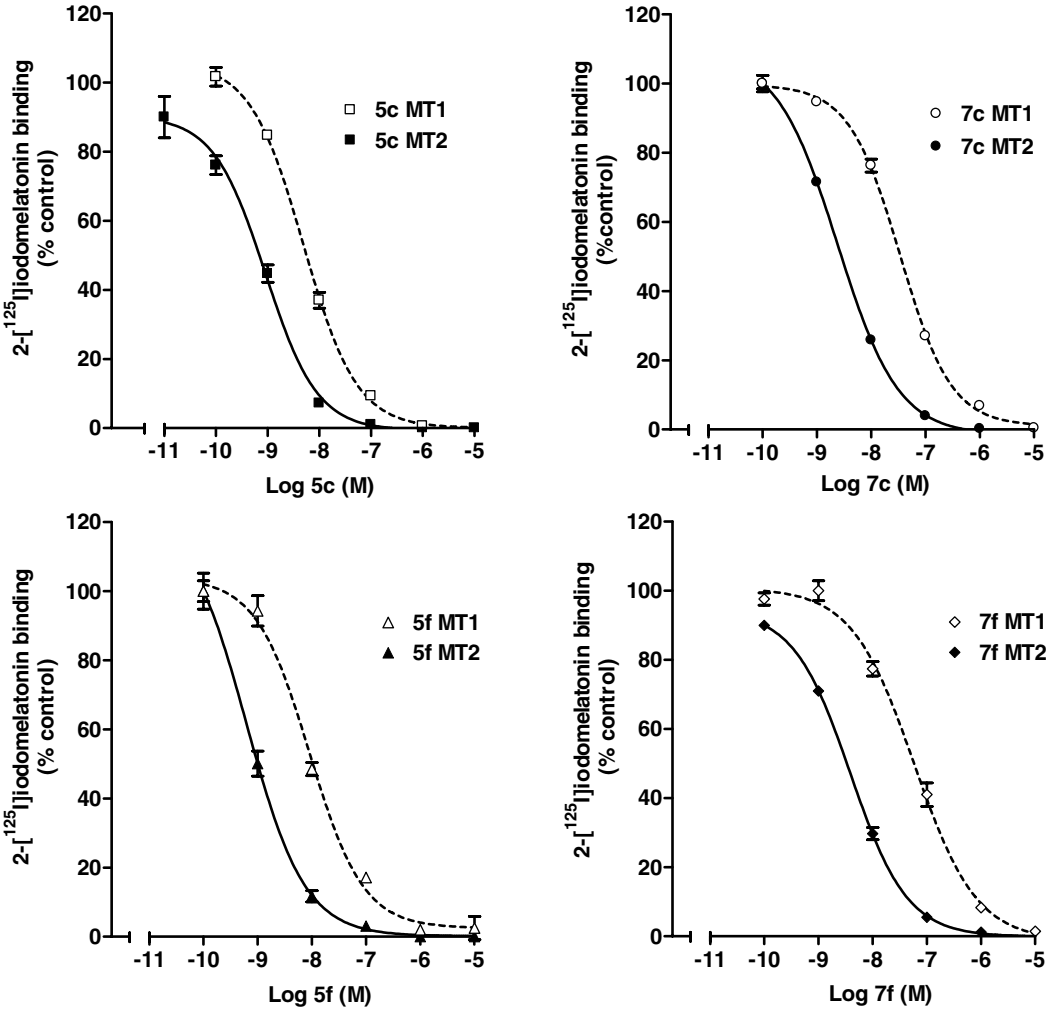


Figure 1. Competition radioligand binding curves for compounds **5c**, **7c**, **5f** and **7f** on recombinant human MT_1 and MT_2 receptor subtypes. Each data point represents the mean ± SEM of triplicate samples.

Introduction of the N-1 methyl group in the 7-methyl series has a rather small effect, decreasing the binding affinity to MT_1, but having little effect on potency at melanophores. In the 7-bromo and 7-phenyl series there is generally a reduction in both binding and potency, with *N*-propanoyl 5-methoxy-1-methyl-7-phenyltryptamine (**9b**) and the *N*-butanoyl analogue **9c** being inactive on melanophores but binding weakly to the human receptors. All of the 7-substituted derivatives show a higher binding affinity for MT_2 over MT_1 except for the 7-phenyl derivatives **8b** and **8c**, which are equipotent. The behaviour of compound **8a** is somewhat anomalous in that it shows lower binding affinity to MT_1 and MT_2 than would have been expected from its affinity to melanophores and it also has less binding affinity than the corresponding *N*-methyl derivative **9a**.

The 7-methyl analogue **7c** (N^1Me, R = Pr) and the 7-bromo analogues **5f** (N^1H, R = Pr) and **7f** (N^1Me, R = Pr) may provide leads to compounds with differing activities at the human MT_1 and MT_2 receptors. Although these compounds have a lower binding affinity than melatonin, they already show some preference for binding to the MT_2 receptor and β-substitution, for example, may increase both the binding affinity and the discrimination between receptors.[21] Since 7-bromomelatonin shows a higher binding affinity than 7-methylmelatonin, β-substituted 7-fluoromelatonin analogues may be the targets of choice. We are currently exploring these concepts.

3. Experimental

3.1. Chemistry

Melting points were determined either in glass capillary tubes on a Gallenkamp Melting Point Apparatus or a Reichert-Jung Thermovar hot-stage and are uncorrected. EI mass spectra were recorded on a VG ZAB-2F, CI mass spectra on a VG 12-250, FAB on a M550 and GCMS on a Shimadzu QP5050 mass spectrometer. Only molecular (M^+) or $(M+1)^+$ ions and the most significant peaks are reported. ^{1}H NMR spectra were taken on Varian VXR-400, Varian Gemini 2000, Varian Mercury, or Bruker AC300 spectrometer in $CDCl_3$ unless stated otherwise and are reported in δ. C^{13} NMR spectra were taken in $CDCl_3$, unless stated otherwise, and are

reported in δ. Solvents were dried over sodium where appropriate or over activated sieves. Chromatography was carried out on Sorbsil c60-silica or Merck silica gel. Analytical TLC was carried out on DC-Alufolien plates visualised with ultraviolet light, iodine, potassium permanganate or ninhydrin. Microanalyses were performed by the Microanalytical Section, Department of Chemistry, UCL, or the Analytic Research Department, H. Lundbeck A/S, Denmark. Satisfactory analyses or high resolution mass spectra data were obtained for all new analogues.

3.1.1. 5-Methoxy-7-methyl-3-(2-nitrovinyl)indole (4a). Trifluoroacetic acid (TFA) (1.82 g, 16 mmol) in CH_2Cl_2(4 mL) was added to a suspension of 1-dimethylamino-2-nitroethylene (0.95 g, 8.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C. A solution of 5-methoxy-7-methylindole[26] (**2a**, 0.89 g, 5.5 mol) in CH_2Cl_2 (5 mL) was then added and the mixture stirred at 0 °C for 30 min and then allowed to come to room temperature and stirred for 5 h. Ice (5 g) was added and the mixture was separated and the aqueous layer extracted with CH_2Cl_2 (3× 25 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (3× 20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give **4a** as an orange solid, 0.83 g (3.6 mmol, 65%), mp 225–226 °C; ^{1}H NMR 3.89 (s, 3H), 6.77 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.86 (d, J = 13.4 Hz, 1H), 8.08 (d, J = 2.9 Hz, 1H), 8.35 (d, J = 13.4 Hz, 1H), 11.20 (br s, 1H); ^{13}C NMR δ 16.9, 110.2, 118.2, 121.5, 122.8, 124.9, 131.9, 131.8, 133.0, 133.5, 136.0, 138.0; MS *m/e* 202 (100), 155, 129. Found: 203.0820. $C_{11}H_{11}N_2O_2$ (M^++1) requires 203.0815.

3.2. General method for the preparation of amides (5a–c)

A solution of **4a** (0.20 g, 0.86 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.19 g, 5.16 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirring was continued for 18 h. Water (3 mL), aqueous NaOH (2 M, 2.2 mL) and ether (6 mL) were then added sequentially and the mixture was filtered and the precipitate washed with water and THF. The combined filtrate was separated and the aqueous layer extracted with ether (3× 25 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). A stirred solution of the crude tryptamine (0.16 g, 0.80 mmol) in CH_2Cl_2 at 0 °C was then treated with the appropriate acid chloride (0.80 mmol), the solution allowed to warm to room temperature and stirring continued for 4 h. The solution was washed with aqueous HCl (10%, 25 mL), saturated $NHCO_3$ (25 mL) and brine (25 mL) and the organic phase dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the brown oil purified by flash chromatography on silica gel, eluting with ether/acetone, to give the amide.

3.2.1. 7-Methylmelatonin (*N*-acetyl 5-methoxy-7-methyltryptamine) (5a). White solid, 0.40 g (29% from **4a**) mp 125–126 °C; ^{1}H NMR δ 1.90 (s, 3H), 2.43 (s, 3 H), 2.91 (t, J = 6.5 Hz, 2H), 3.56 (d, J = 6.5 Hz, 2 H), 3.82 (s, 3H), 5.57 (s, 1H), 6.68 (d, J = 1.2 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR δ 16.6, 23.3, 25.3, 39.7, 55.8, 97.8, 105.0, 113.0, 121.5, 122.3, 127.0, 131.1, 154.2, 170.0, 177.8; MS *m/e* 246 (100), 187, 174. Anal. ($C_{12}H_{12}N_2O$) C, H, N.

3.2.2. *N*-Propanoyl 5-methoxy-7-methyltryptamine (5b). Brown oil, 0.60 g (41% from **4a**); ^{1}H NMR δ 1.09 (t, J = 7.6 Hz, 3 H), 2.43 (s, 3H), 2.91 (t, J = 6.6 Hz, 2H), 3.46 (d, J = 7.0 Hz 2H), 3.57 (d, J = 6.5 Hz, 2H), 3.82 (s, 3H), 5.48 (s, 1H), 6.68 (d, J = 1.4 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 7.86 (s, 1H); MS *m/e* 260 (100), 187, 174. Found: 261.1603. $C_{15}H_{21}O_2N_2$ (M^++1) requires 261.1610.

3.2.3. *N*-Butanoyl 5-methoxy-7-methyltryptamine (5c). Brown oil, 0.33 g 22% from **4a**: ^{1}H NMR d 0.89 (t, J = 7.3 Hz, 3H), 1.60 (q, 7.3 Hz, 3H), 1.60 (m, 2H), 2.06 (t, 7.3 Hz, 2H), 2.43 (s, 3H), 2.91 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 5.48 (s, 1H), 6.68 (d, J = 1.4 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H),7.85 (s, 1H); ^{13}C NMR δ 13.7, 16.6, 19.1, 25.4, 38.8, 39.4, 55.8, 97.9, 113.3, 121.5, 122.3, 127.1, 131.2, 154.3, 164.5, 172.9; MS *m/e* 274 (100), 187, 174. Found: 275.1760. $C_{16}H_{23}O_2N_2$ (M^++1) requires 275.1750.

3.2.4. 7-Bromo-3-formyl-5-methoxyindole (3). 7-Bromo-5-methoxyindole[27] in CH_2Cl_2 was added dropwise to a cold (0–5 °C), stirred mixture of $POCl_3$ (0.30 g, 1.95 mmol) and DMF (0.14 g, 1.95 mmol) in CH_2Cl_2 under N_2. The reaction mixture was allowed to warm to room temperature and then refluxed for 2 h. After cooling, aqueous NaOAc (8 mL, 2 M) was added and the vigorously stirred mixture refluxed for 15 min. After cooling, CH_2Cl_2 (10 mL) and water (10 mL) were added, the mixture was separated and the aqueous phase extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were washed with saturated Na_2CO_3 solution (3× 15 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed under vacuo and the residue chromatographed on silica gel, eluting with EtOAc/petroleum ether 800–100 (2:1), to give **3** as pale yellow crystals, 0.30 g, 67%, mp 166–168 °C: ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H), 7.14 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 2.75 Hz, 1H), 9.90 (s, 1H), 12.26 (br s, 1H); ^{13}C NMR 55.6, 102.2, 104.8, 115.3, 118.5, 125.8, 130.3, 139.1, 155.8, 184.9. Anal. ($C_{10}H_8BrNO_2$) C, H, N.

3.2.5. 7-Bromo-5-methoxy-3-(2-nitrovinyl)indole (4b). The aldehyde **3** (0.20 g, 0.79 mmol) and NH_4Ac (0.066 g, 0.87 mmol), $MeNO_2$ (47 μL, 0.87 mmol) were dissolved in THF (3 mL) and refluxed for 20 h. The mixture was cooled to room temperature and water (6 mL) was added. The aqueous layer was extracted with EtOAc (3× 10 mL), the organic phases combined and washed with saturated $NaHCO_3$ (2 mL), brine (5 mL) and dried ($MgSO_4$). The solvent was removed under vacuo and the residue purified by column chromatography (SiO_2, petrol/EtOAc, 50:50) to give **4b** (174 mg, 0.59 mmol, 75%), as yellow crystals, mp 209–211 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 7.13 (d, J = 2.2 Hz, 1H), 7.45 (d, J = 2.2 Hz, 1H), 8.09 (d,

J = 13.2 Hz, 1H), 8.26 (d, J = 2.75 Hz, 1H), 8.31 (d, J = 13.2 Hz, 1H), 12.28 (br s, 1H).

3.2.6. 7-Bromomelatonin (*N*-acetyl 7-bromo-5-methoxytryptamine) (5d). A solution of **4b** (0.15 g, 0.50 mmol) in THF (2.5 mL) was added to a stirred suspension of $LiAlH_4$ (0.09 g, 3.6 mmol) in THF (4 mL) under N_2 at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was poured into ice-cold NaOH solution (2 mL, 1 M) and water (1.0 mL) and ether (15 mL) were added and the mixture filtered. Ether (15 mL) was added and the solution dried over $MgSO_4$. The solvent was removed under vacuo and the residue (0.19 g) was dissolved in dry THF (3 mL) at 0 °C and Et_3N (0.15 mL, 1.1 mmol) was added and the mixture stirred for 5 min before the addition of acetic anhydride (0.10 mL, 1.1 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. It was then extracted with HCl (2× 25 mL, 2 M), saturated $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$). Chromatography on silica gel, eluting with EtOAc/petroleum ether (3:1), gave **5d**, 0.072 g (0.21 mmol, 42%) as white crystals, mp 141–143 °C: ^{1}H NMR (CD_3OD) δ 1.91 (s, 3H), 2.87 (t, J = 7.2 Hz, 2H), 3.40–3.47 (m, 2H), 3.81 (s, 3H), 6.94 (d, J = 2.2 Hz, 1H), 7.05 (d, J = 2.2 Hz), 7.10 (s, 1H), 8.04 (br s, 1H), 10.32 (br s, 1H); ^{13}C NMR (CD_3OD) δ 22.7, 26.3, 41.4, 56.5, 100.9, 105.4, 114.3, 114.9, 125.3, 130.0, 131.8, 155.2, 173.1. Anal. ($C_{13}H_{15}BrN_2O_2$) C, H, N.

3.2.7. *N*-Propanoyl 7-bromo-5-methoxytryptamine (5e). Prepared from **4b** as for **5d**, acylating with proprionic anhydride; 0.042 g (0.130 mmol, 62%), off-white crystals, mp 95 °C (EtOAc); ^{1}H NMR δ 1.00 (t, J = 7.5 Hz, 3H), 2.04 (q, J = 7.6 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 3.29 (q, J = 7.0 Hz, 2H), 3.77 (s, 3H), 6.96 (d, J = 2.1 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.83 (bt, 1H), 10.86 (s, 1H); ^{13}C NMR (DMSO) 13.6, 18.6, 25.1, 37.4, 39.0, 39.7, 55.7, 75.5, 100.3, 113.1, 124.8; MS *m/e* 326, 324, 253, 251, 240, 238. Anal. ($C_{14}H_{17}BrN_2O_2$) C, H, N.

3.2.8. *N*-Butanoyl 7-bromo-5-methoxytryptamine (5f). Prepared from **4b** as for **5d**, acylating with butyric anhydride; 0.044 g (0.130 mmol, 62%), off-white crystals, mp 87 °C (EtOAc); ^{1}H NMR δ 0.81 (t, J = 7.4 Hz. 3H), 1.48 (m, 2H), 2.01 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 3.30 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 6.95 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 2.1, 1H), 7.15 (d, J = 2.3 Hz, 1H), 7.85 (bt, 1H), 10.86 (s, 1H); ^{13}C NMR (DMSO) δ 13.6, 18.6, 25.15, 37.4, 55.75, 100.3, 104.0, 113.1, 124.8, 128.7, 129.1, 153.3, 171.8; MS *m/e* 342, 340, 253, 251, 240, 238. Anal. ($C_{15}H_{19}BrN_2O_2$) C, H, N.

3.2.9. 1,7-Dimethyl-5-methoxy-3-(2-nitrovinyl)indole (6). Sodium hydride (1 mmol, 55–65% in oil) was added to a stirred solution of **4a** (0.20 g, 0.86 mmol) in DMF (5 mL) at 0 °C. After 30 min iodomethane (0.14 g, 1.0 mmol) was added and the mixture allowed to warm to room temperature and stirred for 16 h. The mixture was poured into water (10 mL), the solution brought to pH 7 by addition of aqueous HCl (2 M) and allowed to stand for 4 h at 4 °C. The orange precipitate was removed by filtration, dried under vacuo and purified by chromatography on silica gel, eluting with CH_2Cl_2/acetone, to give **6**, 0.11 g (0.45 mmol, 52%); ^{1}H NMR δ 2.69 (s, 3H), 3.85 (s, 3H), 4.05 (s, 3H), 6.68 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 7.34 (s, 1H), 8.63 (d, J = 13.4 Hz, 1H), 8.20 (d, J = 13.4 Hz, 1H); ^{13}C NMR δ 19.5, 37.8, 55.7, 100.1, 107.4, 116.4, 123.8, 127.7, 131.3, 132.0, 133.4, 137.8, 155.9; MS *m/e* 246 (100), 203, 188.

3.2.10. General method for the preparation of amides (7a–c). A solution of **6** (0.20 g, 0.86 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.19 g, 5.16 mmol) in THF (10 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 18 h. Water (3 mL), aqueous NaOH (2.2 mL, 2 M) and ether (6 mL) were added sequentially and the mixture was filtered. The residue was washed with THF (5 mL) and ether (5 mL) and the combined filtrates were separated and the aqueous layer extracted with ether (3× 25 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the amine, which was used without further purification. The crude amine (0.80 mmol) was dissolved in CH_2Cl_2 (5 mL), the stirred solution cooled to 0 °C and Et_3N (0.10 mL, 0.77 mmol) and the appropriate acid chloride (0.80 mmol) added. The mixture was allowed to warm to room temperature and stirred for 4 h. The solution was then extracted with aqueous HCl (5 mL, 10%), satd $NaHCO_3$ solution (5 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$), the solvent removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with ether/acetone, to give the desired amide.

3.2.11. 1,7-Dimethylmelatonin (*N*-acetyl 5-methoxy-1,7-dimethyltryptamine) (7a). White solid, 0.10 g (0.38 mmol, 44%), mp 131–133 °C; ^{1}H NMR δ 2.42 (s, 3H), 3.19 (s, 3H), 3.37 (t, J = 6.6 Hz, 2H), 4.04 (d, J = 6.6 Hz, 2H), 4.32 (s, 3H), 4.46 (s, 3H), 6.07 (s,1H), 7.09 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR δ 19.5, 23.4, 25.0, 36.5, 39.7, 55.7, 97.8, 110.6, 114.7, 122.6, 128.9, 129.1, 131.1, 153.6, 169.9; MS *m/e* 260, 201, 188, 173. $C_{15}H_{20}O_2N_2$ requires 260.1510. Found: 260.1525.

3.2.12. *N*-Propanoyl 5-methoxy-1,7-dimethyltryptamine (7b). White solid, 0.11 g (0.40 mmol, 45%), mp 107–109 °C (EtOAc); ^{1}H NMR δ 1.62 (t, J = 7.5 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 3.20 (s, 3H), 3.38 (t, J = 6.6 Hz, 2H), 4.05 (q, J = 6.6 Hz, 2H), 4.33 (s, 3H), 4.47 (s, 3H), 6.04 (s, 1H), 7.10 (d, J = 2.5 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H) 7.76 (s, 1H); ^{13}C NMR δ 9.8, 19.5, 25.1, 29.8, 36.5, 39.6, 55.7, 97.8, 110.7, 114.7, 122.6, 128.9, 129.1, 131.1, 153.6, 173.6; MS *m/e* 274, 201, 188, 173. Anal. ($C_{16}H_{22}N_2O_2$) C, H, N.

3.2.13. *N*-Butanoyl 5-methoxy-1,7-dimethyltryptamine (7c). White solid, 0.16 g (0.56 mmol, 65%), mp 106–107 °C; ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, 3H), 1.61 (m,

2H), 2.07 (t, $J = 7.4$ Hz, 2H), 2.68 (s, 3H), 2.85 (t, $J = 6.6$ Hz, 2H), 3.54 (q, $J = 6.6$ Hz, 2H), 3.80 (s, 3H), 3.95 (s, 3H), 5.49 (s, 1H), 6.58 (d, $J = 2.0$ Hz, 1H), 6.71 (s, 1H), 6.79 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR δ 13.7, 19.1, 19.5, 25.1, 36.5, 38.8, 39.5, 55.7, 97.8, 110.7, 114.7, 122.6, 128.9, 129.1, 131.1, 153.6, 172.8; MS *m/e* 288, 201, 188, 173. Found: 288.1838. $C_{17}H_{24}N_2O_2$ requires 288.1850.

3.2.14. 7-Bromo-1-methylmelatonin (*N*-acetyl 7-bromo-5-methoxy-1-methyltryptamine) (7d). Sodium hydride (20 mg, 0.48 mmol) was added to a stirred solution of **5d** (0.070 g, 0.218 mmol) in dry THF (1.0 mL) at 0 °C and stirring continued for 30 min. Iodomethane (27 μL, 0.436 mmol) was then added, the mixture allowed to warm to room temperature and stirred for 5 h. Water (2.0 mL) and EtOAc (2 mL) were then added, the organic layer separated. The aqueous layer was extracted with EtOAc (3× 2 mL) and the combined organic fractions were washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc) and recrystallised from CH_2Cl_2–petrol to give **7d** (0.010 g, 0.031 mmol, 14%); mp 109 °C; ^{1}H NMR (CD_2Cl_2) δ 1.88 (s, 3H), 2.85 (t, $J = 6.7$ Hz, 2H), 3.47 (m, $J = 6.7$ Hz, 2H), 3.81 (s, 3H), 4.05 (s, 3H), 5.55 (br s, 1H), 6.84 (s, 1H), 6.97 (d, $J = 2.2$ Hz, 1H), 7.01 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.4, 25.3, 36.7, 39.9, 56.2, 100.5, 104.2, 111.4, 116.6, 129.4, 130.9, 131.2, 154.1, 169.9; MS *m/e* 326 (33, M+2), 324 (32, M^+), 252 (100). Found: M^+ 324.0481. $C_{14}H_{17}{}^{79}BrN_2O_2$ requires 324.0473.

3.2.15. *N*-Propanoyl 7-bromo-5-methoxy-1-methyltryptamine (7e). From **5e** by the same procedure as for **7d**. 0.028 g, 0.067 mmol, 67%; white crystals, mp 93 °C (CH_2Cl_2, petrol); ^{1}H NMR (CD_2Cl_2) δ 1.08 (t, $J = 7.6$ Hz, 3H), 2.12 (q, $J = 7.6$ Hz, 2H), 2.85 (t, $J = 6.9$ Hz, 2H), 2.85 (t, $J = 6.9$ Hz, 2H), 3.48 (q, $J = 6.6$ Hz, 2H), 3.81 (s, 3H), 4.04 (s, 3H), 5.61 (br s, 1H), 6.83 (s, 1H), 6.97 (d, $J = 2.3$ Hz), 7.05 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 10.0, 25.4, 30.0, 36.7, 39.9, 56.3, 100.6, 104.3, 111.5, 116.7, 129.4, 131.0, 131.3, 154.1, 173.7; MS *m/e* 340, 338, 265, 267, 252, 254. Found: 338.0632. $C_{15}H_{19}N_2O_2{}^{79}Br$ requires 338.0630.

3.2.16. *N*-Butanoyl 7-bromo-5-methoxy-1-methyltryptamine (7f). From **5f** by the same procedure as for **7d**. 0.012 g, 0.034 mmol, 55%; white crystals, mp 111 °C (EtOAc/petrol); ^{1}H NMR (DMSO) δ 0.82 (t, $J = 7.4$ Hz, 3H), 1.49 (m, 2H), 2.00 (t, 7.3 Hz, 2H), 2.72 (t, $J = 7.3$ Hz, 2H), 3.26 (q, $J = 6.8$ Hz, 2H), 3.76 (s, 3H), 3.97 (s, 3H), 6.94 (d, $J = 2.2$ Hz, 1H), 7.05 (d, $J = 2.2$ Hz, 1H), 7.11 (s, 1H), 7.86 (m, 1H); ^{13}C NMR (DMSO) δ 13.6, 18.6, 24.7, 35.9, 37.4, 38.6, 55.6. 100.5, 103.1, 111.1, 115.2, 128.1, 130.8, 131.1, 153.1, 171.8; MS *m/e* 355, 353, 275. Found: 353.0857. $C_{16}H_{22}N_2O_2{}^{79}Br$ (M^++1) requires 353.0865.

3.2.17. 7-Phenylmelatonin (*N*-acetyl 5-methoxy-7-phenyltryptamine) (8a). A solution of aqueous potassium carbonate (3 M, 0.3 mL) was added to a solution of 7-bromomelatonin **5d** (0.115 g, 0.37 mmol) and phenylboronic acid (0.090 g, 0.74 mmol) in DMF (4.5 mL) was added. The resulting mixture was flushed with argon and $Pd(PPh_3)_2Cl_2$ (0.029 g, 0.04 mmol) was added rapidly. The mixture was stirred at 100 °C for 20 h and then allowed to cool to room temperature before being filtered through Celite. EtOAc (50 mL) was added to the filtrate and the organic phase separated, washed with water (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by HPLC (Chiralpak AD, 20 × 250, 10 Å, 10 mL min^{-1}, hexane/IPA 80:20, 254 nm, 1 mL loop, room temperature = 18.5 min) to give **8a** 0.017 g, (0.055 mmol, 15%), white solid, mp 62 °C; ^{1}H NMR (CD_2Cl_2) δ 1.89 (3H, s), 2.95 (t, $J = 6.7$ Hz, 2H), 3.55 (m, 2H), 3.88 (s, 3H), 5.61 (br s, 1H) 6.89 (d, $J = 2.4$ Hz, 1H), 7.06 (d, $J = 2.3$ Hz, 1H), 7.08 (d, $J = 2.4$ Hz, 1H) 7.41–7.65 (m, 5H), 8.25 (br s, 1H); ^{13}C δ (CD_2Cl_2) 24.9, 27.2, 41.5, 57.7, 101.6, 113.7, 115.0, 124.9, 128.2, 129.4, 129.9, 130.2, 130.9, 131.2, 140.5, 156.3, 171.5; MS *m/e* 308 (6%, M^+), 249, 235 86, 84 (100). Found: M^+ 308.1514. $C_{19}H_{20}N_2O_2$ requires 308.1525.

3.2.18. *N*-Propanoyl 5-methoxy-7-phenyltryptamine (8b). 0.052 g (0.161 mmol, 40%), white crystals, mp 48 °C; ^{1}H NMR (CD_2Cl_2) δ 1.08 ($J = 7.6$ Hz, 3H), 2.12 (q, $J = 7.6$ Hz, 2H), 2.94 (t, $J = 6.8$ Hz, 2H), 3.56 (q, $J = 6.5$ Hz, 2H), 3.88 (s, 3H), 5.61 (br s, 1H), 6.89 (d, $J = 2.3$ Hz, 1H), 7.06 (m, 2H), 7.43 (m, 1H), 7.52 (m, 2H), 7.65 (m, 2H), 8.30 (br s, 1H); ^{13}C NMR (CD_2Cl_2) 11.5, 27.25, 31.4, 41.4, 57.67, 101.7, 113.7, 115.0, 125.0, 128.2, 129.4, 129.9, 130.2, 130.9, 131.2, 140.6, 156.2, 175.3; MS *m/e* 322, 249 (100), 236. Found: 322.1683. $C_{20}H_{22}N_2O_2$ requires 322.1681.

3.2.19. *N*-Butanoyl 5-methoxy-7-phenyltryptamine (8c). 0.051g (0.151 mmol, 38%), colourless oil; ^{1}H NMR (CD_2Cl_2) δ 0.84 (t, $J = 5.5$ Hz, 3H), 1.53 (t, $J = 5.6$ Hz, 2H), 2.01 (t, $J = 5.6$ Hz, 2H), 2.88 (t, $J = 5.2$ Hz, 2H), 3.49 (q, $J = 4.9$ Hz, 2H), 3.82 (s, 3H), 5.67 (br s, 1H), 6.83 (d, $J = 1.6$ Hz, 1H), 6.99 (d, $J = 1.6$ Hz, 1H), 7.00 (d, $J = 1.5$ Hz, 1H), 7.36 (m, 1H), 7.42 (m, 1H), 7.57 (m, 2H), 8.39 (br s, 1H); ^{13}C NMR (CD_2Cl_2) δ 15.4, 21.0, 40.4, 41.3, 57.6, 101.7, 113.7, 125.0, 128.2, 129.4, 129.9, 130.2, 130.9, 131.2, 140.6, 156.2, 174.5; MS *m/e* 337, 336, 250, 249, 236. Found: 337.1907. $C_{21}H_{24}N_2O_2$ requires 337.1916.

3.2.20. 1-Methyl-7-phenylmelatonin (*N*-acetyl 1-methyl-5-methoxy-7-phenyltryptamine) (9a). Sodium hydride (11 mg, 0.27 mmol) was added to a solution of **8a** (38 mg, 0.12 mmol) in dry THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min and iodomethane (15 μL, 0.25 mmol) was added and the mixture stirred for a further 2 h at room temperature. It was then quenched with water (2.0 mL), EtOAc (2 mL) and the aqueous layer extracted with EtOAc (3× 2 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc) followed by preparative HPLC (Chiralpak AD, 20 × 250, 10 Å, 10 mL min^{-1}, hexane/IPA 80:20, 254 nm, 1 mL loop, retention time = 11.8 min) to give **9a**, 0.023 g (0.071 mmol, 59%), white crystals, mp

111 °C; ^{1}H NMR (CD_2Cl_2) δ 1.85 (s, 3H), 2.85 (t, J = 6.8 Hz, 2H), 3.15 (s, 3H), 3.47 (m, J = 6.8 Hz, 2H), 3.79 (s, 3H), 5.69 (br s, 1H), 6.61 (d, J = 2.5 Hz, 1H), 6.75 (s, 1H), 6.98 (d, J = 2.5 Hz, 1H) 7.37–7.34 (m, 5H); ^{13}C NMR (CD_2Cl_2) δ 24.9, 27.0, 38.1, 41.6, 57.5, 101.5, 112.8, 115.7, 129.1, 129.5, 129.6, 129.6, 131.3, 131.5, 131.7, 141.7, 154.9, 171.5; MS *m/e* 322 (23%, M^+), 263, 250 (100). Found: M^+ 322.1677. $C_{20}H_{22}N_2O_2$ requires 322.1681.

3.2.21. *N*-Propanoyl 5-methoxy-1-methyl-7-phenyltryptamine (9b). 0.0313 g, 0.0932 mmol, 73%, white crystals, mp 109 °C (CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 1.10 (t, J = 5.7 Hz, 3H), 2.14 (q, J = 5.7 Hz, 2H), 2.91 (t, J = 5.1 Hz, 2H), 3.21 (s, 3H), 3.54 (q, J = 4.9 Hz, 2H), 3.85 (s, 3H), 5.64 (br s, 1H), 6.67 (d, J = 1.9 Hz, 1H), 6.80 (s, 1H), 7.03 (d, J = 1.9 Hz, 1H), 7.38–7.43 (m, 5H); ^{13}C NMR (CD_2Cl_2) δ 11.5, 27.0, 31.5, 38.1, 41.4, 57.5, 101.5, 112.9, 115.7, 129.1, 129.5, 129.6, 131.3, 131.5, 131.7, 141.7, 154.9, 175.1; MS *m/e* 336, 263, 250 (100). Found: 336.1831. $C_{21}H_{24}N_2O_2$ requires 336.1838.

3.2.22. *N*-Butanoyl 5-methoxy-1-methyl-7-phenyltryptamine (9c). 0.0251 g, 0.072 mmol, 69%, white crystals, mp 109 °C (CH_2Cl_2); ^{1}H NMR δ 0.92 (t, J = 5.5 Hz, 3H), 1.61 (m, 2H), 2.09 (t, J = 5.6 Hz, 2H), 2.92 (t, J = 5.1 Hz, 2H), 3.21 (s, 3H), 3.55 (q, J = 4.9 Hz, 2H), 3.86 (s, 3H), 5.64 (br s, 1H), 6.67 (d, J = 1.8 Hz, 1H), 6.80 (s, 1H), 7.04 (d, J = 1.8 Hz, 1H), 7.39–7.44 m, 5H; ^{13}C NMR (CD_2Cl_2) δ 15.33, 20.9, 27.1, 38.1, 40.4, 41.4, 57.6, 101.6, 112.9, 115.7, 129.1, 129.5, 129.6, 131.3, 131.5, 131.7, 131.8, 141.7, 155.0, 174.3; MS *m/e* 350, 263, 250 (100). Found: 350.1995. $C_{22}H_{26}N_2O_2$ requires 350.1994.

3.3. Pharmacology

The affinity of the analogues was determined in competition radioligand binding assays using 2-[^{125}I]iodomelatonin (specific activity 2000 Ci/mol, GE Healthcare, UK) as described previously[28] on the recombinant human MT_1 and MT_2 receptor subtypes expressed in NIH 3T3 cells, kindly supplied by Dr. S. M. Reppert (Harvard Medical School, Boston, MA). The biological activity of the analogues was assessed in a well established, specific model of melatonin action, the pigment aggregation response of *X. laevis* melanophores.[1] In these cells, melatonin triggers a translocation of pigment, normally distributed throughout the cell, towards the cell centre. This response is termed pigment aggregation and is quantified by measuring the change in light (630 nm) absorbance of the cells as the pigment concentrates near the cell centre. In the present study, a clonal melanophore line, generously provided by Dr. Michael Lerner (Department of Dermatology, University of Texas), was used.

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