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Bioorganic & Medicinal Chemistry 12 (2004) 4601–4611
Bioorganic & Medicinal Chemistry

Chronobiotic activity of *N*-[2-(2,7-dimethoxyfluoren-9-yl)ethyl]-propanamide. Synthesis and melatonergic pharmacology of fluoren-9-ylethyl amides

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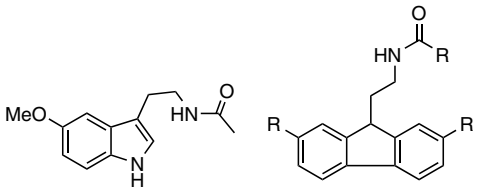
Received 20 January 2004; revised 29 June 2004; accepted 1 July 2004

Abstract—A series of fluoren-9-yl ethyl amides (**2**) were synthesized and evaluated for human melatonin MT_1 and MT_2 receptor binding. *N*-[2-(2,7-dimethoxyfluoren-9-yl)ethyl]propanamide (**2b**) was selected and evaluated in functional assays measuring intrinsic activity at the human MT_1 and MT_2 receptors and demonstrated full agonism at both receptors. The chronobiotic properties of **2b** were demonstrated in both acute and chronic rat models where **2b** produced an acute phase advance of 32 min at 1 mg/kg and chronically entrained free-running rats with a mean effective dose of 0.23 mg/kg. Compound **2b** is significantly less efficacious than melatonin in constricting human coronary artery.

1. Introduction

Melatonin (**1**) is a neurohormone secreted primarily by the pineal gland and involved in the regulation of circadian[1] and photoperiodic[2] information. Melatonin levels show a cyclical pattern—high at night and low during the day.[3] Melatonin exerts its effect, in part, through specific G-protein coupled receptors.[4] These receptors include the human MT_1 and MT_2 receptors, which have been cloned.[5,6] The MT_1 and MT_2 receptors are found in different parts of the brain including the suprachiasmatic nucleus (SCN), the site of the biological clock.[7] The most noted physiological effect of melatonin is on the sleep/wake cycle, and the roles of these receptors on chronobiotic behavior are being pursued.[8] The chronobiotic effects of melatonin have led to a number of potential therapeutic targets[9] including jet lag,[10] work shift disturbances,[11] seasonal affective disorder,[12] delayed sleep phase syndrome,[13] and age related alterations of the biological clock.[14] Maintenance of a suitable melatonin rhythm is felt to be important in promoting normal sleep patterns, and melatonin receptor agonists may prove effective in the treatment of certain sleep disorders.

Because the MT_1 receptor has high levels of expression in the SCN,[15] we originally postulated that chronobiotic properties would reside with this receptor subtype. More recent evidence implicates the MT_2 receptor for chronobiotic properties.[16] However, at the time this research was conducted, our goals were to evaluate compounds that had potent binding at both receptors. We now report a series of novel fluoren-9-yl ethyl amides (**2**) possessing potent affinity at both human MT_1 and MT_2



1 *Melatonin* **2**

Keywords: Melatonin; Chronobiotic.
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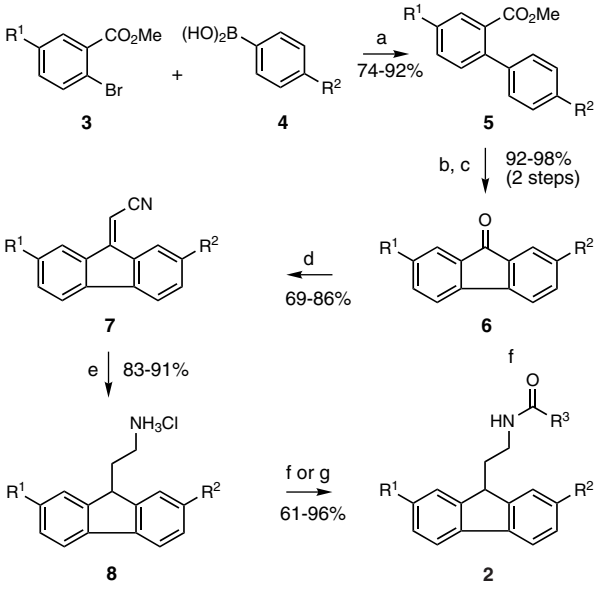
doi:10.1016/j.bmc.2004.07.002

receptors. From this group of compounds, *N*-[2-(2,7-dimethoxyfluoren-9-yl)ethyl]propanamide (**2b**) was selected for further evaluation in acute and chronic rat models and demonstrated chronobiotic efficacy comparable to melatonin in both models.

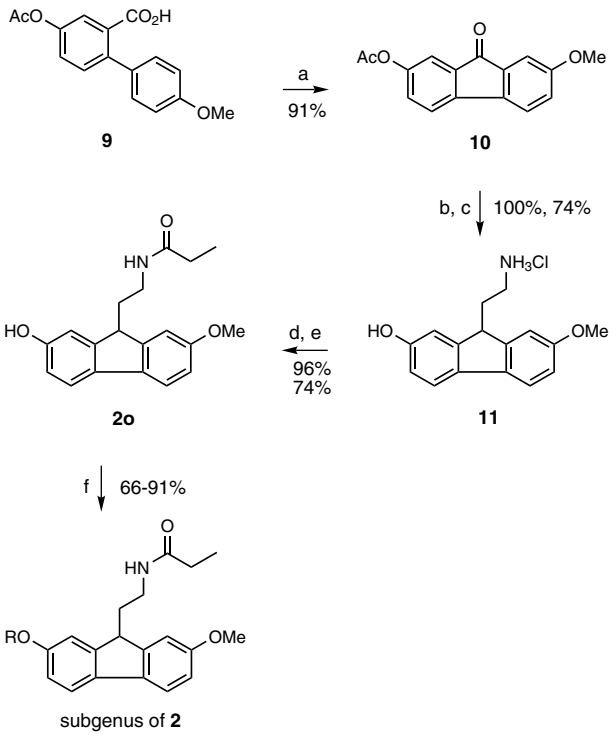
2. Results and discussion

The syntheses of the 2,7-disubstituted fluorenyl compounds described below were simplified as a result of their symmetrical nature. The concise and general synthesis of **2** lent itself to modifying the 2- and 7-positions. Compound **2b** serves as an example of the synthesis (Scheme 1, where R^1 and R^2 are methoxy). Other compounds in this series were prepared using this synthesis starting from appropriate aryl halides **3** and aryl boronic acids **4**, which were purchased or prepared by literature methods. An additional series of compounds were made from 2-hydroxy-7-methoxy amide **2o** by alkylating the phenolic moiety with a series of agents (Scheme 2).

The synthesis of **2b** began with the Suzuki coupling[17] of methyl 2-bromo-5-methoxy benzoate[18] (**3**) with commercially available 4-methoxyphenylboronic acid (**4**) in 84% yield. Whereas palladium acetate and tetrakistriphenylphosphine palladium failed to effect complete conversion to the biphenyl compound, palladium dibenzylideneacetone proved to be an effective catalyst for this reaction. Ester **5** was then hydrolyzed, and the resulting acid was cyclized by intramolecular Friedel–Crafts acylation in refluxing thionyl chloride to provide 2,7-dimethoxyfluorenone (**6**) in 98% yield. Thus, the symmetry of **4** removed all regiochemical issues related to the Friedel–Crafts cyclization to **6**. Horner–Emmons olefination[19] of **6** using diethyl cyanomethylphosphonate was accomplished in 79% yield followed by acidic



Scheme 1. Reaction conditions: (a) Pd_2dba_3, 2 M Na_2CO_3, DME, 85 °C, 16 h; (b) 1 N NaOH, EtOH, 78 °C; (c) $SOCl_2$, 79 °C; (d) $NCCH_2PO(OEt)_2$, NAH, THF; (e) H_2, PtO_2, $CHCl_3$, EtOH; (f) RCOCl or $(RCO)_2O$, cat. DMAP, TEA, CH_2Cl_2; (g) RNCO, CH_2Cl_2.



Scheme 2. Reaction conditions: (a) $SOCl_2$, $AlCl_3$; (b) $NCCH_2PO(OEt)_2$, NaH, DMF; (c) H_2, Pd(C), $CHCl_3$, EtOH; (d) RCOCl, TEA, cat. DMAP, CH_2Cl_2; (e) 1 N NaOH, MeOH; (f) RI or RBr, K_2CO_3, MeCN.

hydrogenation[20] of the olefin and nitrile moieties of **7** to yield amine hydrochloride **8** in 91% yield. Subsequent acylation was accomplished in 60% yield and generated **2b** in 43% overall yield for the entire sequence. The synthetic procedure proceeded with sufficient purity for the preparation of 300 g of **2b** to be completed with only one purification step—flash chromatography of the final product.

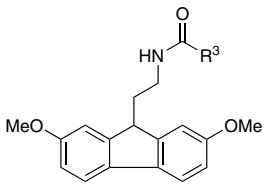
An additional method of preparing certain amides is shown in Scheme 2. Acetoxymethoxy biphenyl **9**[21] was transformed into fluorene **11** using the methods described above. The acidic nature of the hydrogenation reaction leading from **10** to amine **11** resulted in the loss of the phenolic acetyl group of **10**. Because of this exposed phenol moiety, amine **11** was diacylated and the acyloxy intermediate was saponified to give amide **2o**. Amide **2o** was then alkylated to give additional compounds of structure **2**.

2.1. Melatonin receptor pharmacology

Compounds were assayed for human melatonin MT_1 and MT_2 receptor binding using published methods.[6] Binding data are shown in Tables 1 and 2.

Variation of the *N*-acyl group was explored in dimethoxy compounds **2a**–**l** (Table 1). Although there was perhaps a slight trend toward better MT_2 binding, overall the compounds of this series were nonselective ligands. Compounds **2a**–**c** and **2g**–**h** exhibited potent binding affinity at both human MT_1 and MT_2 receptors. The

Table 1. Melatonin receptor binding affinities for compounds **2a–l**



Compound	R^3	MT_1 K_i (nM)	MT_2 K_i (nM)
2a	Me	2.3	0.55
2b	Et	2.0	0.28
2c	*n*-Pr	1.9	0.29
2d	*n*-Bu	140	10
2e	*i*-Pr	33	2.3
2f	*t*-Bu	59	16
2g	*c*-Pr	4.1	0.47
2h	*c*-Bu	3.3	4.4
2i	*c*-Pentyl	150	37
2j	CH_2OMe	28	0.96
2k	CH_2Cl	2.6	0.38
2l	NHEt	350	14
Melatonin		0.40	0.30

K_i values are the mean of at least three separate determinations run at five different concentrations with radioligand at the K_d concentration. Standard errors were typically ±20% of the mean value.

acetamide, propanamide, and butyramide were equipotent, while the valeramide had significantly less binding affinity (examples **2a–d**). These small linear amides also demonstrated greater affinity than small branched amides (examples **2e** and **2f**). Cyclopropyl and cyclobutyl amides **2g** and **2h** showed potent affinity, while cyclopentyl amide **2i** had modest affinity. Chloroacetyl compound **2k** had good affinity while methoxy acetamide **2j** demonstrated good binding only at the MT_2 receptor. *N*-Ethyl urea **2l** also showed some selectivity for the MT_2 receptor, although affinity at both receptors was attenuated.

Variation at the 2- and 7-positions of the fluorene was explored in compounds **2m–dd** (Table 2). When the 2- and 7-positions are differentially substituted, as in **2n**, the C-9 carbon becomes chiral. Thus, many of the compounds in Table 2 are chiral. Because of the good binding affinity of racemic **2n**, the enantiomers were separated by chiral chromatography and separately evaluated. However, other compounds were evaluated as racemic mixtures.

The importance of having at least one methoxy group was demonstrated in compounds **2m** and (−)-**2n**. Compound **2m** was significantly less potent than **2b**, while (−)-**2n** was equipotent to **2b**. The MT_1 binding affinity of the enantiomers of **2n** resided predominantly in the (−)-isomer, while both enantiomers were potent at the MT_2 receptor. Diethoxy compound **2p** had potent MT_2 binding and significantly less MT_1 affinity. Transforming one or both of the methoxy groups into hydroxy groups at the 2- and 7-positions decreased affinity (**2o** and **2cc**). Interestingly, as long as one methoxy group was intact in the 2-position, the 7-position could be substituted with a variety of large ethers and still retained relatively good binding affinity, while symmetrically dialkylated compounds with long ethers were inactive (**2v**). Dialkylated ethers terminated by amines were likewise inactive (**2w** and **2x**). Mono ester **2y** had moderate MT_2 affinity with little MT_1 affinity, while mono acid **2z** was inactive at both receptors. Mono fluoro compound **2aa** had good MT_2 affinity and moderate MT_1 affinity, while difluoro compound **2bb** had decreased MT_2 affinity and lost most affinity at the MT_1 receptor. Compounds **2aa** and **2bb** again highlight the importance of having one methoxy group at the 2- or 7-position.

The necessity for having at least one methoxy group in the 2- or 7-position in the preceding compounds gives rise to a pharmacophore that is isosteric to melatonin. The role of the remaining aryl ring was less clear. The size and variety of substituents that could be tolerated on this ring suggests that there is little real interaction with the MT_1 or MT_2 receptor binding site.

These binding studies suggested further evaluation of a compound for functional and chronobiotic activity, and we selected compound **2b**. While (−)-**2n** showed similar activity to compound **2b**, it offered no advantage due to the added complexity of the chiral center. Compound **2b**, on the other hand, benefited from its symmetry and synthetic simplicity.

2.2. Functional activity of 2b

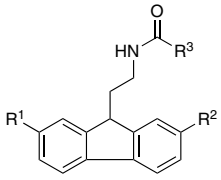
Melatonin and **2b** were evaluated for functional activity in adenyl cyclase assays[22] (Fig. 1). Melatonin induced a concentration-dependent decrease in forskolin-stimulated cAMP accumulation in NIH-3T3 cells stably expressing either MT_1 or MT_2 receptors (MT_1 $EC_{50} = 0.80 \pm 0.19$ nM and MT_2 $EC_{50} = 2.06 \pm 1.12$ nM). Compound **2b** also demonstrated full agonism and similar potency at the MT_1 and MT_2 receptors (MT_1 $EC_{50} = 0.85 \pm 0.25$ nM and MT_2 $EC_{50} = 0.64 \pm 0.28$ nM). Data shown is a composite of three separate experiments each performed in duplicate.

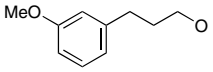
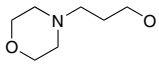
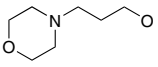
2.3. Chronobiotic activity of 2b

In order to validate rat in vivo studies, **2b** was further evaluated in binding studies with rat melatonin receptors. Compound **2b** bound to the rat MT_1 receptor with a $K_i = 1.70$ nM and to the rat MT_2 receptor with a $K_i = 0.26$ nM. Thus, **2b** binds to both human and rat receptors with similar affinity and in a nonselective manner.

The chronobiotic properties of **2b** were assessed in rats using both an acute treatment paradigm and a chronic administration paradigm.[23] In the acute model, a single injection of **2b**, melatonin, or vehicle was administered approximately 2 h before the expected onset of activity in free-running rats maintained in constant darkness. Compound **2b** dose-dependently produced a phase advance in the onset of wheel activity. The phase advance at 1 mg/kg was 32 min (Fig. 2). Melatonin (1 mg/kg) produced a similar phase advance of 28 min. Vehicle gave no phase advance.

Table 2. Melatonin receptor binding affinities for compounds **2m-dd**



Compound	R^1	R^2	R^3	MT_1 K_i (nM)	MT_2 K_i (nM)
Melatonin				0.40	0.30
2b	MeO	MeO	Et	2.0	0.28
2m	H	H	nPr	66	6.4
(−)-**2n**	MeO	H	Et	2.5	0.50
(+)-**2n**	MeO	H	Et	42	2.7
2o	MeO	HO	Et	83	29
2p	EtO	EtO	Et	150	2.1
2q	MeO	$CH_3(CH_2)_4O$	Et	5.5	4.8
2r	MeO	$CH_3(CH_2)_{10}O$	Et	7.9	7.1
2s	MeO		Et	3.8	17
2t	MeO	$PhCH_2CH_2O$	Et	47	27
2u	MeO	$Ph(CH_2)_3O$	Et	3.5	13
2v	$Ph(CH_2)_6O$	$Ph(CH_2)_6O$	Et	>500	>500
2w	$Et_2NCH_2CH_2O$	$Et_2NCH_2CH_2O$	Et	>500	>500
2x			Et	>500	>500
2y	MeO	MeO_2CCH_2O	Et	290	13
2z	MeO	HO_2CCH_2O	Et	>500	140
2aa	MeO	F	Et	15	1.8
2bb	F	F	Et	200	11
2cc	HO	HO	Et	>500	>500
2dd	AcO	AcO	Et	>500	96

K_i values are the mean of at least three separate determinations run at five different concentrations with radioligand at the K_d concentration. Standard errors were typically 20% of the mean value.

Compound **2b** was also assessed in a chronic entrainment animal model. Rats were maintained in a 12 h light–dark cycle until a reliable pattern was established between the onset of darkness and the onset of running wheel activity. The rats were then maintained in constant darkness to allow each animal's endogenous activity-rest cycle to be expressed. In the rat, this is typically longer than 24 h. The animals then received **2b** (a dose ranging from 0.01 to 1.0 mg/kg), melatonin (1 mg/kg), or vehicle at the same time of day for 39 consecutive days. Animals entrained to **2b** (for 1 mg/kg, $n = 10$ and 8 animals became entrained) and melatonin ($n = 9$), while no animals entrained to vehicle ($n = 7$). The median effective dose for **2b** was 0.23 mg/kg. Entrainment occurred when the time of administration coincided with the onset of activity. Examples of actograms from three different rats are shown in Figure 3. In these actograms, each horizontal line represents one 24 h period that is double-plotted (the 24 h period is repeated) for ease of viewing. Day one is the top line and day 39 is the bottom line. Dark areas of each line represent activity and light areas represent the absence of activity. The vertical bar represents the administration of compound or vehicle. In the first actogram, no effect was seen in the animal's activity-rest cycle when vehicle was administered. In the second and third actograms, the animals entrained to the administration of compound. In the second actogram one can clearly see the entrainment occurred when the administration was at the onset of activity.

2.4. Vascular effects of 2b

Melatonin mediates vasoconstriction in human coronary artery preconstricted with KCl.[24] The ability to constrict vascular smooth muscle, particularly human coronary artery, would be undesirable in any melatonergic clinical candidate. Preliminary evaluation in human coronary artery showed **2b** to be less efficacious than melatonin (Fig. 4). The E_{max} for **2b** was 0.23 g ($n = 8$ rings from 1 donor) while the E_{max} for melatonin was 0.83 g ($n = 28$ from 3 donors). This data correlated with in-house data from pig coronary artery, rat cerebral artery, and rat caudal artery. In all models, the efficacy of **2b** was significantly less than melatonin.

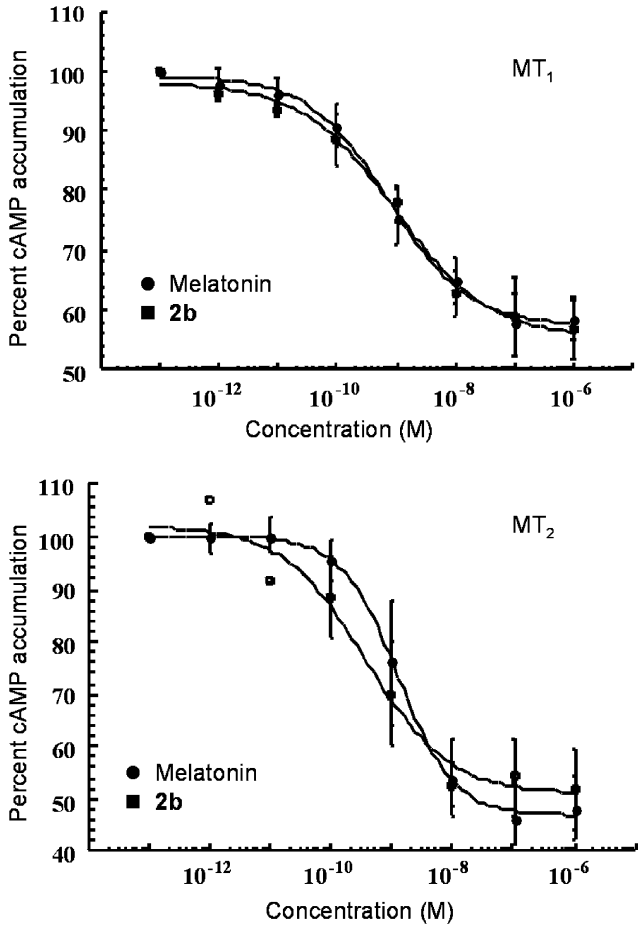


Figure 1. The effect of melatonin and **2b** on forskolin-stimulated cyclic AMP accumulation in NIH-3T3 cells stably expressing the human MT_1 or MT_2 receptor. Data shown is a composite of three separate experiments each performed in duplicate. Nonlinear regression analysis yielded EC_{50} values of 0.80 ± 0.19 and 0.85 ± 0.25 nM and E_{max} values (% inhibition) of 42 ± 5 and 44 ± 4 for melatonin and **2b**, respectively, at the MT_1 receptor and EC_{50} values of 2.06 ± 1.12 and 0.64 ± 0.28 nM and E_{max} values (% inhibition) of 52 ± 6 and 50 ± 3 for melatonin and **2b**, respectively, at the MT_2 receptor.

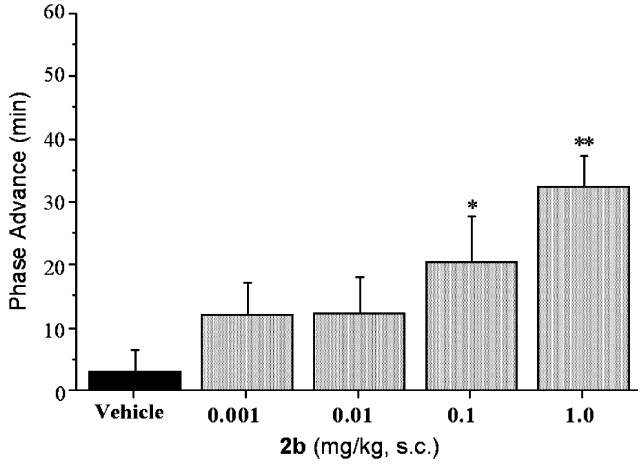


Figure 2. Acute effects of **2b** on circadian phase advance. Mean phase advance of running wheel activity rhythm onset after a single injection of **2b** or vehicle.

3. Conclusion

We have discovered a series of fluorenes, which are potent melatonergic ligands. Small linear and cyclic amides in the series demonstrate potent binding at both human MT_1 and MT_2 receptors. Compound **2b** was shown to be an agonist at both human MT_1 and MT_2 receptors. Compound **2b** was effective in both acute and chronic rat models on a level comparable to melatonin. In acute rat studies, compound **2b** produced an acute phase advance of 32 min at 1 mg/kg. In chronic studies, compound **2b** entrained free-running rats with a mean effective dose of 0.23 mg/kg. In contrast to chronobiotic activity, compound **2b** is distinguished from melatonin by being significantly less efficacious at constricting human coronary artery, an important criteria for any clinical candidate.

4. Experimental

4.1. General

Unless otherwise stated, all reagents were used from the commercial sources without further purification. Chromatographic purification was by way of flash chromatography unless otherwise stated. Melting points are uncorrected. NMR data was collected on a Bruker AC-300 spectrometer and are reported conventionally.

4.2. 4,4′-Dimethoxy-[1,1′-biphenyl]-2-carboxylic acid, methyl ester (5b)

Methyl 2-bromo-5-methoxybenzoate (1.60 g, 6.53 mmol), 4-methoxyphenylboronic acid (1.30 g, 8.55 mmol), and tris(dibenzylideneacetone)dipalladium (0) (0.20 g, 0.22 mmol) were added to dimethoxyethane (25 mL) and 2 M sodium carbonate (25 mL). The suspension was stirred at reflux for 16 h at which time TLC analysis indicated the reaction was complete. The reaction mixture was filtered and extracted with ethyl acetate. The combined organic extracts were dried and the solvent removed by rotary evaporation to afford 1.50 g (84%) of **5b**, mp 55–56 °C. ^{1}H NMR ($CDCl_3$) δ 7.30–7.27 (m, 2H), 7.19 (d, $J = 6.6$ Hz, 2H), 7.04 (dd, $J = 8.5$, 2.8 Hz, 1H), 6.90 (d, $J = 6.6$ Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 158.7, 158.4, 134.6, 133.4, 131.9, 131.6, 129.5, 117.5, 114.3, 113.5, 55.6, 55.3, 52.1. Anal. ($C_{16}H_{16}O_4$) C, H.

4.3. 2,7-Dimethoxy-9*H*-fluoren-9-one (6b)

Ester **5b** (10.80 g, 39.70 mmol) was hydrolyzed with 1 N sodium hydroxide (80 mL) in refluxing ethanol (500 mL). The cooled reaction mixture was extracted with methylene chloride and acidified with 1 N hydrochloric acid. The acidic solution was then extracted with methylene chloride. The organic extracts were combined, dried with magnesium sulfate, and filtered. The filtrate was concentrated by rotary evaporation to give 9.00 g (88%) of the acid.

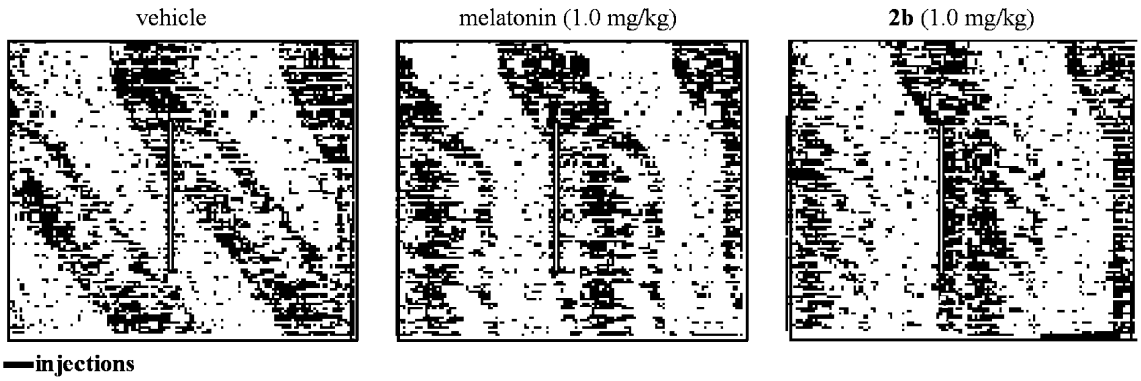


Figure 3. Entrainment of rats given chronic injections of vehicle, melatonin, or **2b**. Each actogram represents the results for one animal. Each horizontal line of an actogram represents a 24 period (double-plotted for ease of viewing). Day 1 is the top line and day 39 is the bottom line. The dark areas of a given line represent animal activity. The vertical bar represents the time of injection.

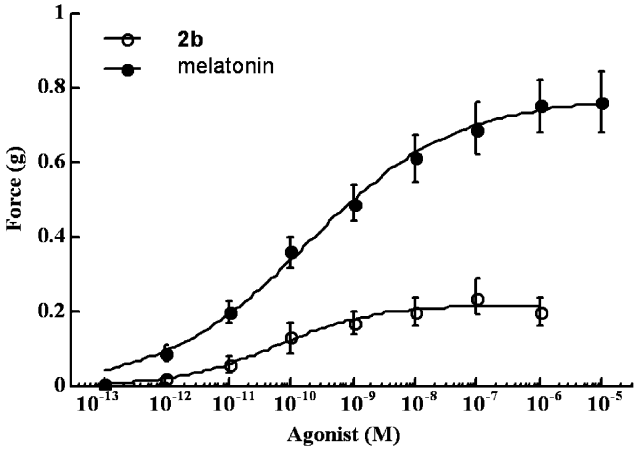


Figure 4. The effect of melatonin ($n = 28$ rings from three donors) and **2b** ($n = 8$ rings from one donor) on human coronary artery precontracted with 30 mM KCl. Nonlinear regression analysis yielded an $E_{max} = 0.83 \pm 0.07$ g for melatonin and $E_{max} = 0.23 \pm 0.04$ for **2b**.

9.00 g (34.88 mmol) of the acid was dissolved in thionyl chloride (250 mL) and stirred at reflux for 6 h at which time TLC analysis indicated the reaction was complete. The solution was cooled and the solvent removed by rotary evaporation to give 8.20 g (98%) of **6b** as a red solid, mp 116–118 °C. ^{1}H NMR ($CDCl_3$) δ 7.22 (d, $J = 6.6$ Hz, 2H), 7.17 (d, $J = 2.8$ Hz, 2H), 6.89 (dd, $J = 8.5$, 2.8 Hz, 1H).

4.4. (2,7-Dimethoxy-9*H*-fluoren-9-ylidene)acetonitrile (7b)

Diethyl cyanomethylphosphonate (7.43 g, 0.042 mol) was slowly added to a suspension of NaH (1.61 g, 0.067 mol) in THF (200 mL) at room temperature. The reaction was stirred for 15 min and the solution turned pale yellow. A solution of **6b** (8.89 g, 0.042 mol) in THF (100 mL) was added dropwise and the reaction was stirred for 16 h. The solvent was removed in vacuo and the residue dissolved in methylene chloride. The organic solution was washed with water, dried over magnesium sulfate, and concentrated to produce an orange solid. This residue was dissolved in acetonitrile and washed with hexane and concentrated by rotary evaporation to produce 8.76 g (79%) of **7b** as an orange semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, $J = 2.1$ Hz, 1H), 7.32 (dd, $J = 6.7$, 2.1 Hz, 2H), 7.03 (d, $J = 2.3$ Hz, 1H), 6.89 (dd, $J = 6.7$, 2.3 Hz, 2H), 5.99 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H); MS (DCI) $MH^+ = 264$.

4.5. 2-(2,7-Dimethoxy-9*H*-fluoren-9-yl)ethylamine (8b)

A suspension of **7b** (7.72 g, 0.033 mol), PtO_2 (0.77 g), $CHCl_3$ (23 mL), in EtOH (150 mL) was hydrogenated on a Parr shaker (50 psi) for 18 h. The mixture was filtered and the filtrate concentrated to afford a white solid. The solid was washed with ether and dried in vacuo to obtain 6.94 g (69%) of **8b** as a white solid. This crude solid was used directly in subsequent acylations.

4.6. General procedure for acylating amine 8a

A solution of **8a** (1 equiv), triethylamine (2.2 equiv), and DMAP (1 equiv) in methylene chloride was cooled to 0 °C and the appropriate acid chloride (1.1 equiv) was slowly added. The reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with 1 N HCl and extracted with methylene chloride. The organic layers were washed with 1 N HCl, 10% $NaHCO_3$, satd NaCl, dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography.

4.7. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]acetamide (2a)

Prepared from **8a** according to the general procedure using acetyl chloride. Compound **2a** was obtained as a white solid (79%), mp 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.3$ Hz, 2H), 7.01 (d, $J = 2.1$ Hz, 2H), 6.89 (d, $J = 2.3$ Hz, 1H), 6.85 (d, $J = 2.3$ Hz, 1H), 4.94 (s, 1H), 3.97 (t, $J = 5.1$ Hz, 1H), 3.83 (s, 6H), 3.02 (q, $J = 6.6$ Hz, 2H), 2.27 (q, $J = 6.6$ Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 158.7, 147.6, 133.9, 119.9, 113.1, 110.1, 55.6, 45.6, 36.2, 31.8, 22.9; IR (KBr) 3268, 1646, 1574, 1240 cm^{-1}; MS (DCI) $MH^+ = 312$; Anal. ($C_{19}H_{21}N_1O_3$) C, H, N.

4.8. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]propanamide (2b)

Prepared from **8a** according to the general procedure using propanoyl chloride. Compound **2b** was obtained as a white solid (60%), mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.3 Hz, 2H), 7.06 (d, 2H), 6.88 (d, J = 2.3, 1H), 6.85 (d, J = 2.3, 1H), 4.87 (s, 1H), 3.98 (t, J = 5.1 Hz, 1H), 3.83 (s, 6H), 3.04 (q, J = 6.5 Hz, 2H), 2.29 (q, J = 6.6 Hz, 2H), 1.96–1.82 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 158.8, 147.7, 133.9, 119.9, 113.0, 110.1, 55.6, 45.7, 36.1, 31.9, 29.5, 9.49; IR (KBr) 3260, 1640, 1240 cm^{-1}; MS (DCI) MH^+ = 326; Anal. ($C_{20}H_{23}N_1O_3$) C, H, N.

4.9. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]butanamide (2c)

Prepared from **8a** according to the general procedure using butyryl chloride. Compound **2c** was obtained as a white solid (74%), mp 126–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 2.1 Hz, 2H), 6.90 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 23 Hz, 1H), 4.92 (br s, 1H), 3.99 (t, J = 5.1 Hz, 1H), 3.85 (s, 6H), 3.07 (q, J = 6.7 Hz, 2H), 2.30 (q, J = 6.7 Hz, 2H), 1.84 (t, J = 7.2 Hz, 2H), 1.51–1.38 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 158.7, 147.6, 133.9, 119.9, 113.0, 110.2, 55.6, 45.6, 38.5, 36.0, 32.0, 28.7, 18.9, 13.7, 4.8; IR (KBr) 3300, 1634, 1540, 804 cm^{-1}; MS (DCI) MH^+ = 340; Anal. ($C_{21}H_{25}N_1O_3$) C, H, N.

4.10. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]-pentanamide (2d)

Prepared from **8a** by the general procedure using valeroyl chloride. Compound **2d** was obtained as a white solid (66%), mp 130–131 °C. IR (KBr) 3306, 1634, 1540, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 1.8 Hz, 2H), 6.89 (dd, J = 8.3, 2.1 Hz, 2H), 4.94 (br s, 1H), 4.01–3.48 (m, 1H), 3.85 (s, 6H), 3.10–3.03 (m, 2H), 2.33–2.27 (m, 2H), 1.86 (t, J = 7.3 Hz, 2H), 1.40 (pent, J = 6.8 Hz, 2H), 1.23 (sex, J = 6.9 Hz, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 158.7, 147.6, 133.9, 119.8, 113.0, 110.2, 55.5, 45.6, 36.3, 36.1, 31.9, 27.5, 22.3, 13.6. MS (ESI) $M-H^+$ = 354. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4.11. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]-2-methylpropanamide (2e)

Prepared from **8a** by the general procedure using isobutyryl chloride. Compound **2e** was obtained as a white solid (57%), mp 144–145 °C. IR (KBr) 3324, 1646, 1554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.04 (m, 2H), 6.89 (dd, J = 8.3, 2.2 Hz, 2H), 4.96 (br s, 1H), 4.01 (m, 1H), 3.85 (s, 6H), 3.10–3.03 (m, 2H), 2.02 (pent, J = 6.8 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 158.7, 147.6, 133.9, 119.9, 113.0, 110.2, 55.5, 45.6, 36.0, 35.4, 32.6, 19.3. MS (ESI) $M-H^+$ = 340. Anal. ($C_{21}H_{25}NO_3$) C, H, N.

4.12. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]-2,2-dimethylpropanamide (2f)

Prepared from **8a** by the general procedure using pivaloyl chloride. Compound **2f** was obtained as a white solid (51%), mp 88–89 °C. IR (KBr) 1628, 1528 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 2.0 Hz, 2H), 6.85 (dd, J = 8.3, 2.4 Hz, 2H), 5.11 (br s, 1H), 4.00–3.97 (m,1H), 3.83 (s, 6H), 3.06–3.00 (m, 2H), 2.34–2.28 (m, 2H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.0, 158.8, 147.6, 133.9, 119.9, 113.0, 110.3, 55.5, 45.5, 38.3, 36.2, 31.7, 27.2. MS (ESI) $M-H^+$ = 354. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4.13. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]cyclopropane carboxamide (2g)

Prepared from **8a** according to the general procedure using cyclopropanecarbonyl chloride. Compound **2g** was obtained as a viscous oil (65%), mp 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 87.52 (d, J = 8.30 Hz, 2H), 7.02 (s, 2H), 6.08 (d, J = 2 Hz, 1H), 6.85 (d, J = 2 Hz, 1H), 5.05 (br s, 1H), 3.98 (t, J = 5.1 Hz, 1H), 3.83 (s, 6H), 3.06 (q, J = 6 Hz, 2H), 2.28 (q, J = 6.6 Hz, 2H), 0.95–0.08 (m, 1H), 0.81–0.78 (m, 2H), 0.60–0.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 158.7, 147.7, 134.0, 119.8, 113.1, 110.1, 55.5, 45.7, 36.3, 32.1, 14.5, 6.8; IR (KBr) 3300, 1640, 1240, 1030, 800 cm^{-1}; MS (DCI) MH^+ = 338. Anal. ($C_{21}H_{23}N_1O_3 \cdot 0.5H_2O$) C, H, N.

4.14. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]cyclobutane carboxamide (2h)

Prepared from **8a** by the general procedure using cyclobutanecarbonyl chloride. Compound **2h** was obtained as a white solid (61%), mp 145–146 °C. IR (KBr) 3310, 1632, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 7.0 Hz, 2H), 6.88 (dd, J = 8.3, 2.4 Hz, 2H), 4.80 (br s, 1H), 3.98 (t, J = 7.0 Hz, 1H), 3.83 (s, 6H), 3.04–3.02 (m, 2H), 2.62 (pent, J = 8.5 Hz, 1H), 2.30–2.29 (m, 2H), 1.98–1.94 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.5, 158.7, 147.6, 133.9, 119.9, 113.1, 110.1, 55.5, 45.7, 39.7, 36.6, 31.9, 25.1, 17.4. MS (ESI) $M-H^+$ = 352. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

4.15. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]cyclopentane carboxamide (2i)

Prepared from **8a** by the general procedure using cyclopentanecarbonyl chloride. Compound **2i** was obtained as viscous oil (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 2.3 Hz, 2H), 6.87 (dd, J = 8.3, 2.3 Hz, 2H), 5.0 (br s, 1H), 3.97 (t, J = 5.1 Hz, 1H), 3.83 (s, 6H), 3.06 (q, J = 6.1 Hz, 2H), 2.27 (q, J = 6.6 Hz, 2H), 2.13 (m, 1H), 1.57 (m, 8H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 158.6, 147.6, 133.8, 119.8, 112.9, 110.1, 55.4, 45.7, 45.5, 36.0, 32.0, 30.0, 25.7; Anal. ($C_{23}H_{27}N_1O_3$) C, H, N.

4.16. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]methoxyacetamide (2j)

Prepared from **8a** according to the general procedure using methoxyacetyl chloride. Compound **2j** was obtained as viscous oil (74%), mp 94–95 °C. ^{1}H NMR (300 MHz, CDCl3) δ 7.52 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 2.1 Hz, 2H), 6.89 (d, J = 2.3 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 4.94 (s, 1H), 3.97 (t, J = 5.1 Hz, 1H), 3.83 (s, 6H), 3.02 (q, J = 6.6 Hz, 2H), 2.27 (q, J = 6.7 Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 158.7, 147.4, 133.9, 119.9, 113.1, 110.1, 71.8, 58.9, 55.6, 45.6, 35.4, 32.1, 7.7; IR (KBr) 3298, 1646, 1574, 1240 cm^{-1}; MS (DCI) MH^+ = 312. Anal. ($C_{20}H_{23}N_1O_4$) C, H, N.

4.17. *N*-[2-(2,7-Dimethoxyfluoren-9-yl)ethyl]-2-chloroacetamide (2k)

Prepared by the from **8a** general procedure using chloroacetyl chloride. Compound **2k** was obtained as a white solid (62%), mp 122–123 °C. IR (KBr) 1640, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 2.0 Hz, 2H), 6.88 (dd, J = 8.3, 2.2 Hz, 2H), 6.04 (br s, 1H), 4.02–3.94 (m, 1H), 3.84 (s, 6H), 3.77 (s, 2H), 3.09–3.02 (m, 2H), 2.39–2.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 165.5, 158.8, 147.2, 134.0, 120.0, 113.1, 110.1, 55.5, 45.5, 42.3, 36.3, 31.3. MS (ESI) $M-H^-$ 344. LC retention time 10.9 min (45% MeCN/H_2O, no buffer, 1.5 mL/min C-18 Zorbax).

4.18. *N*-[2-(2,7-Dimethoxy-9*H*-fluoren-9-yl)ethyl]-*N*′-ethylurea (2l)

Ethyl isocyanate (25 mg, 0.35 mmol) was slowly added to a suspension of **8b** (100 mg, 0.33 mmol) in methylene chloride at 0 °C. The reaction was allowed to warm to room temperature, quenched with 1 N HCl, and extracted with methylene chloride. The organic extracts were washed with solutions of 10% $NaHCO_3$ and satd NaCl, dried with magnesium sulfate, and concentrated by rotary evaporation. The crude product was purified by flash chromatography to afford 115 mg (93%) of **2l** as a tan solid, mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.01 (m, 2H), 6.86 (dd, J = 9.0, 2.1 Hz, 2H), 3.98 (t, J = 5 Hz, 1H), 3.38 (s, 6H), 2.97–2.90 (m, 4H), 2.27 (dt, J = 6.3, 5.7 Hz, 2H), 1.00 (t, J = 8.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.74, 157.85, 147.88, 133.90, 119.84, 113.01, 110.12, 55.55, 45.62, 37.08, 35.21, 32.66, 15.24; IR (KBr) 1628, 1578, 1242, 1028 cm^{-1}; MS (DCI) MH^+ = 341. Anal. ($C_{20}H_{24}N_2O_3 \cdot 0.07H_20$) C, H, N.

4.19. *N*-[2-(9*H*-Fluoren-9-yl)ethyl]propanamide (2m)

Prepared from commercially available fluorenone by the methods used for **2b**, mp 127–128 °C. MS (DCI) MH^+ = 280. Anal. ($C_{19}H_{21}NO$) C, H, N.

4.20. *N*-[2-(2-Methoxyfluoren-9-yl)ethyl]propanamide (2n)

Prepared using phenylboronic acid and employing the methods of Scheme 1. Separated by chiral HPLC (Chiracel OD-R, 4.6 mm × 25 cm, 0.7 mL/min at 0.5 kpsi using acetonitrile and water with a 0.5 M sodium perchlorate buffer). (−)-**2n**. Mp 117–119 °C; Retention time: 29.4 min; $[\alpha]_D$ −29.6; MS (DCI) MH^+ = 296. Anal. ($C_{19}H_{21}NO_2$) C, H, N. (+)-**2n**. Mp 118–120 °C; Retention time: 32.6 min; $[\alpha]_D$ 32.2; MS (DCI) MH^+ = 296. Anal. ($C_{19}H_{21}NO_2$) C, H, N.

4.21. *N*-[[(2,7-Diethoxy)-9-fluorenyl]ethyl]propanamide (2p)

Prepared in an analogous fashion to **2b** and obtained as a white solid, mp 125–128 °C. IR (KBr) 1644, 1550, 1236, 1048 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 5.4 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.08 (s, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.03 (q, J = 7.2 Hz, 4H), 3.87 (t, J = 5.7 Hz, 1H), 2.87 (q, J = 6.3 Hz, 2H), 1.99 (m, 4H), 1.32 (t, J = 6.9 Hz, 6H), 0.93 (t, J = 7.5 Hz, 3H); MS (ESI) MH^+ = 354. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4.22. 2-Acetoxy-7-methoxyfluoreneone (10)

A solution of acid **9** (3.20 g, 11.2 mmol) in thionyl chloride was stirred at reflux for 4 h. The solution was cooled to room temperature and concentrated in vacuo to afford a yellow residue. The residue was dissolved in dichloromethane and cautiously treated with aluminum chloride (1.50 g, 11.2 mmol). After stirring for 16 h, the reaction mixture was poured into a slurry of 1 N HCl and ice. The mixture was extracted with dichloromethane and the extracts dried over magnesium sulfate, filtered, concentrated by rotary evaporation. The crude product was purified by column chromatography (15% ethyl acetate/hexane) to afford 2.7 g (90%) of **10** as a red solid. ^{1}H NMR ($CDCl_3$): δ 7.33 (dd, J = 4.9, 1.4 Hz, 2H), 7.24 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 12.0, 2.5 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 8.2, 2.5 Hz, 1H), 3.78 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.7, 169.3, 160.8, 150.7, 142.3, 136.6, 136.2, 135.8, 127.5, 121.4, 120.6, 120.3, 118.2, 109.7, 55.8, 21.1; MS (DCI) MH^+ = 270. Anal. ($C_{16}H_{12}O_4 \cdot 0.25H_2O$) C, H.

4.23. 2-Hydroxy-7-methoxy-9-ethylaminofluorene hydrochloride (11)

Diethylcyanomethyl phosphate (1.57 mL, 9.69 mmol, 1.1 equiv) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 0.32 g, 9.69 mmol, 1.1 equiv) in THF at room temperature under nitrogen. After stirring 30 min, compound **10** (2.36 g, 8.81 mmol, 1 equiv) in THF was added dropwise. The reaction was stirred at room temperature for 16 h. The reaction mixture was quenched with water and extracted with ethyl ether. The extracts were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to give 2.85 g (quantitative yield) of the crude nitrile as a red-brown solid.

A suspension of the crude nitrile (21.5 g, 73.9 mmol) and 10% palladium on carbon (7.0 g) in absolute ethanol and chloroform (5:1) was hydrogenated on a Parr shaker at 45 psi. After 16 h at room temperature, the reaction mixture was filtered through Celite and concentrated in vacuo to an oil. The oil was dissolved in ethyl ether and extracted with 1 N HCl. The aqueous layer was concentrated to dryness to afford 1.84 g (7.5%) of an off-white solid, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 9.60 (s, 1H), 8.04 (br s, 2H), 7.57 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.08 (s, 1H), 6.93 (s, 1H), 6.88 (dd, J = 8.4, 2.3 Hz, 1H), 6.75 (dd, J = 8.4, 2.3 Hz, 1H), 3.90 (m, 1H), 3.78 (s, 3H), 2.40 (m, 2H), 2.26 (m, 2H); MS (DCI) M+H$^+$ = 256.

4.24. *N*-[2-(Hydroxy-7-methoxyfluoren-9-yl)]ethyl propanamide (2o)

A suspension of 2-hydroxy-7-methoxy-9-ethylaminofluorene hydrochloride (1.84 g, 6.30 mmol), triethylamine (2.2 mL, 15.8 mmol, 2.5 equiv), and dimethylaminopyridine (0.77 g, 6.30 mmol, 1 equiv) in anhydrous dichloromethane was stirred at room temperature for 15 min. Propionyl chloride (1.1 mL, 12.6 mmol, 2 equiv) was slowly added and the mixture was stirred for 16 h. The reaction mixture was acidified with 1 M HCl solution and extracted with dichloromethane. The extracts were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to give a brown oil. The crude oil was purified by column chromatography (2–5% methanol/dichloromethane) to give 1.12 g (48%) of a dipropionylated product as a yellow oil.

A solution of the dipropionylated product (1.0 g, 2.72 mmol) in methanol was saponified with 1 N sodium hydroxide at room temperature. After 30 min, the reaction mixture was acidified with 1 N HCl and extracted into ethyl acetate. The extracts were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to give 0.78 g (92%) obtained as a white foam, mp 38–42 °C. IR (KBr) 3294, 1642, 1540, 1210, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, J = 8.3, 2.8 Hz, 2H), 7.00 (m, 2H), 6.85 (dt, J = 8.4, 2.8 Hz, 2H), 5.01 (m, 1H), 3.94 (m, 1H), 3.84 (s, 3H), 3.07 (q, 2H), 2.35 (m, 1H), 2.23 (m, 1H), 1.91 (q, J = 7.6 Hz, 2H), 2.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 158.7, 155.8, 147.8, 147.5, 134.4, 133.1, 120.2, 119.8, 114.8, 112.9, 111.8, 110.3, 55.7, 45.5, 36.5, 31.7, 29.5, 9.6; MS (ESI) M−H$^+$ = 310.1. Anal. ($C_{19}H_{21}NO_3$·0.5H_2O) C, H, N.

4.25. General procedure for alkylating 2o

Acid chloride or alkylhalide (1 equiv) was slowly added to a suspension of **2o** (1 equiv) and potassium carbonate (1 equiv) in anhydrous acetonitrile at room temperature and the suspension was stirred for 16 h. The reaction was quenched with water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to give the products as oils (66–91%).

4.26. *N*-[2-Undecoxy-7-methoxyfluoren-9-yl]ethyl propanamide (2r)

Prepared from **2o** and obtained as a yellow solid, mp 91–94 °C. ^{1}H NMR ($CDCl_3$) δ 7.52 (dd, J = 8.3, 2.1 Hz, 2H), 7.01 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.85 (br s, 1H), 3.97 (m, 3H), 3.83 (s, 3H), 3.03 (q, 2H), 2.29 (q, J = 5.5 Hz, 2H), 1.85 (q, J = 7.7 Hz, 2H), 1.25 (br, 18H), 0.92 (t, J = 7.7 Hz, 3H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 158.8, 158.4, 147.7, 134.1, 133.8, 119.9, 113.7, 113.2, 110.9, 110.3, 68.5, 55.7, 45.8, 36.2, 32.0, 31.9, 29.7, 29.5, 29.4, 26.2, 22.8, 14.2, 9.6; MS (ESI) M−H$^+$ = 464. Anal. ($C_{30}H_{43}NO_3$·0.75-H_2O) C, H, N.

4.27. *N*-[2-(2-Methoxy-7-(3-(3-methoxyphenyl)propox-1-y))-fluoren-9-yl]ethyl propanamide (2s)

Prepared from **2o** and obtained as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 2H), 7.21 (t, J = 7.8 Hz, 2H), 7.03 (s, 2H), 6.91–6.73 (m, 4H), 4.92 (br s, 1H), 4.01 (m, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.06 (q, J = 6.2 Hz, 2H), 2.82 (t, J = 7.9 Hz, 2H), 2.28 (q, J = 6.6 Hz, 2H), 2.12 (p, J = 7.8 Hz, 2H) 1.89 (q, J = 7.6 Hz, 2H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 158.8, 158.1, 147.7, 143.2, 133.9, 130.4, 128.4, 120.9, 118.8, 114.7, 114.2, 112.5, 112.0, 111.2, 110.2, 109.9, 109.2, 67.3, 56.5, 54.2, 46.5, 36.1, 32.2, 31.9, 30.8, 29.4, 10.4, 8.7. Anal. ($C_{29}H_{33}N_1O_4$·0.67 H_2O) C, H, N.

4.28. *N*-[2-((2-Phenyl)ethoxy)-7-methoxy fluorene-9-yl] ethyl propanamide (2t)

Prepared from **2o** and obtained as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.47 (dd, J = 8.4, 3.0 Hz, 2H), 7.25 (m, 5H), 6.95 (m, 2H), 6.82 (dd, J = 8.4, 2.3 Hz, 2H), 4.82 (br, 1H), 4.15 (t, J = 7.2 Hz, 2H), 3.90 (m, 1H), 3.78 (s, 3H), 3.06 (t, J = 7.1 Hz, 2H), 2.97 (q, J = 6.2 Hz, 2H), 2.24 (q, J = 6.5 Hz, 2H), 1.80 (q, J = 7.7 Hz, 2H), 0.86 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 190.0, 173.4, 158.9, 158.1, 147.7, 138.3, 134.1, 134.0, 129.1, 128.6, 126.6, 120.0, 113.8, 113.2, 111.0, 110.3, 69.2, 55.7, 45.8, 36.2, 36.0, 31.9, 29.5, 9.5; MS (ESI) M−H$^+$ = 414. Anal. ($C_{27}H_{29}NO_3$·0.9H_2O) C, H, N.

4.29. *N*-[2-(2-(3-Phenyl-1-propanoxy))-7-methoxy fluorene-9-yl] ethyl propanamide (2u)

Prepared from **2o** and obtained as a white solid, mp 106–109 °C. ^{1}H NMR ($CDCl_3$) δ 7.47 (dd, J = 8.3, 2.7 Hz, 2H), 7.15 (m, 5H), 6.95 (s, 2H), 6.81 (m, 2H), 4.83 (br, 1H), 3.93 (m, 3H), 3.79 (s, 3H), 2.99 (q, J = 6.6 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.23 (q, J = 6.7 Hz, 2H), 2.04 (q, J = 6.4 Hz, 2H), 1.86 (q, J = 7.6 Hz, 2H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 193.2, 173.5, 158.843, 158.3, 147.8, 147.7, 141.6, 134.1, 134.0, 128.6, 128.5, 126.0, 120.0, 113.7, 113.2, 111.0, 110.3, 67.4, 55.7, 45.8, 36.2, 32.3, 31.9, 31.0, 29.5, 9.6; MS (ESI) M−H$^+$ = 428. Anal. ($C_{28}H_{31}NO_3$·0.5H_2O) C, H, N.

4.30. [[7-Methoxy-9-[2-[(1-oxopropyl)amino]ethyl]-9*H*-fluoren-2-yl]oxy]acetic acid,methyl ester (2y)

Prepared from **2o** and obtained as an off-white solid, mp 91–94 °C. ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.03 (dd, J = 7.9, 2.2 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.91 (br, 1H), 4.66 (s, 2H), 3.97 (t, J = 5.4 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.03 (q, J = 7.2 Hz, 2H), 2.29 (q, J = 6.1 Hz, 2H), 1.89 (q, J = 7.6 Hz, 2H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 169.5, 158.1, 157.0, 147.9, 147.8, 135.2, 133.7, 120.2, 120.0, 113.7, 113.3, 111.4, 110.2, 65.8, 55.6, 52.3, 45.7, 36.2, 32.0, 29.5, 9.6; MS (ESI) $M-H^+$ = 382. Anal. ($C_{22}H_{25}NO_5 \cdot 0.5H_2O$) C, H, N.

4.31. [[7-Methoxy-9-[2-[(1-oxopropyl)amino]ethyl]-9*H*-fluoren-2-yl]oxy]acetic acid (2z)

Ester **2y** (0.22 g, 0.57 mmol) was dissolved in methanol at room temperature. Sodium hydroxide (as a 1 N solution in water, 0.6 mL, 0.57 mmol) was added, then the mixture was stirred for 8 h. The reaction mixture was acidified with 1 M HCl solution, then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 0.17 g of an off-white solid (81%) obtained as an off-white solid, mp 55–59 °C. ^{1}H NMR ($CDCl_3$) δ 8.82 (br, 1H), 7.50 (dd, J = 8.3, 4.9 Hz, 2H), 7.02 (d, J = 2.1 Hz, 1H), 6.97 (d, J = 2.1 Hz, 1H), 6.84 (dt, J = 8.3, 2.3 Hz, 2H), 5.12 (t, J = 5.6 Hz, 1H), 4.65 (s, 2H), 3.89 (t, J = 4.9 Hz, 1H), 3.81 (s, 3H), 2.97 (q, J = 6.5 Hz, 2H), 2.19 (m, 2H), 1.96 (q, J = 7.7 Hz, 2H), 0.91 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 171.3, 159.0, 156.9, 147.7, 147.6, 134.8, 133.9, 120.2, 120.1, 114.8, 113.1, 110.5, 110.2, 65.6, 55.7, 45.5, 36.4, 31.6, 29.4, 9.6; MS (ESI) $M-H^+$ = 368. Anal. ($C_{21}H_{23}NO_5 \cdot 1H_2O$) C, H, N.

4.32. *N*-2-(2-Methoxy-7-fluorofluoren-9-yl)ethyl propanamide (2aa)

Prepared in an analogous fashion to **2b** and obtained as a white solid, mp 72–73 °C. IR (film) 1644, 1558, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.59–7.54 (m, 2H), 7.15 (dd J = 8.6, 1.7 Hz, 1H), 7.06–7.00 (m, 2H), 6.91 (dd J = 8.3, 2.3 Hz, 1H), 4.94 (br s, 1H), 4.03–3.99 (m, 1H), 3.85 (s, 3H), 3.08–3.02 (m, 2H), 2.33–2.26 (m, 2H), 1.42 (q J = 7.6 Hz, 2H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 120.3, 119.4, 119.8, 114.3, 114.0, 113, 2, 111.6, 111.3, 109.9, 55.4, 45.5, 35.9, 31.7, 29.3, 9.3; MS (ESI) $M-H^+$ = 312. Anal. ($C_{19}H_{20}FNO_2$) C, H, N.

4.33. *N*-[2-(2,7-Difluorofluoren-9-yl)ethyl]-propanamide (2bb)

Prepared in an analogous fashion to **2b** and obtained as a white solid, mp 125–126 °C. IR (film) 1642, 1554, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.62–7.58 (m, 2H), 7.22–7.18 (m, 2H), 7.08–7.02 (m, 2H), 5.00 (br s, 1H), 4.01–4.00 (m, 1H), 3.06–2.99 (m, 2H), 2.30–2.24 (m, 2H), 1.94 (q, J = 7.6 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 136.1, 120.7, 120.6, 114.7, 114.4, 111.9, 111.6, 45.6, 36.0, 31.8, 24.4, 9.5; MS (ESI) $M-H^+$ = 300. Anal. ($C_{18}H_{17}F_3NO_3$) C, H, N.

References and notes

1. (a) Cassone, V. M. Effects of Melatonin on Vertabrate Circadian Systems. *Trends Neurosci.* **1990**, *13*, 457–464; (b) Reppert, S. M.; Weaver, D. R. Coordination of Circadian Timing in Mammals. *Nature* **2002**, *418*(6901), 935–941.
2. (a) Goldman, B. D.; Darrow, J. M. The Pineal Gland and Mammalian Photoperiodism. *Neuroendocrinology* **1983**, *37*, 386–396; (b) Benloucif, S.; Dubokovich, M. L. Melatonin and Light Induce Phase Shifts of Circadian Rhythms in the C3H/HeN Mouse. *J. Biol. Rhythms* **1996**, *11*, 113–125.
3. Reviewed in Arendt, J. *Melatonin and the Mammalian Pineal Gland*; Chapman and Hall: London, 1995.
4. Reppert, S. M.; Weaver, K. R.; Godson, C. Melatonin Receptors Step into the Light: Cloning and Identification of Subtypes. *Trends Pharmacol.* **1996**, *17*, 100–102.
5. Formerly the mel_{1a} and mel_{1b} receptors, see: Dubowkovich, M. L.; Cardinali, D. P.; Delagrange, P.; Krause, D. N.; Strosberg, A. D.; Sugden, D.; Yocca, F. D. *The IUPHAR Compendium of Receptor Characterization and Classification*; IUPHAR media: London, 1995; pp 271–277.
6. (a) Reppert, S. M.; Weaver, D. R.; Ebisawa, T. Cloning and Characterization of a Mammalian Melatonin Receptor that Mediates Reproductive and Circadian Responses. *Neuron* **1994**, *13*, 1177–1185; (b) Reppert, S. M.; Godson, C.; Mahle, C. D.; Weaver, D. R.; Slaugenhaupt, S. A.; Gusella, J. F. Molecular Characterization of a Second Melatonin Receptor Expressed in Human Retina and Brain: the Mel_{1b} Receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 8734–8738.
7. Reppert, S. M.; Weaver, D. R. Coordination of Circadian Timing in Mammals. *Nature* **2002**, *418*, 935–941.
8. (a) Liu, C.; Weaver, D. M.; Jin, X.; Shearman, L. P.; Pieschl, R. L.; Gribkoff, V. K.; Reppert, S. M. Molecular Dissection of Two Distinct Actions of Melatonin on the Suprachiasmatic Circadian Clock. *Neuron* **1997**, *19*, 91–102; (b) Dubokovich, M. L.; Yun, K.; Al-Ghoul, W. M.; Benloucif, S.; Masana, M. I. Selective MT_2 Melatonin Receptor Antagonists Block Melatonin-Mediated Phase Advances of Circadian Rhythms. *FASEB J.* **1998**, *12*, 1211–1220.
9. (a) Mahle, C. D.; Watson, A. J. Melatonin Receptors: Potential Targets for Central Nervous System Disorders. *Exp. Opin. Invest. Drugs* **1997**, *6*, 399–406; (b) Li, P.-K.; Witt-Enderby, P. A. Melatonin Receptors as Potential Targets for Drug Discovery. *Drugs Fut.* **2000**, *25*, 945–957.
10. (a) Petrie, K.; Conaglen, J. V.; Thompson, L.; Chamberlain, K. Effect of Melatonin on Jet Lag After Long Haul Flights. *Br. Med. J.* **1989**, *298*, 705–707; (b) Arendt, J. Melatonin in Humans: Jet-Lag and After. *Adv. Pineal Res.* **1991**, *5*, 299–302.
11. Sack, R. L.; Blood, M. L.; Lewy, A. J. Melatonin Rhythms in Night Shift Workers. *Sleep* **1992**, *15*, 434–441.
12. Rosenthal, N. E.; Sack, D. A.; Jacobsen, F. M.; James, S. P.; Parry, B. L.; Arendt, J.; Tamarkin, L.; Wehr, T. A. Melatonin in Seasonal Affective Disorder and Phototherapy. *J. Neural. Transm. Suppl.* **1986**, *21*, 257–267.
13. (a) Wehr, T. A. The Durations of Human Melatonin Secretion and Sleep Respond to Changes in Daylength (Photoperiod). *J. Clin. Endocrinol. Metab.* **1991**, *73*, 1276–1280; (b) Oldani, A.; Ferini-Strambi, L.; Zucconi,

M.; Stankov, B.; Fraschini, F.; Smirne, S. Melatonin and Delayed Sleep Phase Syndrome: Ambulatory Polygraphic Evaluation. *Neuroreport* **1994**, *6*, 132–134.
14. Zhdanova, I. V.; Wurtman, R. J.; Regan, M. M.; Taylor, J. A.; Shi, J. P.; Leclair, O. U. Melatonin Treatment for Age-Related Insomnia. *J. Clin. Endocrin. Met.* **2001**, *86*(10), 4727–4730.
15. Weaver, D. R.; Reppert, S. M. The Mel_{1a} Melatonin Receptor Gene is Expressed in Human Suprachiasmatic Nuclei. *Neuroreport* **1996**, *8*(1), 109–112.
16. (a) Liu, C.; Weaver, D. R.; Jin, X.; Shearman, L. P.; Pieschl, R. L.; Gribkoff, V. K.; Reppert, S. M. Molecular Dissection of Two Distinct Actions of Melatonin on the Suprachiasmatic Circadian Clock. *Neuron* **1997**, *19*(1), 91–102; (b) Nonno, R.; Pannacci, M.; Lucini, V.; Angeloni, D.; Fraschini, F.; Stankov, B. Ligand Efficacy and Potency at Recombinant Human MT_2 Melatonin Receptors: Evidence for Agonist Activity of Some MT_1-Antagonists. *Brit. J. Pharmacol.* **1999**, *127*, 1288; (c) Dubocovich, M. L.; Yun, K.; Al-Ghoul, W. M.; Benlowcif, S.; Masana, M. I. Selective MT_2 Melatonin Receptor Antagonists Block Melatonin-Mediated Phase Advances of Circadian Rhythms. *FASEB J.* **1998**, *12*, 1211.
17. For a review see: Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995–1998. *J. Organometall. Chem.* **1999**, *576*(1–2), 147–168.
18. Prepared from the acid by Fischer esterification. The acid failed to undergo Suzuki coupling.
19. Wadsworth, W. S.; Emmons, W. D. The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
20. Secrist, J. A.; Logue, M. W. Amine Hydrochlorides by Reduction in the Presence of Chloroform. *J. Org. Chem.* **1972**, *37*, 335–336.
21. Prepared in three steps from methyl 3-hydroxy-5-bromobenzoate by coupling with 4-methoxyphenylboronic acid followed by hydrolysis and acetylation.
22. Mattson, R. J.; Catt, J. D.; Keavy, D.; Sloan, C. P.; Epperson, J. R.; Gao, Q.; Iben, L.; Hodges, D.; Mahle, C.; Ryan, E.; Yocca, F. D. Indanyl Piperazine Melatonergic MT_2 Selective Agents. *Bioorg. Med. Chem. Lett.* **2003**, *13*(6), 1199–1202.
23. Warren, W. S.; Hodges, D. B.; Cassone, V. M. Pinealectomized Rats Entrain and Phase-Shift to Melatonin Injections in a Dose-Dependent Manner. *J. Biol. Rhythms* **1993**, *8*(3), 233–245.
24. Mahle, C. D.; Goggins, G. D.; Agarwal, P.; Ryan, E.; Watson, A. J. Melatonin Modulates Vascular Smooth Muscle Tone. *J. Biol. Rhythms* **1997**, *12*(6), 690–696.