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Synthesis of a Small Library of Phenylalkylamide Derivatives as Melatoninergic Ligands for Human mt_1 and MT_2 Receptors

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Abstract—Focused small libraries of melatonin receptor ligands from arylalkylamine derivatives were synthesised by combinatorial chemistry using the mix and split method in the solid phase. A library of 108 compounds was then synthesised from 12 arylalkyl amines and nine carboxylic acids. The compound mixtures were evaluated on chicken brain melatonin and recombinant human mt_1 and MT_2 receptors. Deconvolution of the most potent mixture demonstrated the superiority of 3-methoxy and 2,5-dimethoxy substitution on the phenyl ring with isopropyl, propyl and ethyl amido chains. Several compounds with nanomolar affinity for human melatonin receptors were obtained.

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone secreted during darkness.[1] It is now well recognised that it regulates the circadian rhythm[2] in a large number of animals and in man. It can be used to control diseases associated with circadian rhythm disorders.[3]

Melatonin alleviates jet-lag, regulates delayed sleep phase syndrome[4] and induces sleep.[5] Conversely, it has been implicated in seasonal and winter depression.[6] Melatonin controls the breeding cycle in photoperiodic species and can be used to induce reproduction outside of the breeding season.[7] Melatonin has also been reported to have antiproliferative effects on mammary cell lines.[8]

It has been demonstrated that a number of the effects of melatonin are mediated through G protein-coupled receptors[9] and coupling to one of the G_i family of G-proteins appears to be the common signalling pathway for the receptors characterised to date.[10] Cloning studies have revealed two recombinant mammalian melatonin receptors recently termed mt_1 and MT_2 receptors.[11,12]

Considerable interest has evolved in the search for new molecules capable of mimicking or antagonising the response to melatonin.[13,14] These novel compounds were derived from the indole ring or the bioisosteric naphthalene moiety. Compounds such as agomelatine (S 20098) was claimed to control circadian rhythm disorders.[15] Naphthalene melatonergic ligands were structurally characterised by the position of the methoxy group which can occupy the melatonin-like position 7[16] or be located in the *ortho* position of the ethylacetamido chain.[17] However, several reports have shown that simple derivatives, such as the amido derivatives of phenethylamine or phenylpropylamine, can provide ligands for melatonergic receptors.[17,18] The design and preparation of molecules selective for the recently identified mt_1 and MT_2 receptors are important steps for their pharmacological characterisation. Several molecules have been claimed as possessing agonist or antagonist properties for one or other of these receptors. However, few structure–activity relationship (SAR) studies have been published and no clear structural information is available. It seemed to us of interest to explore, as a preliminary approach, the SAR for both human receptors

Keywords: melatonin; combinatorial chemistry; solid phase; hmt_1 and hMT_2 receptors; phenylalkyl amides.

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of a small focused library of phenylalkylamido compounds which were synthesised by solid-phase combinatorial chemistry.[19]

Chemistry

With a view to checking the efficiency of the method for the selected synthesis, we prepared as the initial step, by the mix and split method, a model library of compounds which were evaluated in binding assays using chicken brain melatonin receptors which are a mixture[11] of mt_1, MT_2 and, doubtless, Mel_{1c} receptors with 2[^{125}I]-iodomelatonin as the radioligand. The results were compared to those obtained with the theoretical library prepared with the pure compounds.

The synthetic pathway is represented in Scheme 1. The Merrifield resin was derived by alkylation with 4-hydroxy-2,6-dimethoxybenzaldehyde prepared according to the process already reported[20] and provided resin-bound aldehyde **1**, characterised by its IR spectra ($\nu_{CO} = 1680\,cm^{-1}$). 3-Methoxyphenethylamine and 2,5-dimethoxyphenethylamine were selected because several amido derivatives had been prepared previously and evaluated on melatonin receptors. The amines were condensed by reductive amination with $NaBH(OAc)_3$ in DMF in the presence of 1% AcOH.[21] The level of resin substitution was evaluated with the picric acid method[22] (0.7–0.9 mmol g^{-1} resin) and by micro-analysis. The individual pools of the amino resins **2** (Ar = 3-$MeOC_6H_4$ or 2,5-$(MeO)_2C_6H_3$, X = CH_2) were mixed and redivided into five batches which were acylated independently. The acylated compounds **3** (R′ = Me, Et, Pr, cPr, Ph) were obtained by various methods: the amino resin **2** was reacted with acetic, propionic and butyric anhydrides in pyridine in the presence of 4-dimethylaminopyridine (DMAP) and with cyclopropanecarbonyl and benzoyl chlorides in dichloroethane in the presence of Et_3N. The resin amides **3** were characterised by their IR spectra, which indicated the presence of the new amide carbonyl stretch ($\nu_{CO} = 1640$–$1645\,cm^{-1}$) and by the lack of the free amine evaluated by the picric acid method. It was also demonstrated that dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) could be used in the condensation step of the acids to give the identical resin amides **3**. The cleavage was accomplished with good yield and high purity by treatment with a TFA:Me_2S:H_2O (90:5:5) mixture which gave the amido compounds **4**. Gas chromatographic (GC) analysis of all the mixtures indicated a 45:55 ratio of the compounds.

The different mixtures were evaluated in binding assays using 2[^{125}I]-iodomelatonin as the radioligand and chicken brain membranes.[17] They were compared to the theoretical mixture prepared from the authentic compounds synthesised according to classical methods. The results are reported in Figure 1.

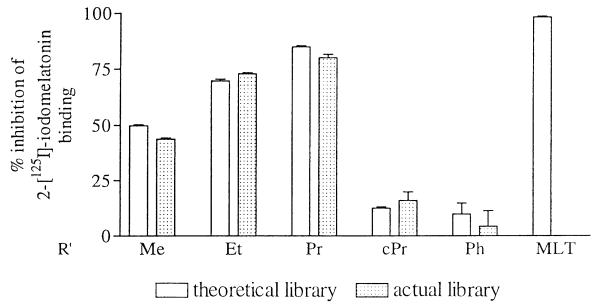
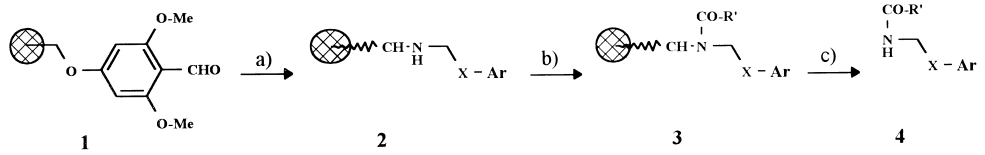


Figure 1. Inhibition of 2-[^{125}I]-iodomelatonin binding by compounds **4** (Ar = 3-$MeOC_6H_4$- and 2,5-$(MeO)_2C_6H_3$-, X = CH_2) at 5×10^{-8} M. (2-[^{125}I]-iodomelatonin was used as the radioligand and the binding assays were carried out using membranes prepared from chicken brain. Membrane aliquots (30 μL) were incubated in a total volume of 0.25 μL of Tris–HCl buffer (50 nM, pH 7.4) with 0.05 nM 2-[^{125}I]-iodomelatonin and one concentration (10−7 M) of the mixture under test. Each binding assay was performed in triplicate. Non-specific binding was defined with 10 μM melatonin and represented about 10% of the total binding. Melatonin (MLT) was tested at the same concentration.)

The compounds were tested at 10^{-7} M by their ability to inhibit the binding of 2[^{125}I]-iodomelatonin and compared to melatonin at the same concentration. The data showed that the results obtained with the theoretical mixture and the same compounds prepared by the solid phase were identical, demonstrating the efficiency of the chemical process. Furthermore, the experiments confirmed the results of the previous SAR[14] on the influence of the alkyl chain of the acyl group on the affinity of the compounds for melatonin receptors, the butyramido compounds (**4**, R′ = Pr, Ar = 3-$MeOC_6H_4$ or 2,5-$(MeO)_2C_6H_3$, X = CH_2) being the most potent.

Subsequently, a compound library of 108 molecules was prepared according to this method from a set of 12 phenylalkylamine derivatives **a**–**l** represented in Table 1. The amines substituted with one or two methoxy groups were chosen in particular as they were commercially available or could be synthesised by classical methods. They were independently condensed onto the resin aldehyde **1** (Scheme 1) and the resin amines **2** ($X = CH_2$, CH_2–CH_2, CH(Me)) were then mixed and split into 9 batches. Every batch was acylated via the DCC process with the acids **5**–**13** reported in Table 1.

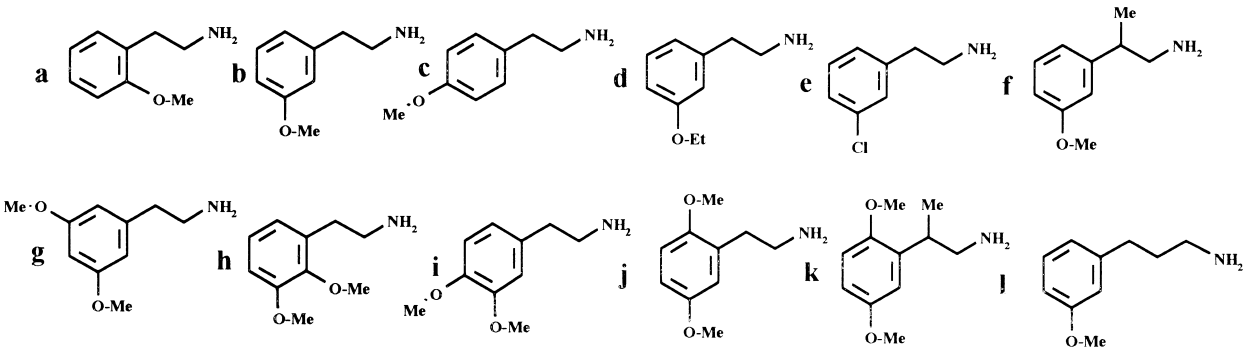
The nine mixtures of 12 compounds were filtered on silica after TFA treatment to remove the by-products due to the cleavage of the resin linker. The different



Scheme 1. (a) $NaBH(OAc)_3$, DMF, 1% AcOH; (b) $(R'CO)_2O$, Pyridine, DMAP or R′COCl, dichloroethane, rt; (c) TFA:Me_2S:H_2O 90:5:5.

Table 1. Phenylalkylamines and carboxylic acids used to prepare the library of phenylalkylamindo derivatives

The phenylalkylamines **a–l** used in the compound library synthesis



The different acids **5–13** used in the acylation reaction

$MeCO_2H$	$EtCO_2H$	$PrCO_2H$	$nBuCO_2H$	$iBuCO_2H$	$ClCH_2CO_2H$	$MeO–CH_2–CO_2H$	$MeO–(CH_2)_2–CO_2H$	$cPr–CO_2H$
5	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**

mixtures were isolated with a range of yields from 40 to 70%. They were characterised by [^{1}H] and [^{13}C]-NMR spectra, where the presence of the principal chemical groups was noted and by GC analysis which showed the presence of 12 compounds.

Results and Discussion

The compounds in the different mixtures were evaluated on chicken brain melatonin receptors by their ability to inhibit the binding of 2-[^{125}I]-iodomelatonin at 1.2×10^{-8} M (Fig. 2) and by the K_i values of the different mixtures determined for human mt_1 and MT_2 receptors expressed in HEK 293 cells[23] (Table 2). The results on the chicken brain receptors demonstrated the marked dependence of the affinity on the nature of the acyl groups. Only the propionyl, butyryl and chloracetyl groups provided mixtures of compounds capable of inhibiting over 50% of the binding of 2-[^{125}I]-iodomelatonin at the theoretical concentration of 1.2×10^{-8} M and possessed affinity values in the 10 nM range at human mt_1 and MT_2 receptors on the basis of the theoretical average molecular weight of the mixture of 12 compounds. These results demonstrated the high affinity for the human melatonin receptors of the butyramido and chloracetamido derivatives of arylalkyl-amines, but no selectivity for the different human melatonin receptors was observed. Consequently, the **7a–l** and **10a–l** mixtures, which possessed *n*-butyramido and chloracetamido groups, were independently synthesised by the process described above, using the high-throughput organic synthesizer ACT 496.[24] After TFA cleavage, the compounds were washed with ether to remove the insoluble dicyclohexyl urea (DCU) and were filtered on silica gel. The structure and purity of compounds were evaluated by [^{1}H] and [^{13}C]-NMR spectra, mass spectra. GC analysis were performed on 12 compounds and, in all cases, purity was over 80%.

Every compound in the **7a–l** and **10a–l** groups was evaluated in binding assays at 10^{-7} M on the chicken brain melatonin receptors (Fig. 3) and K_i values for human mt_1 and MT_2 receptors were determined and

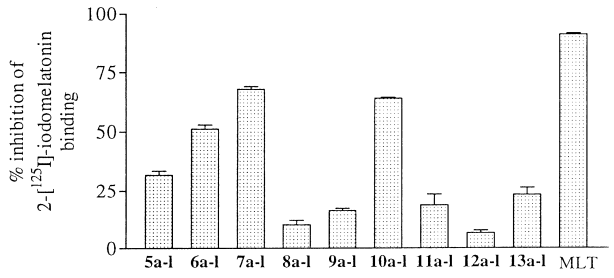


Figure 2. Inhibition of 2-[^{125}I]-iodomelatonin binding by the mixture of compounds **5–13** (**a–l**) at 10^{-7} M. See notes in parentheses under Figure 1. The theoretical concentration of every compound in the mixture tested was 1.2×10^{-8} M. Melatonin (MLT) was tested at the same concentration.

Table 2. Inhibition of 2-[^{125}I]-iodomelatonin binding by the mixture of the compounds **5–13(a–l)**

Compound	hmt_1 receptors[a] K_i (nM)	hMT_2 receptors[a] K_i (nM)
5a–l	35.1 (0.6)	43.9 (10)
6a–l	7.06 (0.8)	7.56 (2.6)
7a–l	7.83 (0.15)	4.07 (1.39)
8a–l	> 500	> 500
9a–l	115 (16)	69.6 (11.1)
10a–l	5.78 (0.72)	5.95 (0.47)
11a–l	65.2 (2/1)	48.1 (8.1)
12a–l	377 (58)	388 (96)
13a–l	15.9 (1.5)	32.3 (19.4)
Melatonin	0.2 (0.1)	0.53 (0.15)

[a]2-[^{125}I]-iodomelatonin was used as the radioligand and the binding assays were carried out using membranes prepared from HEK 293 cells (Ref. 23) which expressed human (h) mt_1 and hMT_2 receptors. Membrane aliquots were incubated for 2 h at 37 °C with 0.025 nM and 0.2 nM 2-[^{125}I]-iodomelatonin for hmt_1 and hMT_2 receptors, respectively. Non-specific binding was defined with 10 μM 2-iodomelatonin. K_i values were calculated on the basis of the theoretical average molecular weight of the mixture. Experiments were performed twice and the difference between the two values obtained are showin in parentheses.

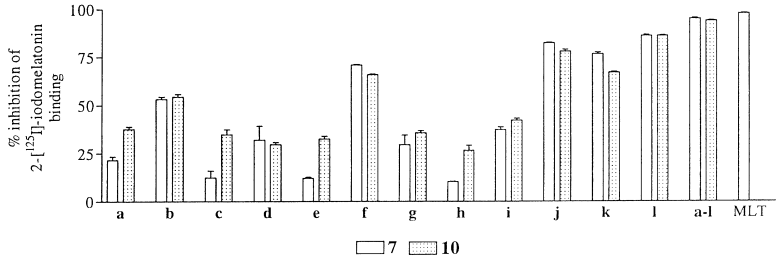


Figure 3. Inhibition of 2-[^{125}I]-iodomelatonin binding by compounds **7a–l** and **10a–l** at 10^{-7} M. See notes in parentheses under to Figure 1.

compared to those of the most potent compounds (compounds **7f**, **7j–l**, **10f**, **10j–l**) at chicken brain receptors (Table 3). **7f**, **j–l**, **10f**, **j–l** were identical to the compounds obtained by the classical methods. The results agreed with the data obtained previously by Garratt[18] and our group[17] and demonstrated the superiority of compounds with methoxy groups in the *meta* position or the presence of two methoxy groups in the 2 and 5 positions over the other substitutions. The favourable effect of β-methyl substitution and increasing chain length were also confirmed. Butyramido and chloracetamido groups did not influence the selectivity for the different human receptors as no significant differences between the affinities were observed with the pairs of compounds **7** and **10**. The data showed the highly potent affinities for human receptors of compounds with 2,5-dimethoxy substitution (compounds **7j**,**k** and **10j**,**k**), β-methyl substitution (compounds **7f**,**k** and **10f**,**k**) and a propyl chain (compounds **7l** and **10l**) which had nanomolar affinity, compound **7l** being the most potent ($K_i = 0.6$ and 0.7 nM for mt_1 and MT_2 receptors, respectively). These structural properties were well recognised by the both receptors and resulted in a clear increase in affinity with regard to the parent compounds **7b** and **10b**, but they did not introduce any selectivity into the molecules. However, comparison of the data obtained with the *ortho* and *meta* methoxy compounds (compounds **7a**,**b** and **10a**,**b**) showed clearly that compounds with a methoxy substituent in the *ortho* position had higher affinity for MT_2 receptors ($K_i = 6.5$ and 15.3 nM, respectively) than for the mt_1 receptors ($K_i = 81$ and 129 nM, respectively). This point may constitute an approach to design more selective compounds in the future.

Table 3. Inhibition of 2-[^{125}I]-iodomelatonin binding by compounds **7a–l** and **10a–l**

Compound	hmt_1 receptors[a] K_i (nM)	hmt_2 receptors[a] K_i (nM)	Chicken brain receptors[a] K_i (nM)
7a	81.2 (18.1)	6.56 (2.48)	NT
7b	62.1 (6.7)	56.5 (19.7)	NT
7c	> 1000	> 100	NT
7d	44.5 (0.7)	91.6 (52.8)	NT
7e	96.4 (27.3)	26.2 (7.5)	NT
7f	4.3 (0.9)	4.04 (0.13)	7.5 (5)
7g	92.7 (6.5)	80.7 (30.7)	NT
7h	275 (147)	61.8 (39.5)	NT
7i	84 (6.8)	297 (313)	NT
7j	3.5 (0.2)	1.36 (0.45)	2.1 (1.1)
7k	3.6 (0.4)	1.19 (0.792)	13 (7.8)
7l	0.6 (0.5)	0.70 (0.59)	4.5 (3.2)
10a	129 (5)	15.3 (4.4)	NT
10b	37.7 (7.7)	64.4 (47.4)	NT
10c	> 1000	> 1000	NT
10d	99.5 (5)	376 (339)	NT
10e	104 (8.1)	667 (415)	NT
10f	4.2 (0.8)	9.62 (6.76)	15 (9)
10g	81.8 (16.8)	139 (110.8)	NT
10h	261 (120)	36.5 (29.3)	NT
10i	110 (40.4)	154 (86)	NT
10j	4.9 (0.5)	3.02 (0.77)	7.9 (5.1)
10k	6.5 (2.5)	2.0 (0.24)	24 (23.7)
10l	1.4 (0.1)	1.58 (0.13)	4.0 (3.3)
Melatonin	0.2 (0.1)	0.53 (0.15)	0.7 (0.8)

[a]See footnotes to Tables 1 and 2 and Experimental.

In summary, the exploration of the affinities of the phenylalkylamido derivatives for the human melatoninergic receptors, mt_1 and MT_2, has been realised by the synthesis of a series of 108 compounds prepared by the combinatorial approach in solid-phase. The data indicated that, as has been found previously for chicken brain receptors, potent nanomolar compounds for both receptor types were obtained. β-Methyl substitution and a propyl chain were favourable structural parameters for potency, but no selectivity was observed except for *N*-[2-(*o*-methoxyphenyl)ethyl]butyramide **7a**, which was 10-fold more potent for MT_2 receptors than for mt_1 receptors.

Experimental

^{1}H and ^{13}C spectra were recorded on a BRUKER AC 200 spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) in δ units. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), quin (quintuplet), sx (sextuplet), m (multiplet) and br (broad). Coupling constants are in hertz. Elemental analyses were performed at the Microanalysis Service in Châtenay-Malabry Faculty (France). IR spectra were recorded on a Perkin–Elmer PE 481 spectrometer. Column chromatography was performed using SDS Silica 60-A (35–70 μm) as the stationary phase. Gas chromatography was performed on a Carlo Erba FTV series 4000 instrument equipped with a 12 m capillary column (0.32 mm i.d.). The retention time t_R was measured under the following conditions: injector temperature 300 °C, oven temperature from 150 to 280 °C at 5 °C/min. Electrospray mass spectra were obtained on a Hewlett-Packard Bruker Esquire-LC spectrometer. Melting

points were determined on a Kofler 7841 apparatus and are uncorrected. 2-(3-Ethoxyphenyl)ethylamine, 2-(3-methoxyphenyl)ethylamine, 2-(3,5-dimethoxyphenyl)-ethylamine, 2-(2,3-dimethoxyphenyl)ethylamine, 2-(2,5-dimethoxyphenyl) ethylamine were synthesised according to processes already reported.[17] 2-(3-Chlorophenyl)-ethylamine, 2-(2-methoxyphenyl)ethylamine, 2-(3-methoxyphenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 2-(3,4-dimethoxyphenyl)ethylamine were purchased from Aldrich (France). The 2-(3-methoxyphenyl)propyl and 2-(2,5-dimethoxyphenyl)propyl amines were obtained by alkylation of the benzyl cyanides with iodomethane followed by catalytic hydrogenation. 3-(3-methoxyphenyl)propionic acid was converted to the corresponding amide which was reduced to 3-(3-methoxyphenyl)propylamine.

Preparation of aldehyde-derived polystyrene 1

To NaH (1.78 g, 44.6 mmol, 60% in mineral oil) in dry DMF (60 mL) was added a solution of 4-hydroxy-2,6-dimethoxybenzaldehyde (8.12 g, 44.6 mmol) in dry DMF (200 mL) under argon. The contents were shaken for 30 min, then Merrifield resin (chloromethylpolystyrene, 2% divinylbenzene, loading level 1 mmol/g, 8.9 g, 8.9 mmol) was added. The suspension was stirred for 63 h while being heated at 50 °C. After the addition of CH_3OH (100 mL), the resin was filtered off and washed with DMF (6×200 mL), CH_2Cl_2 (2×200 mL) and CH_3OH (2×200 mL). The resin **1** was dried under vacuo. IR (KBr, cm^{-1}): 1680 (CHO).

General procedure for loading of amines onto the solid support 1

The resin **1** (1.9 g, 0.87 mmol/g, 1.6 mmol) was suspended in dry DMF (20 mL) containing 1% HOAc. To this was added the amine hydrochloride (8.3 mmol) and DIEA (1.5 mL, 8.3 mmol). When the free amine was used, no base was needed. The mixture was stirred for 3 h. Solid $NaBH(OAc)_3$ (1.75 g, 8.3 mmol) was added in portions to this suspension and the reaction continued for 66 h at room temperature. After the addition of MeOH (20 mL), the resin was filtered, rinsed with DMF (4×40 mL), CH_2Cl_2 (3×40 mL) and CH_3OH (1×40 mL) and finally dried under vacuo to afford resin-bound amines **2**. IR (KBr): disappearance of carbonyl stretch. Resin **2a**: anal. found: C 83.70, H 7.89, N 1.02. Resin **2b**: anal. found: C 86.50, H 7.64, N 0.98. Resin **2c**: anal. found: C 85.12, H 7.80, N 1.08. Resin **2d**: anal. found: C 83.51, H 7.66, N 1.26. Resin **2e**: anal. found: C 84.59, H 7.85, N 0.99. Resin **2f**: anal. found: C 82.95, H 7.73, N 1.36. Resin **2g**: anal. found: C 84.18, H 7.67, N 1.22. Resin **2h**: anal. found: C 83.83, H 7.85, N 1.16. Resin **2i**: anal. found: C 84.48, H 8.02, N 1.02. Resin **2j**: anal. found: C 85.65, H 7.63, N 0.99. Resin **2k**: anal. found: C 82.99, H 7.88, N 1.30. Resin **2l**: anal. found: C 85.23, H 7.99, N 1.02.

Equimolar mixing for 10 compound library

Resin **2b** (1.5 g, 1.0 mmol) and resin **2j** (1.5 g, 1.0 mmol) were mixed in CH_2Cl_2 (20 mL) for few minutes, filtered and dried under vacuo to afford mixture A. Equimolar mixing for 108 compound library: Resin **2a** (0.41 g, 0.32 mmol), resin **2b** (0.41 g, 0.32 mmol), resin **2c** (0.41 g, 0.32 mmol), resin **2d** (0.42 g, 0.32 mmol), resin **2e** (0.41 g, 0.32 mmol), resin **2f** (0.42 g, 0.32 mmol), resin **2g** (0.42 g, 0.32 mmol), resin **2h** (0.42 g, 0.32 mmol), resin **2i** (0.42 g, 0.32 mmol), resin **2j** (0.42 g, 0.32 mmol), resin **2k** (0.43 g, 0.32 mmol) and resin **2l** (0.42 g, 0.32 mmol) were mixed in CH_2Cl_2 (20 mL) for few minutes, filtered and dried under vacuo to afford mixture **B**.

Acylation of resin-bound amines by anhydrides

The loaded resin (0.6 g, 0.42 mmol) was added to a 2/1 mixture of pyridine and acid anhydride (24 mL). A catalytic amount of 4-(dimethylamino)pyridine (DMAP) was introduced and the suspension was stirred at 50 °C for 12 h. The resin was then filtered, washed with DMF (7×20 mL), CH_2Cl_2 (7×20 mL) and CH_3OH (3×10 mL) and dried under vacuo. IR (KBr, cm^{-1}): 1720–1740 (CO).

Acylation of resin-bound amines by acyl chlorides

A suspension of the loaded resin (0.6 g, 0.42 mmol) in 1,2-dichloroethane (10 mL) was treated with triethylamine (0.58 mL, 4.2 mmol) and the acid chloride (4.2 mmol). The mixture was shaken at room temperature for 20 h. The resin was filtered, washed with DMF (7×20 mL), CH_2Cl_2 (7×20 mL) and CH_3OH (3×10 mL) and dried under vacuo. IR (KBr, cm^{-1}): 1720–1740 (CO).

Acylation of resin-bound amines by carboxylic acids

To the loaded resin **2** (0.32 mmol) were added DCC (0.32 g, 1.6 mmol), HOBt (0.21 g, 1.6 mmol), the carboxylic acid (1.6 mmol) and dry DMF. The suspension was stirred at room temperature for 15 h and filtered. The resin was washed with DMF (4×10 mL), CH_2Cl_2 (3×10 mL) and CH_3OH (1×10 mL) and dried under vacuo to afford resin-bound amides **3**. IR (KBr, cm^{-1}): 1720–1740 (CO).

General procedure for cleavage of amides

The resin **3** (0.32 mmol) was suspended in CH_2Cl_2 (5 mL) with 90:5:5 TFA:Me_2S:H_2O (20 mL). The mixture was stirred for 15 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (2×10 mL) and CH_3OH (2×10 mL). The filtrate was concentrated and the residual compound was chromatographed on silica gel, and eluted with 3:97 CH_3OH:CH_2Cl_2, to yield the desired secondary amides.

Preparation of the 10 compound library

Resin A (0.6 g) was acylated with acetic anhydride to give after cleavage 25.6 mg (46%) of *N*-[2-(3-methoxyphenyl)ethyl]acetamide and *N*-[2-(2,5-dimethoxyphenyl)ethyl]acetamide (46:54). GC (t_R, min): 9.56, 13.27 (100%). Resin **A** (0.6 g) was acylated with propionic anhydride to give after cleavage 54.2 mg (91%) of

N-[2-(3-methoxyphenyl)ethyl]propionamide and *N*-[2-(2,5-dimethoxyphenyl)ethyl]propionamide (47/53). GC (t_R, min): 10.99, 14.53 (100%). Resin **A** (0.6 g) was acylated with butyric anhydride to give after cleavage 65.7 mg (100%) of *N*-[2-(3-methoxyphenyl)ethyl]butyramide and *N*-[2-(2,5-dimethoxyphenyl)ethyl]butyramide (50/50). GC (t_R, min): 4.89, 7.34 (100%). Resin **A** (0.6 g) was acylated with cyclopropanecarboxylic chloride to give after cleavage 66.4 mg (100%) of *N*-[2-(3-methoxyphenyl)ethyl]cyclopropylformamide and *N*-[2-(2,5-dimethoxyphenyl)ethyl]cyclopropylformamide (48/52). GC (t_R, min): 10.10, 13.36 (100%). Resin **A** (0.6 g) was acylated with benzoyl chloride to give after cleavage 64.9 mg (94%) of *N*-[2-(3-methoxyphenyl)ethyl]benzamide and *N*-[2-(2,5-dimethoxyphenyl)ethyl]benzamide (46/54). GC (t_R, min): 10.44, 13.32 (100%).

Preparation of the 108 compound library

Resin **B** (0.41 g) was acylated with acetic acid to give after cleavage 27 mg (39%) of acetamides **5a–l**. Resin **B** (0.41 g) was acylated with propionic acid to give after cleavage 37 mg (50%) of propionamides **6a–l**. Resin **B** (0.41 g) was acylated with butyric acid to give after cleavage 44 mg (56%) of butyramides **7a–l**. Resin **B** (0.41 g) was acylated with valeric acid to give after cleavage 43 mg (52%) of valeramides **8a–l**. Resin **B** (0.41 g) was acylated with isovaleric acid to give after cleavage 43 mg (52%) of isovaleramides **9a–l**. Resin B (0.41 g) was acylated with chloroacetic acid to give after cleavage 54 mg (67%) of chloroacetamides **10a–l**. GC (t_R, min): 13.53, 13.66, 14.33, 14.57, 14.76, 15.43, 16.47, 17.03, 17.75, 17.89, 18.28, 18.77. Resin **B** (0.41 g) was acylated with methoxyacetic acid to give after cleavage 51 mg (64%) of methoxyacetamides **11a–l**. Resin **B** (0.41 g) was acylated with methoxypropionic acid to give after cleavage 21 mg (25%) of methoxypropionamides **12a–l**. Resin B (0.41 g) was acylated with cyclopropanecarboxylic acid to give after cleavage 44 mg (56%) of cyclopropaneformamides **13a–l**.

Deconvolution of 108 compound library

Resin **2a** (0.2 g) was acylated with butyric acid to give after cleavage 32 mg (100%) of *N*-[2-(2-methoxyphenyl)ethyl]butyramide **7a** which was isolated as an oil[18]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H); 1.58 (sx, J = 7.5 Hz, 2H); 2.16 (t, J = 7.5 Hz, 2H); 2.83 (t, J = 6.6 Hz, 2H); 3.50 (q, J = 6.2 Hz, 2H); 3.83 (s, 3H); 6.18 (brs, 1H); 6.89 (t, J = 8.8 Hz, 2H); 7.10 (d, J = 8.8 Hz, 1H); 7.20 (d, J = 8.8 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.59, 19.17, 29.84, 38.45, 40.42, 55.37, 110.56, 120.92, 128.14, 130.67, 137.98, 157.6, 174.81. ESI MS: 222.1 (MH^+); 244.1 (MNa^+); MW = 221.

Resin **2a** (0.2 g) was acylated with chloroacetic acid to give after cleavage 33 mg (100%) of *N*-[2-(2-methoxyphenyl)ethyl]chloroacetamide **10a** which was isolated as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (t, J = 6.5 Hz, 2H); 3.52 (q, J = 6.6 Hz, 2H); 3.85 (s, 3H); 4.00 (s, 2H); 6.87–6.95 (m + brs, 3H); 7.11–7.29 (m, 2H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 29.58, 40.84, 42.63, 55.33, 110.36, 120.89, 128.16, 130.70, 142.46, 159.52, 169.50. ESI MS: 228.0 (MH^+); 249.9 (MNa^+); MW = 227. GC (t_R, min):13.63 (83%).

Resin **2b** (0.2 g) was acylated with butyric acid to give after cleavage 31 mg (100%) of *N*-[2-(3-methoxyphenyl)ethyl]butyramide **7b** which was isolated as an oil.[18] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H); 1.60 (sx, J = 7.5 Hz, 2H); 2.14 (t, J = 7.5 Hz, 2H); 2.78 (t, J = 6.9 Hz, 2H); 3.52 (q, J = 6.2 Hz, 2H); 3.78 (s, 3H); 5.75 (brs, 1H); 6.72–6.78 (m, 3H); 7.22 (t, J = 7.9 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.55, 18.95, 35.58, 38.50, 40.21, 54.97, 111.64, 114.23, 120.90, 129.40, 140.40, 159.6, 172.83. ESI MS: 222.1 (MH^+); 244.1 (MNa^+); MW = 221.

Resin **2b** (0.2 g) was acylated with chloroacetic acid to give after cleavage 32 mg (100%) of *N*-[2-(3-methoxyphenyl)ethyl]chloroacetamide **10b**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (t, J = 7.0 Hz, 2H); 3.55 (q, J = 6.5 Hz, 2H); 3.80 (s, 3H); 4.02 (s, 2H); 6.63 (brs, 1H); 6.74–6.81 (m, 3H); 7.23 (t, J = 7.5 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 35.54, 40.88, 42.67, 55.22, 112.20, 114.40, 121.04, 129.77, 159.94 165.86. ESI MS: 228.0 (MH^+); 249.9 (MNa^+); MW = 227. GC (t_R, min):14.46 (91%). It was identical to the compound synthesised by the classical method, mp: 56 °C. Anal. ($C_{11}H_{14}NO_2Cl$) Calc. C 58.02, H 6.2, N 6.15; F. C 58.12, H 6.36, N 6.02.

Resin **2c** (0.2 g) was acylated with butyric acid to give after cleavage 34 mg (100%) of *N*-[2-(4-methoxyphenyl)-ethyl]butyramide **7c** as an oil.[18] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H); 1.59 (sx, J = 7.4 Hz, 2H); 2.14 (t, J = 7.5 Hz, 2H); 2.74 (t, J = 6.9 Hz, 2H); 3.48 (q, J = 6.2 Hz, 2H); 3.77 (s, 3H); 5.92 (brs, 1H); 6.82 (d, J = 8.6 Hz, 2H); 7.07 (d, J = 8.5 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.61, 19.24, 34.54, 38.50, 41.02, 55.28, 114.13, 129.67, 130.49, 158.39, 174.50. ESI MS: 222.1 (MH^+); 244.1 (MNa^+); MW = 221.

Resin **2c** (0.2 g) was acylated with chloroacetic acid to give after cleavage 35 mg (100%) of *N*-[2-(4-methoxyphenyl)-ethyl]chloroacetamide **10c** as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.78 (t, J = 7.0 Hz, 2H); 3.52 (q, J = 6.6 Hz, 2H); 3.79 (s, 3H); 4.01 (s, 2H); 6.59 (brs, 1H); 6.85 (d, J = 8.5 Hz, 2H); 7.11 (d, J = 8.5 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 34.60, 41.16, 42.67, 55.29, 114.19, 129.68, 130.31, 158.46, 165.79. ESI MS: 228.0 (MH^+); 249.9 (MNa^+); MW = 227. GC (t_R, min): 14.75 (89%).

Resin **2d** (0.2 g) was acylated with butyric acid to give after cleavage 22 mg (52%) of *N*-[2-(3-ethoxyphenyl)ethyl]butyramide **7d** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H); 1.40 (t, J = 7.0 Hz, 3H); 1.60 (sx, J = 7.4 Hz, 2H); 2.12 (t, J = 7.4 Hz, 2H); 2.77 (t, J = 6.8 Hz, 2H); 3.52 (q, J = 6.5 Hz, 2H); 4.01 (s, 3H); 5.58 (brs, 1H); 6.73–6.78 (m, 3H); 7.20 (t, J = 7.9 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.67, 14.85, 19.18, 35.63, 38.63, 40.52, 63.40, 112.52, 115.07, 120.94, 129.66, 140.31, 159.21, 173.68. ESI MS: 236.1 (MH^+); 258.1 (MNa^+); MW = 235.

Resin **2d** (0.2 g) was acylated with chloroacetic acid to give after cleavage 29 mg (67%) of *N*-[2-(3-ethoxyphenyl)ethyl]chloroacetamide **10d** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H); 2.81 (t, J = 7.0 Hz, 2H); 3.56 (q, J = 6.5 Hz, 2H); 4.02 (q, 2H); 4.02 (s, 2H); 6.61 (brs, 1H); 6.75–6.79 (m, 3H); 7.22 (t, J = 7.5 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.05, 35.51, 41.05, 43.24, 63.38, 112.77, 114.66, 120.93, 129.75, 139.52, 159.21, 165.83. ESI MS: 242.0 (MH^+); 264.0 (MNa^+); MW = 241. GC (t_R, min):15.45 (85%).

Resin **2e** (0.2 g) was acylated with butyric acid to give after cleavage 32 mg (100%) of *N*-[2-(3-chlorophenyl)-ethyl]butyramide **7e** as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 8.0 Hz, 3H); 1.60 (sx, J = 7.4 Hz, 2H); 2.14 (t, J = 7.5 Hz, 2H); 2.78 (t, J = 7.0 Hz, 2H); 3.50 (q, J = 7.0 Hz, 2H); 5.83 (brs, 1H); 7.02–7.07 (m, 1H); 7.15–7.22 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.61, 19.23, 35.16, 38.47, 40.63, 126.91 (2C); 129.87, 129.96, 134.37, 140.62, 174.62. ESI MS: 226.1 (MH^+); 248.0 (MNa^+); MW = 225.

Resin **2e** (0.2 g) was acylated with chloroacetic acid to give after cleavage 33 mg (100%) of *N*-[2-(3-chlorophenyl)ethyl]chloroacetamide **10e** as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (t, J = 7.0 Hz, 2H); 3.54 (q, J = 6.7 Hz, 2H); 4.03 (s, 2H); 6.63 (brs, 1H); 7.05–7.10 (m, 1H); 7.20–7.24 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 35.18, 40.76, 42.62, 126.98 (2C);128.90, 130.00, 134.69, 140.36, 166.05. ESI MS: 232.0 (MH^+); 253.9 (MNa^+); MW = 231. GC (t_R, min):13.80 (83%).

Resin **2f** (0.2 g) was acylated with butyric acid to give after cleavage 22 mg (48%) of *N*-[2-(3-methoxyphenyl)-propyl]butyramide **7f** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H); 1.24 (d, J = 6.9 Hz, 3H); 1.57 (sx, J = 7.5 Hz, 2H); 2.06 (t, J = 7.5 Hz, 2H); 2.81-3.00 (m, 1H); 3.13-3.28 (m, 1H); 3.56–3.71 (m, 1H); 3.80 (s, 3H); 5.37 (brs, 1H); 6.74–6.80 (m, 3H); 7.24 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.68, 19.20, 19.38, 38.72, 39.86, 45.96, 55.22, 111.86, 113.13, 119.54, 129.75, 145.83, 160.31, 173.31. ESI MS: 236.1 (MH^+); 258.1 (MNa^+); MW = 235. It was identical to the compound synthesised by the classical method isolated as an oil. Anal. ($C_{14}H_{21}NO_2$) calc. C 71.46, H 8.99, N 5.95; F. C 7120, H 9.09, N 6.10.

Resin **2f** (0.2 g) was acylated with chloroacetic acid to give after cleavage 24 mg (51%) of *N*-[2-(3-methoxyphenyl)propyl]chloroacetamide **10f**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 3H); 2.89–3.00 (m, 1H); 3.22–3.37 (m, 1H); 3.55–3.69 (m, 1H); 3.80 (s, 3H); 3.98 (s, 2H); 6.48 (brs, 1H); 6.75–6.82 (m, 3H); 7.24 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 19.98, 39.63, 42.66, 46.33, 55.25, 112.13, 113.04, 119.47, 129.84, 145.24, 159.94, 165.87. ESI MS: 242.1 (MH^+); 264.0 (MNa^+); MW = 241. GC (t_R, min):14.68 (91%). It was identical to the compound synthesised by the classical method isolated as an oil. Anal. ($C_{12}H_{16}NO_2Cl$) calc. C 59.63, H 6.67, N 5.79; F. C 59.62, H 6.95, N 5.62.

Resin **2g** (0.2 g) was acylated with butyric acid to give after cleavage 29 mg (66%) of *N*-[2-(3,5-dimethoxyphenyl)ethyl]butyramide **7g** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H); 1.61 (sx, J = 7.6 Hz, 2H); 2.13 (t, J = 7.4 Hz, 2H); 2.74 (t, J = 6.8 Hz, 2H); 3.51 (q, J = 6.3 Hz, 2H); 3.77 (s, 6H); 5.63 (brs, 1H); 6.33 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.67, 19.19, 35.84, 38.61, 40.45, 55.30 (2C), 98.52, 106.75 (2C); 140.92, 161.06 (2C), 176.38. ESI MS: 252.1 (MH^+); 274.1 (MNa^+); MW = 251.

Resin **2g** (0.2 g) was acylated with chloroacetic acid to give after cleavage 33 mg (73%) of *N*-[2-(3,5-dimethoxyphenyl)ethyl]chloroacetamide **10g** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.78 (t, J = 6.9 Hz, 2H); 3.55 (q, J = 6.5 Hz, 2H); 3.77 (s, 6H); 4.03 (s, 2H); 6.35 (s, 3H); 6.63 (brs, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 35.77, 40.61, 42.67, 55.34 (2C), 98.79, 106.72 (2C), 140.61, 161.13, 165.83. ESI MS: 258.0 (MH^+); 280.0 (MNa^+); MW = 257. GC (t_R, min): 18.78 (86%).

Resin **2h** (0.2 g) was acylated with butyric acid to give after cleavage 29 mg (69%) of *N*-[2-(2,3-dimethoxyphenyl)ethyl]butyramide **7h** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H); 1.58 (sx, J = 7.5 Hz, 2H); 2.15 (t, J = 7.5 Hz, 2H); 2.82 (t, J = 6.5 Hz, 2H); 3.48 (q, J = 6.3 Hz, 2H); 3.83–3.86 (2xs, 6H); 6.32 (brs, 1H); 6.72–6.83 (s, 2H); 7.00 (t, J = 7.9 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.52, 19.09, 29.50, 38.44, 41.12, 55.69, 60.66, 111.12, 122.34, 124.49, 132.10, 152.20 (2C), 174.50. ESI MS: 252.1 (MH^+); 274.1 (MNa^+); MW = 251.

Resin **2h** (0.2 g) was acylated with chloroacetic acid to give after cleavage 37 mg (86%) of *N*-[2-(2,3-dimethoxyphenyl)ethyl]chloroacetamide **10h** isolated as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.86 (t, J = 6.7 Hz, 2H); 3.52 (q, J = 5.9 Hz, 2H); 3.84–3.86 (2xs, 6H); 4.00 (s, 2H); 6.35 (brs, 1H); 6.74–6.85 (m, 2H); 7.00 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 29.68, 40.97, 42.57, 55.79, 60.64, 111.40, 122.33, 124.25, 132.15, 153.07, 166.37. ESI MS: 258.0 (MH^+); 280.0 (MNa^+); MW = 257. GC (t_R, min):16.53 (81%).

Resin **2i** (0.2 g) was acylated with butyric acid to give after cleavage 37 mg (100%) of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-butyramide **7i** as a solid, mp: 48.5–49.5 °C.[18] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H); 1.59 (sx, J = 7.4 Hz, 2H); 2.12 (t, J = 7.2 Hz, 2H); 2.74 (t, J = 6.9 Hz, 2H); 3.49 (q, J = 6.1 Hz, 2H); 3.85 (s, 6H); 5.72 (brs, 1H); 6.68–6.71 (m, 2H); 6.79 (d, J = 8.6 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.65, 19.22, 35.13, 38.62, 40.80, 55.93 (2C), 111.46, 111.95, 120.66, 131.19, 148.12, 149.12, 174.06. ESI MS: 252.1 (MH^+); 274.1 (MNa^+); MW = 251.

Resin **2i** (0.2 g) was acylated with chloroacetic acid to give after cleavage 22 mg (58%) of *N*-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide **10i** isolated as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.78 (t, J = 6.9 Hz, 2H); 3.53 (q, J = 6.1 Hz, 2H); 3.86–3.87 (2xs, 6H); 4.03 (s, 2H); 4.88 (brs, 1H); 6.71–6.83 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 35.06, 41.13, 42.67, 55.92

(2C), 111.52, 111.92, 120.70, 139.21, 145.83, 147.98 (2C), 166.14. ESI MS: 258.0 (MH^+); 280.0 (MNa^+); MW = 258. GC (t_R, min):18.36 (89%).

Resin **2j** (0.2 g) was acylated with butyric acid to give after cleavage 18 mg (48%) of *N*-[2-(2,5-dimethoxyphenyl)ethyl]butyramide **7j**. It was identical to the authentic sample, mp: 88 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H); 1.58 (sx, J = 7.5 Hz, 2H); 2.24 (t, J = 7.5 Hz, 2H); 2.83 (t, J = 6.3 Hz, 2H); 3.48 (q, J = 6.4 Hz, 2H); 3.77–3.82 (2xs, 6H); 5.73 (brs, 1H); 6.70–6.80 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.35, 19.71, 30.92, 39.38, 40.40, 55.49, 56.27, 111.98, 112.55, 117.35, 128.67, 151.67, 153.60, 172.80. ESI MS: 252.1 (MH^+); 274.1 (MNa^+); MW = 251.

Resin **2j** (0.2 g) was acylated with chloroacetic acid to give after cleavage 19 mg (50%) of *N*-[2-(2,5-dimethoxyphenyl)ethyl]chloroacetamide **10j** isolated as a solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2H); 3.52 (q, J = 6.1 Hz, 2H); 3.76–3.81 (2xs, 6H); 4.00 (s, 2H); 6.72–6.78 (m, 3H); 7.00 (brs, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 29.73, 40.86, 42.63, 55.82 (2C); 111.24, 112.32, 116.81, 128.22, 151.58, 153.68, 165.95. ESI MS: 258.0 (MH^+); 280.0 (MNa^+); MW = 257. GC (t_R, min):17.80 (89%). It was identical to the compound synthesised by the classical method, mp: 87 °C. Anal. ($C_{12}H_{16}NO_3Cl$) calc. C 55.93, H 6.26, N 5.43; F. C 56.10, H 6.34, N 5.33.

Resin **2k** (0.2 g) was acylated with butyric acid to give after cleavage 27 mg (55%) of *N*-[2-(2,5-dimethoxyphenyl)propyl]butyramide **7k** isolated as a solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H); 1.23 (d, J = 6.7 Hz, 3H); 1.54 (sx, J = 7.5 Hz, 2H); 2.09 (t, J = 7.5 Hz, 2H); 3.25–3.56 (m, 3H); 3.76–3.79 (2xs, 6H); 5.75 (brs, 1H); 6.69–6.83 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.61, 18.00, 19.13, 38.59, 43.36, 45.69, 55.70, 56.09, 111.50, 111.76, 113.83, 133.29, 153.99, 175.56. ESI MS: 266.2 (MH^+); 288.1 (MNa^+); MW = 265. It was identical to the compound synthesised by the classical method isolated as a solid, mp: 76 °C. Anal. ($C_{15}H_{23}NO_3$) calc. C 67.90, H 8.74, N 5.28; F. C 67.66, H 8.53, N 5.01.

Resin **2k** (0.2 g) was acylated with chloroacetic acid to give after cleavage 37 mg (74%) of *N*-[2-(2,5-dimethoxyphenyl)propyl]chloroacetamide **10k** as a solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J = 6.8 Hz, 3H); 3.29–3.58 (m, 3H); 3.76–3.79 (2xs, 6H); 3.96 (s, 2H); 6.70–6.84 (m + brs, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.74, 31.78, 42.62, 46.48, 55.70, 55.91, 111.36, 111.59, 113.73, 132.76, 153.38 (2C), 165.92. ESI MS: 272.1 (MH^+); 294.0 (MNa^+); MW = 271. GC (t_R, min):17.69 (82%). It was identical to the compound synthesised by the classical method isolated as a solid, mp: 71 °C. Anal. ($C_{13}H_{23}NO_3$) calc. C 67.90, H 8.74, N 5.28; F. C 67.66, H 8.53, N 5.01.

Resin **2l** (0.2 g) was acylated with butyric acid to give after cleavage 21 mg (62%) of *N*-[3-(3-methoxyphenyl)-propyl]butyramide **7l** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H); 1.60 (sx, J = 7.5 Hz, 2H); 1.83 (quin, J = 7.4 Hz, 2H); 2.12 (t, J = 7.5 Hz, 2H); 2.62 (t, J = 7.5 Hz, 2H); 3.28 (q, J = 6.3 Hz, 2H); 3.78 (s, 3H); 5.62 (brs, 1H); 6.71–6.78 (m, 3H); 7.15–7.24 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.70, 19.28, 31.12, 33.36, 38.72, 39.12, 55.11, 111.19, 114.11, 120.68, 129.41, 139.07, 159.69, 175.39. ESI MS: 236.1 (MH^+); 258.1 (MNa^+); MW = 235. It was identical to the compound synthesised by the classical method isolated as an oil. Anal. ($C_{14}H_{22}NO_2$) calc. C 71.46, H 8.99, N 5.95; F. C 71.29, H 9.14, N 5.79.

Resin **2l** (0.2 g) was acylated with chloroacetic acid to give after cleavage 22 mg (63%) of *N*-[3-(3-methoxyphenyl)propyl]chloroacetamide **10l** isolated as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89 (quin, J = 7.2 Hz, 2H); 2.65 (t, J = 7.5 Hz, 2H); 3.33 (q, J = 6.6 Hz, 2H); 3.79 (s, 3H); 4.02 (s, 2H); 6.57 (brs, 1H); 6.73–6.79 (m, 3H); 7.20 (t, J = 7.2 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 30.66, 33.51, 39.53, 42.67, 55.19, 111.44, 114.19, 120.74, 129.56, 142.46, 159.77, 166.14. ESI MS: 242.1 (MH^+); 264.0 (MNa^+); MW = 241. GC (t_R, min):16.98 (97%). It was identical to the compound synthesised by the classical method isolated as an oil. Anal. ($C_{12}H_{16}NO_2Cl$) calc. C 59.63, H 6.67, N 5.79; F. C 59.81, H 6.86, N 5.60.

Melatonin receptor binding assay

Chicken brain melatonin receptors. Chickens (*Red Brook*, male or female, 4 months (3–4 kg); Cellubio, France) were decapitated at 12 p.m. The brains were quickly removed and stored at −80 °C. They were homogenised (Polytron) in 10 volumes of ice-cold Tris–HCl buffer (50 mM, pH 7.4) and washed twice by centrifugation (44,000 *g*, 25 min, 4 °C). The resulting pellet was resuspended in 10 volumes of the same buffer to a final concentration of 5 or 6 mg protein/mL. The membrane aliquots (30 μL) were incubated in a total volume of 0.25 mL Tris–HCl buffer (50 mM, pH 7.4) with 0.05 nM 2-[^{125}I]iodomelatonin and seven concentrations of the compound under test. Each binding assay was performed in triplicate. The incubation (25 °C, 60 min) was stopped by the addition of 3 mL of ice-cold buffer and immediate vacuum filtration through glass fiber filters (GF/B Whatman strips) presoaked in 0.1% poly(ethyleneimine) using a Brandel cell harvester. The filters were washed (3×4 mL) with buffer, dried, and counted on a γ-counter (Crystal-Packard). Non-specific binding was defined with 10 μM melatonin and represented 10% of the total binding. K_i values were calculated using the Cheng–Prussof equation from the corresponding IC_{50} values using the PRISM program.

Human mt_1 and MT_2 melatonin receptors. Membranes obtained from HEK 293 cells expressing hmt_1 or hMT_2 receptors were incubated in Tris–HCl buffer (50 mM, pH 7.4) with 0.025 or 0.2 nM of 2-[^{125}I]iodomelatonin respectively and seven concentrations of the compound under test. Each binding assay was performed in triplicate. The incubation (37 °C, 2 h) was stopped by immediate vacuum filtration through glass fibre filters (GF/B Unifilters) using a Packard cell harvester as above. The filters were washed, dried, and counted in a

Packard β counter (TopCount). Non-specific binding was defined with 10 μM melatonin K_i values were calculated as above.

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