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Synthesis of New Arylalkoxy Amido Derivatives as Melatoninergic Ligands

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Abstract—Amido derivatives **10**–**18** of the corresponding oxyamines were synthesised as melatoninergic ligands by the reaction of hydroxyphtalimide with the halogeno derivatives or the corresponding alcohols using Mitsunobu reaction conditions. The affinity of the compounds for chicken brain melatonin receptors and recombinant human MT_1 and MT_2 receptors was evaluated using 2-[^{125}I]-iodomelatonin as the radioligand. Overall, the introduction of an oxygen atom in the amido chain was not a favourable parameter as the compounds were less potent than the corresponding deoxy derivatives. However, nanomolar compounds were obtained with the arylethyloxy derivatives (**13c** (R′ = nPr), chicken brain, hMT_1, hMT_2, K_i values: 4.8, 3.86, 2.4 nM, respectively) and the 2,7-dimethoxynaphthalene derivatives (**17c** (R′ = nPr), chicken brain, hMT_1, hMT_2, K_i values: 0.04, 0.13, 0.1 nM, respectively). The functional activity of these compounds was evaluated by the aggregation of melanophores in *Xenopus laevis* tadpoles and the potency was related to the affinity of the molecules for melatonin receptors. The compounds were found to be full agonists and compound **17a** was 20-fold more potent than melatonin in this bioassay.

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone secreted during darkness.[1] It is now well established that it modulates the circadian rhythm[2] in a large number of animals and in humans. It can be used to control diseases associated with circadian rhythm disorders: jet-lag or delayed sleep phase syndrome.[3–5] 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 the breeding season.[7] Melatonin has been also reported to have antiproliferative effects on mammary cell lines[8] and, more recently, a role for melatonin has been suggested in the regulation of vascular tone.[9]

Almost all of the effects of melatonin are mediated through G protein-coupled receptors[10] which have been cloned[11] and characterised as MT_1 and MT_2 receptors.[12] Coupling to the G_i family of G-proteins appears to be the most usual signalling pathway for these receptors.[10] Recently, considerable interest has been focused on the search for new molecules capable of mimicking or antagonising the response to melatonin. These novel compounds[13–15] were derived from the indole ring, a bioisosteric naphthalene moiety such as agomelatine or the simple phenylalkylamide framework. Many structure–activity relationships (SAR) have been described and the essential role of the amido function has been emphasised in the binding of the molecule with the receptor site. Several authors have demonstrated that the melatoninergic activity of the molecules depends upon the stereochemistry of the amidic moiety with regard to that of the aromatic ring. A number of constrained melatoninergic derivatives such as compounds

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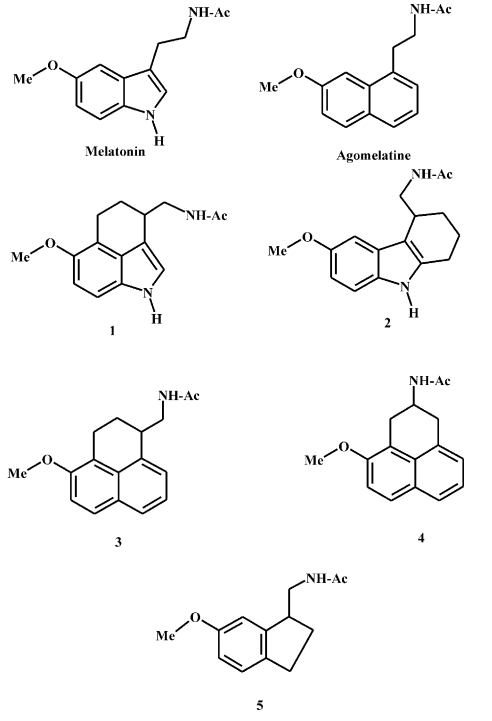
1, **2**, **3**, **4**, **5** highlighted this point.[16–20] Sudgen[21] suggested the existence of a hydrogen bond between the NH amidic group and the asparagine residue of the transmembrane helice IV of the receptor, although no experimental data have confirmed this hypothesis. Consequently, performing chemical modifications centered around the *N*-acyl group was a good way to study the ability of NH group to establish a hydrogen bond with the receptor site. We report herein the synthesis of the *N*-acyl hydroxylamine derivatives **6** (Scheme 1, compounds **10**–**18**) which possess an oxygen atom on the α position of the amido function and aromatic groups R selected from the best melatoninergic ligands described previously[13–15] with nanomolar affinity for melatonin receptors. The compounds were evaluated on chicken brain melatonin receptors[20] and on human MT_1 and MT_2 receptors expressed in HEK-293 cells[22] by their ability to inhibit the binding of 2-[^{125}I]-iodomelatonin. Functional activity at melatonin receptors was evaluated by examining the potency of the compounds to lighten the skin of *Xenopus laevis* tadpoles[23] as it has been clearly demonstrated that melatonin mediates the aggregation of melanophores.[19,24] The degree of dispersion of melanophores on the head and dorsal surface of the tadpoles observed under a microscope can be assessed using the melanophore index scale (1–5) of Hogben and Slome[25] and concentration–effect curves (5 concentrations) can be plotted.



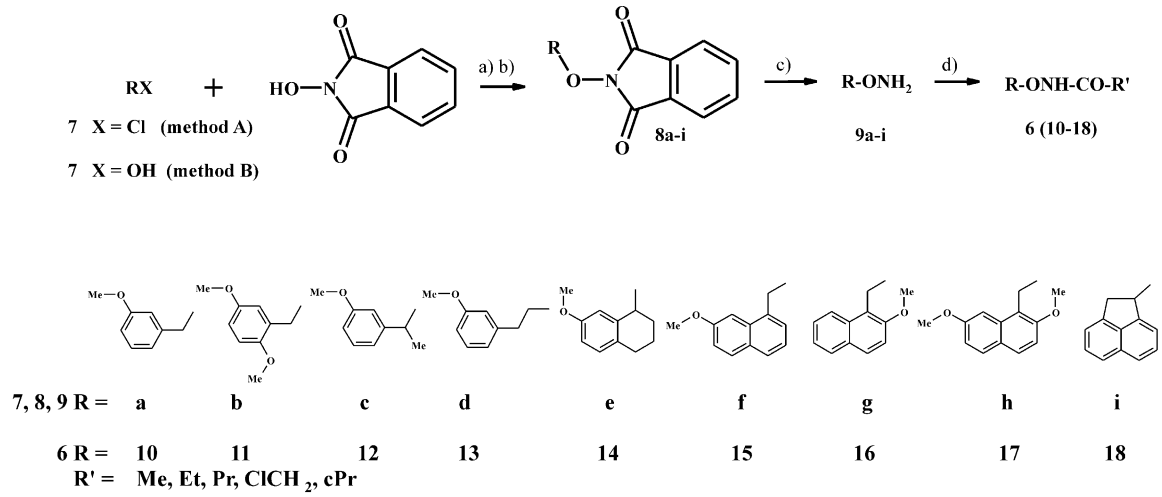
Chemistry

Compounds **6** (**10**–**18**) were synthesised according to the chemical pathway described in the Scheme 1. Two methods were used, according to the process already reported, for the synthesis of the *O*-aryl hydroxylamine. *N*-Hydroxyphthalimide was reacted in DMF[25] at 100 °C with the arylmethyl chloride **7f**, **g** (X = Cl) to give the corresponding phthalimido derivatives **8f**,**g** with good yields (method A). However, the conditions were drastic and condensation of the alcohols **7a**–**e**, **h**, **i** (X = OH) with *N*-hydroxyphthalimide according to the conditions of Mitsunobu reaction[26,27] was preferred (method B). The compounds were reacted in THF at room temperature in the presence of DEAD and PPh_3 and the yields of the *N*-alkoxyphthalimides **8** were good. The *O*-alkylhydroxylamines **9** were prepared by the treatment of **8** with hydrazine in ethanol at reflux and isolated as oils. They were acylated with acid chlorides in the presence of Na_2CO_3 in a biphasic system (CH_2Cl_2/H_2O 1/1) according to the process reported previously.[20] Acyl groups (R′-CO, R′ = Me, Et, n-Pr, CH_2Cl, cPr) were selected according to previous results[12–14] from SAR (structure–activity relationships) obtained with ligands for the melatonin receptors. The new compounds were characterised by NMR spectra and microanalysis.

Results and Discussion

The binding data (K_i, nM) on chicken brain melatonin receptors and human MT_1 and MT_2 receptors are reported in Table 1. By comparison with the corresponding deoxy compounds.[28–30] the results show an overall decrease in affinity for melatonin receptors. The effect was particularly marked with the benzylhydroxylamine derivatives **10**, **11** and **12** which were inactive or weakly active while the potency of 3-methoxyphenethyloxy derivatives such as **13c** was in the nanomolar range and nearly equipotent to the corresponding arylpropyl derivative.[29] A less marked decrease was observed with compounds **14**, **16** and **18** possessing the tetralin, naphthalene and acenaphtene cyclic moieties, respectively. Thus, the naphthalenic derivative **16a** (R′ = Me) with the methoxy in the ortho position was 20-fold less potent than the deoxy derivative prepared previously.[28] Conversely, the naphthalenic analogues of agomelatine **15** and of the corresponding dimethoxy derivatives **17** were nearly equipotent to the ethylamido derivatives. This is particularly clear with compound **17c** (chicken brain, hMT_1, hMT_2, K_i values: 0.04, 0.13, 0.10 nM, respectively) compared to the deoxy analogue[31] (chicken brain, hMT_1, hMT_2, K_i values: 0.08, 0.02, 0.08 nM, respectively). The distance between the methoxy group in the melatonin-like position and the amido group seems to be an important parameter in determining the potency of binding with the receptor site.[32] These two groups were separated by 6 or less bonds in compounds **10**, **11**, **12**, **14** and **16** which were weakly active or inactive, while a distance of 7 bonds was present with the most active compounds such as **13**, **15** and **17**.

The presence of an oxygen atom in the chain produces several changes in structural parameters with regard to those of the deoxy compounds: variation of bond angles, a different range of lower energy conformers, introduction of additional hydrogen bonds or reduction of the flexibility of the chain. Consequently, it was worth examining if the presence of an oxygen atom would modify the stereochemistry of the permissible



Scheme 1. (a) 100 °C, DMF; (b) THF, DEAD, PPh_3, rt; (c) NH_2NH_2, EtOH, Δ; (d) R′COCl, CH_2Cl_2/H_2O, Na_2CO_3.

conformers. Conformational search (Alchemy 2000) was performed on **17a** (R′ = Me) and calculations made around the three rotable bonds C(12)–C(13), C(13)–O(14) and O(14)–N(15) (Fig. 1). A low energy conformer, similar to the putative active conformer previously reported by us for the deoxy compound,[33] was identified among a number of permissible conformers. Thus, **17a** can be superimposed (Fig. 1) on the folded putative active conformer of melatonin determined independently by Sicsic[33] and Marot[34] by the CoMFA method and the potent melatoninergic ligands derived from phenalene derivatives,[20] suggesting that the presence of an oxygen atom exerts a weak influence on the general structure of the pharmacophore. Consequently, electronic rather than steric factors appear to be implicated in the drop in activity for almost all the compounds studied.

Furthermore, results obtained for the affinities of the different compounds for MT_1 and MT_2 receptors indicate that the oxygen atom does not influence selectivity for these receptors.

However, the introduction of an oxygen atom in the amido chain could modify the flexibility or acidic character of the NH group and, therefore, influence the ability of the molecules to activate the receptor. The pharmacological profiles of these compounds were evaluated on the dermal melanocytes of *X. laevis* tadpoles. Melatonin, naphthalenic[20] and indolic[24] compounds have been shown to be potent agonists in this bioassay.

Several of the compounds synthesized (**10**, **12**–**17a**) were studied in the functional assay, and their EC_{50} values are reported in Table 2. Variations in the EC_{50} values of melatonin have been observed between batches of tadpoles at different times of the year; consequently the potency of the molecules was calculated as the EC_{50} (melatonin)/EC_{50} (compound) ratio determined in the same experiment.

All tested compounds were characterised as full agonists (100% of effect) and produced dose-related lightening of the skin of *Xenopus laevis* similarly to melatonin. As previously observed, potency was related to the affinity calculated from the receptor binding assays. Almost all the compounds (Table 1) were less potent than melatonin. However, as in the other series previously studied, the potency of the 2,7-dimethoxynaphthalene derivative **17a** was clearly emphasized (23-fold more potent than melatonin) but to a lesser extent than in the series of corresponding deoxy compounds which were more than 100-fold more potent than melatonin.[19]

In summary, introduction of an oxygen atom in the amido chain of melatoninergic ligands does not modify the pharmacological profile of the compounds since, similarly to the parent compounds, they were full agonists in the functional assay measuring the lightening of the skin of *Xenopus laevis* tadpoles. On the other hand, the presence of an oxygen rather than a carbon atom seems less favourable for binding to the receptor site as almost all the compounds were less potent than the corresponding deoxy derivatives. However, a potent compound, **17a**, was obtained, equipotent to melatonin in the binding assay and clearly superior in the melanophore aggregation assay.

Experimental

^1H and ^{13}C spectra were recorded on a BRUCKER AC 200 spectrometer (200 and 50.3 MHz respectively) with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) in δ units. ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), dd (doublet of doublet), triplet (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 the Châtenay-Malabry Pharmacy 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. 3-Methoxy benzyl alcohol, 2,5-dimethoxy benzyl alcohol, 3-methoxyphenylethanol and

Table 1. Inhibition of 2-[^{125}I]-iodomelatonin binding by compounds **10–18**

Compd	R′	hMT_1 receptors[a] K_i (nM)	hMT_2 receptors[a] K_i (nM)	Chicken brain receptors[b], K_i (nM)
10a	Me	>1000	69.4±6.9	520
10b	Et	>1000	>1000	>1000
10c	nPr	>1000	510	879±375
10d	$ClCH_2$	>1000	640	>1000
10e	cPr	>1000	>1000	>1000
11a	Me	>1000	>1000	>1000
11b	Et	>1000	>1000	>1000
11c	nPr	>1000	185±16.4	>1000
11d	$ClCH_2$	95.8±8.2	46.3±10	170±50
11e	cPr	>1000	>1000	>1000
12a	Me	>1000	>1000	940±180
12b	Et	201±34	186±37	270±65
12c	nPr	172±76.1	89.7±8	210±50
12d	$ClCH_2$	104±15.5	63.7±5.4	160±32
12e	cPr	>1000	>1000	>1000
13a	Me	7.51±2.1	11.7±2	55±17
13b	Et	2.1±0.4	2.6±0.6	20±4
13c	nPr	3.86±0.08	2.4±0.04	4.8±1.2
13d	$ClCH_2$	1.22±0.02	1.3±0.05	4.2±0.7
13e	cPr	1.84±0.5	4.43±0.03	6.6±1.5
14a	Me	27.1±7.8	9.43±0.6	40±11
14b	Et	10.6±3.5	2.32±0.6	17±4
14c	nPr	14±4	1.42±0.01	8.5±1.5
14d	$ClCH_2$	5.57±1.2	0.93±0.05	8.4±1.7
14e	cPr	471±89	96.2±14.8	69±14
15a	Me	NT	NT	1.7±0.4
15c	nPr	0.41±0.01	0.23±0.02	2±0.5
15e	cPr	NT	NT	1.5±0.3
16a	Me	NT	NT	55±3.2
16b	Et	NT	NT	75
16e	cPr	NT	NT	>1000
17a	Me	0. 24±0.07	0. 28±0.07	0.26±0.07
17b	Et	0. 117±0.04	0. 125±0.6	0.08±0.013
17c	nPr	0. 133±0.6	0.01±0.03	0.042±0.012
17d	$ClCH_2$	0.034±0.01	0.059.4±0.02	0.02±0.006
17e	cPr	0. 28±0.08	0.51±0.13	0.34±0.1
18a	Me	286±26	35.1±13.1	>1000
18b	Et	109±11.5	10.4±5.5	370±65
18c	nPr	132±22.5	6.13±2	350±220
18d	$ClCH_2$	23.5±2.5	5.4±0.1	130±60
18e	cPr	43.9±2.5	67±16	500±220
Melatonin		0.54±0.1	0.34±0.1	0.56±0.03

[a]2-[^{125}I]-iodomelatonin was used as radioligand and binding assays were carried out using membranes prepared from HEK 293 cells expressing human MT_1 or MT_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.
[b]Binding assays were carried out using membranes prepared from chicken brain. Membrane aliquots were incubated with 0.05 nM 2-[^{125}I]-iodomelatonin for 1 h at 25 °C. [a,b]Non-specific binding was defined with 10 μM 2-iodomelatonin. Each binding assay was performed in triplicate. Experiments were performed twice.

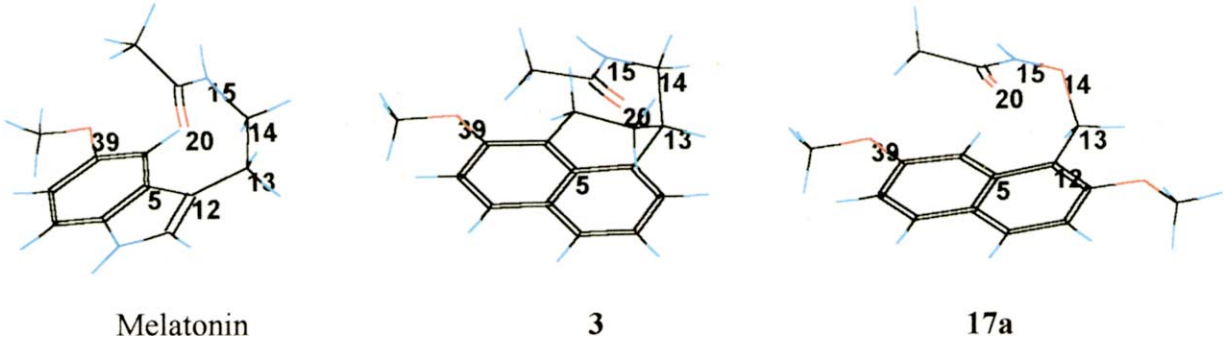


Figure 1. Minimum energy folded conformer of **17a**, melatonin and phenalene derivative **3**. The conformers of **17a** and **3** have been selected by conformational search (Alchemy 2000, version 3.2) and by their structural similarity to the CoMFA model of the melatonin pharmacophore described previously.[33] The fit of the three conformers on carbon atom C(5), nitrogen atom N(15) and oxygen atoms O(20) and O(39) gave a rms value of 0.2.

Table 2. Biological data for compounds **10a**, **12a**, **13a**, **14a**, **15a**, **16a** and **17a** for *X. laevis* melanophore aggregation

Compd	EC_{50} (nM) for melanophore aggregation	Potency with regard to melatonin (=1°)
10a	7.6 [4.9–11.70]	0.0005
12a	6.9 [3.21–14.9]	0.0005
13a	0.068 [0.034–0.13]	0.057
14a	0.34 [0.16–0.73]	0.011
15a	0.008 [0.0034–0.019]	0.48
16a	0.42 [0.19–0.92]	0.009
17a	0.00017 [0.00007–0.0004]	23
Melatonin	0.0039 [0.0022–0.0071]	1
Agomelatine	0.00031 [0.00014–0.00065]	12.5

X. laevis tadpoles were placed in groups of 5 in 100 mL beakers. The compounds under test (5 concentrations) were dissolved in a final volume of 5 mL and added to the beaker. The degree of the melanophore response was determined by examination of the head and body surface using the melanophore index (1–5) of Hogben and Slome.[25] EC_{50} values were determined using the PRISM software package and are the result of 2 separate experiments. The mean value is given with the range of values in brackets. The potency of the molecules was calculated as the EC_{50} (melatonin)/EC_{50} (compound) ratio determined in the same experiment.

acenapht-1-ol were commercially available. 7-Methoxy-1,2,3,4-tetrahydronapht-1-ol was prepared by the reduction of the corresponding ketone with $AlLiH_4$. (2,7-dimethoxynaphth-1-yl) methanol and 1-chloromethyl-2-methoxynaphthalene, 1-chloromethyl-7-methoxynaphthalene were prepared according to the process already reported.[28]

Preparation of *N*-alkoxyphtalimides 8a–i—general procedure. Method A

2 - [(2 - Methoxy - 1 - naphthyl)methoxy] - 1*H* - isoindole - 1,3(2*H*)-dione (8g). Sodium acetate (0.1 M) was added to a solution of *N*-hydroxyphthalimide (0.1 M) in 60 mL of DMSO which turned dark red. 1-Chloromethyl-2-methoxynaphthalene (0.1 M) in 20 mL of DMSO was added slowly to the mixture and the solution was warmed with stirring at 100 °C until decolouration of the solution had occurred. The mixture was extracted with chloroform (500 mL) and the organic solution was washed twice with saturated NaCl solution and dried over Na_2SO_4. The organic solvents were evaporated under reduced pressure and the solid residue was purified by column chromatography (silica gel) and eluted with CH_2Cl_2. The compound was isolated as a white solid (yield: 80%) mp 174 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.90 (s, 3H), 5.80 (s, 2H), 7.20–8.50 (m, 10H).

2 - [(7 - Methoxy - 1 - naphthyl)methoxy] - 1*H* - isoindole - 1,3(2*H*)-dione) (8f). It was prepared according to the previous method described for **8g**. The compound was isolated as a white solid (yield: 90%) mp 202 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 4.05 (s, 3H), 5.50 (s, 2H), 7.10–8.10 (m, 10H).

Method B

2 - [(3 - Methoxyphenyl)methoxy] - 1*H* - isoindole - 1,3(2*H*) - dione (8a). 3-Methoxybenzylic alcohol (2 mL, 16.1 mmol), *N*-hydroxyphthalimide (2.62 g, 16.1 mmol) and triphenylphosphine (4.22 g, 17.7 mmol) were dissolved in 80 mL of anhydrous THF. Diethyl azodicarboxylate (DEAD, 2.79 mL, 17.7 mmol) was added dropwise while stirring to the solution and the mixture was stirred for 25 h at room temperature. The solvent was evaporated under vacuum and the compound isolated as a yellow solid. It was purified by column chromatography (silica gel) and eluted with CH_2Cl_2. 2.26 g (yield: 88%) of white solid was obtained, mp 121 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.82 (s, 3H), 5.19 (s, 2H), 6.87–6.94 (m, 1H), 7.07–7.12 (m, 2H), 7.28 (t, J=7.8 Hz, 1H), 7.70–7.83 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 55.34, 79.77, 114.65, 115.46, 121.98, 129.57, 129.09, 135.40, 159.52, 163.56. Anal. ($C_{16}H_{13}NO_4$) calcd C 67.84H 4.62 N 4.94; F. C 67.71H 4.73 N 4.93.

2 - [(2,5 - Dimethoxyphenyl)methoxy] - 1*H* - isoindole - 1,3(2*H*)-dione (8b). It was prepared according to the previous method described for **8a**. The compound was crystallised in an EtOAc/hexane mixture to give white crystals (yield: 75%), mp 130 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.71–3.75 (2s, 6H), 5.25 (s, 2H), 6.86 (dd, J=9.4 Hz, J=3.0 Hz, 1H), 7.05 (sd, J=2.9 Hz, 1H), 7.71–7.78 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 55.83, 56.19, 74.50, 111.95, 115.94, 117.08, 123.35,134.30, 129.02,130.00, 152.46,153.46, 163.46. Anal. ($C_{17}H_{15}NO_5$) calcd C 65.17 H 4.82 N 4.47; F. C 65.12 H 4.75 N 4.43.

2 - [1 - (3 - Methoxyphenyl)ethoxy] - 1*H* - isoindole - 1,3(2*H*) - dione (8c). It was prepared according to the previous method described for **8a**. The compound was isolated as a colourless oil (yield: 92%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.69 (d, J=6.5 Hz, 3H), 3.81 (s, 3H), 5.49 (q, J=6.6 Hz, 1H), 6.82–7.10 (m, 3H), 7.22 (t, J=7.9 Hz, 1H), 7.67–7.73 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 20.79, 55.31, 85.04, 112.52, 114.92, 119.83, 129.35, 123.38, 134.32, 128.98, 140.81, 159.61, 163.82. Anal. ($C_{17}H_{15}NO_4$) calcd C 68.68 H 5.08 N 4.71; F. C 68.54 H 5.06 N 4.67.

2-[(3-Methoxyphenethyl)oxy]-1*H*-isoindole-1,3(2*H*)-dione (8d). It was prepared according to the previous method described for **8a**. The compound was crystallised after chromatography in an EtOAc/hexane mixture to give a white powder (yield: 83%), mp 85 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.13 (t, J=7.3 Hz, 2H), 3.80 (s, 3H), 4.43 (t, J=7.3 Hz, 2H), 6.71–6.90 (m, 3H), 7.20 (t, J=8.2 Hz, 1H), 7.71–7.8 ((m, 4H).). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 34.66, 55.21, 78.39, 112.29, 114.40, 121.16, 129.54, 123.54,134.50, 128.96, 138.41, 159.80, 163.68. Anal. ($C_{17}H_{15}NO_4$) calcd C 68.68 H 5.08 N 4.71; F. C 68.59 H 5.03 N 4.65.

2 - [(7 - Methoxy - 1,2,3,4 - tetrahydro - 1 - naphthalenyl)methoxy]-1*H*-isoindole-1,3(2*H*)-dione (8e). It was prepared according to the previous method described for **8a**. The compound was crystallised in an EtOAc/hexane mixture to give a white powder (yield: 69%), mp 88 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.74–2.92 (m, 6H), 3.77 (s, 3H), 5.26 (t, J=3.7 Hz), 6.83 (dd, J=8.4 Hz,

$J = 2.9$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 7.27 (sd, $J = 2.7$ Hz, 1H), 7.71–7.84 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 18. 13, 27. 55, 28. 25, 55.34, 83.69, 114.88, 116.46, 129.96, 123.44,134.47, 129.09, 130.94, 132.76, 157.72, 164.32. Anal. ($C_{19}H_{17}NO_4$) calcd C 70.58 H 5.34 N 4.33; F. C 70.37 H 5.25 N 4.28.

2-[(2,7-Dimethoxy-1-naphthyloxy]-1*H*-isoindole-1,3(2*H*)-dione (8h). It was prepared according to the previous method described for **8a**. The compound was crystallised in an EtOAc/hexane mixture to give a light yellow solid (yield: 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.97–4.11 (2s, 6H), 5.74 (s, 2H), 7.02 (dd, $J = 8.9$ Hz, $J = 2.5$ Hz, 1H), 7.10 (d, $J = 9.0$ Hz, 1H), 7.64–7.89 (m, 6H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 55.76, 56.97, 70.53, 101.97, 110.44, 117.05, 128.78, 131.72, 113.56, 124.79, 145.90, 123.43,134.38, 129.40, 157.68, 159.33, 163.13.

2-[1,2-Dihydro-1-acenaphthylenyloxy)-1*H*-isoindole-1,3(2*H*)-dione) (8i). It was prepared according to the previous method described for **8a**. The compound was crystallised in an EtOAc/hexane mixture to give light yellow solid (yield: 81%), mp 158 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.74 (dd, $J = 17.0$ Hz, $J = 6.6$ Hz, 1H), 3.69 (d, $J = 17.2$ Hz, 1H), 6.24 (sd, $J = 6.5$ Hz, 1H), 7.35 (d, $J = 6.8$ Hz, 1H), 7.47–7.58 (m, 2H), 7.65–7.88 (m, 7H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 38.11, 87.33, 120.13, 123.67, 122.90, 126.29, 127.78, 128.21, 123.58, 134.51, 129.41, 132.75, 139.39, 142.22, 142.75, 163.69. Anal. ($C_{20}H_{13}NO_3$) calcd C 76.18 H 4.15 N 4.44; F. C 76.09 H 4.26 N 4.40.

Preparation of *O*-alkylhydroxylamines—general procedure

1-[(Aminooxy)methyl]-3-methoxybenzene (9a). The phthalimide derivative **8a** (1.75 g, 6.2 mmol) was dissolved in 12 mL of EtOH. Hydrazine (0.3 mL, 6.2 mmol) was added slowly and the mixture was refluxed for 1 h. The mixture was cooled and poured into a solution (20 mL) of Na_2CO_3 (3%). The mixture was extracted with diethyl ether and the organic solution was dried over $MgSO_4$. The organic solvent was evaporated under vacuum and the hydroxylamine was obtained as a colourless oil (0.84 g, yield: 88%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.77 (s, 3H); 4.62 (s, 2H); 5.06 (br s, 2H), 6.81–6.92 (m, 3H); 7.24 (t, $J = 7.9$ Hz, 1H); 7.70–7.83 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 55.67, 78.83, 114.59, 114.67, 121.52, 130.50, 140.27, 161.33. Anal. ($C_8H_{11}NO_2$) calcd C 62.73 H 7.24 N 9.14; F. C 62.54 H 7.28 N 8.97.

1-[(Aminooxy)methyl]-2,5-dimethoxybenzene (9b). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil (yield: 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.03 (br s, 2H), 3.77–3.79 (2s, 6H), 4.73 (s, 2H), 6.80–6.94 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 55.79, 56.16, 72.96, 111.76, 113.80, 115.78, 126.62, 151.92, 153.58. Anal. ($C_9H_{13}NO_3$) calcd C 59.00 H 7.15 N 7.64; F. C 58.71 H 7.18 N 7.61.

1-[1-(Aminooxy)ethyl]-3-methoxybenzene (9c). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil (yield: 95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.41 (d, $J = 6.5$ Hz, 3H), 3.82 (s, 3H), 4.64 (q, $J = 6.5$ Hz, 1H, br s, 2H), 6.80–6.94 (m, 3H), 7.28 (t, $J = 7.5$ Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 221.93, 55.23, 82.90, 111.69, 113.21, 118.67, 129.65, 144.77, 159.91.

1-[2-(Aminooxy)ethyl]-3-methoxybenzene (9d). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil (yield: 89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm)) 2.88 (t, $J = 6.9$ Hz, 2H), 3.79 (s, 3H), 3.89 (t, $J = 6.9$ Hz, 2H), 4.95 (br s, 2H), 6.75–6.84 (m, 3H), 7.22 (t, $J = 8.4$ Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 35.11, 55.16, 76.38, 111.57, 114.72, 121.28, 129.40, 140.51, 159.71. Anal. ($C_9H_{15}NO_2$) calcd C 64.65 H 7.84 N 8.38; F. C 63.73 H 7.50 N 8.31.

1-(Aminooxy)-7-methoxy-1,2,3,4-tetrahydronaphthalene (9e). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil (yield: 83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.61–2.86 (m, 6H), 3.79 (s, 3H), 4.61 (t, $J = 3.7$ Hz, br s, 2H), 6.79 (dd, $J = 8.4$ Hz, $J = 2.7$ Hz, 1H), 6.97 (ds, $J = 2.7$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 18.96, 27.14, 28.58, 55.37, 79.81, 113.91, 114.65, 129.93, 130.33, 139.18, 157.68. Anal. ($C_{11}H_{15}NO_2$) calcd C 68.37 H 7.82 N 7.25; F. C 68.17 H 7.80 N 7.21.

1-[(Aminooxy)methyl]-7-methoxynaphthalene (9f). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm), 3.95 (s, 3H), 5.25 (s, 2H), 5.30 (s, 2H), 7.05–8.20 (m, 6H).

1-[(Aminooxy)methyl]-2-methoxynaphthalene (9g). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm), 3.90 (s, 3H), 5.25 (s, 2H), 5.30 (s, 2H), 7.05–8.20 (m, 6H).

1-[(Aminooxy)methyl]-2,7-dimethoxynaphthalene hydrochloride (9h). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil. The hydrochloride was prepared by the addition of HCl in diethyl ether (yield: 60%) mp 178 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 3.94–3.98 (2s, 6H), 5.57 (s, 2H), 7.01 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H), 7.24 (d, $J = 9.1$ Hz, 1H), 7.32 (ds, $J = 2.5$ Hz, 1H) 7.71 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 9.2$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 56.06, 56.99, 68.80, 102.50, 111.27, 117.50, 131.33, 133.46, 113.09, 125.99, 136.60, 159.13, 160.79. Anal. ($C_{13}H_{16}NO_3Cl$) calcd C 57.81 H 5.98 N 5.19; F. C 57.70 H 5.99 N 5.20.

1-(Aminooxy)-1,2-dihydroacenaphthylene (9i). It was prepared according to the previous method described for **9a**. The compound was isolated as a colourless oil (yield: 83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.40 (dd, $J = 16.5$ Hz, $J = 2.5$ Hz, 1H), 3.63 (dd, $J = 16.9$ Hz, $J = 7.0$ Hz, 1H), 7.30 (d, $J = 6.4$ Hz, 1H), 7.42–7.65 (m, 4H), 7.75 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ

(ppm) 38.15, 86.07, 120.62, 122.20, 123.59, 126.12, 128.66, 128.96, 132.28, 139.54, 142.33, 142.77. Anal. ($C_{12}H_{11}NO$) calcd C 77.81 H 5.98 N 7.56; F. C 77.57 H 6.21 N 7.40.

Preparation of the *N*-acyl-*O*-alkylhydroxylamines—general procedure

***N*-[(3-Methoxy-1-phenyl)methoxy]acetamide (10a).** The amine **9a** (0.3 g, 1.9 mmol) was dissolved in a biphasic system CH_2Cl_2/H_2O (10 mL/10 mL) in the presence of Na_2CO_3 (1.41 g, 13.3 mmol). Acetyl chloride (135 μL, 13.3 mmol) was added slowly while stirring at 0 °C. The mixture was stirred at room temperature for 3 h. The organic phase was separated, washed with a 1 N HCl solution and a NaCl saturated solution. The organic solution was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography (silica gel) and eluted with CH_2Cl_2 and a CH_2Cl_2/MeOH mixture (97/3) to give a yellow oil (0.13 g, yield: 34%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.82 (s, 3H), 3.77 (s, 3H), 4.79 (s, 2H), 6.86–6.98 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.46, 55.72, 78.91, 115.35, 115.48, 122.34, 130.52, 138.52, 170.12. Anal. ($C_{10}H_{13}NO_3$) calcd C 60.96 H 6.70 N 7.11; F. C 60.90 H 6.97 N 6.80.

***N*-[(3-Methoxy-1-phenyl)methoxy]propionamide (10b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a yellow oil (yield: 42%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.09 (t, J = 7.6 Hz, 3H), 2.05 (q, J = 7.6 Hz, 2H), 3.79 (s, 3H), 4.79 (s, 2H), 6.86–6.97 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.23, 27.11, 55.73, 78.87, 115.35, 115.50, 122.42, 130.50, 138.49, 161.30, 173.85. Anal. ($C_{11}H_{15}NO_3$) calcd C 63.14 H 7.22 N 6.69; F. C 62.95 H 7.31 N 6.54.

***N*-[(3-Methoxy-1-phenyl)methoxy]butyramide (10c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a colourless oil (yield: 86%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.89 (t, J = 7.4 Hz, 3H), 1.59 (sx, J = 7.3 Hz, 2H), 2.01 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 4.80 (s, 2H), 6.86–6.98 (m, 3H), 7.25 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.85, 20.09, 35.70, 55.73, 78.90, 115.38, 115.47, 122.42, 130.51, 138.52, 161.30, 172.82. Anal. ($C_{12}H_{17}NO_3$) calcd C 64.55 H 7.67 N 6.27; F. C 64.64 H 7.80 N 6.20.

***N*-[(3-Methoxy-1-phenyl)methoxy]chloracetamide (10d).** It was prepared according to the previous method described for **10a** with chloracetyl chloride. The compound was isolated as a white solid (yield: 86%) mp 88 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 3.78 (s, 3H); 3.92 (s, 2H), 4.83 (s, 2H), 6.86–6.98 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 40.90, 55.78, 79.00, 115.38, 115.57, 122.53, 130.59, 138.12, 161.31, 166.37. Anal. ($C_{10}H_{12}NO_3Cl$) calcd C 52.30 H 5.27 N 6.10; F. C 52.28 H 5.34 N 6.03.

***N*-[(3-Methoxy-1-phenyl)methoxy]cyclopropylcarboxamide (10e).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a white solid (yield: 81%) mp 87 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.73–0.88 (m, 4H), 1.28–1.46 (m, 1H), 3.79 (s, 3H), 4.79 (s, 2H), 6.87–6.98 (m, 3H); 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 7.09, 12.13, 55.72, 79.00, 115.33, 115.51, 122.37, 130.52, 138.58, 161.30, 173.81. Anal. ($C_{12}H_{15}NO_3$) calcd C 65.15 H 6.83 N 6.33; F. C 65.01 H 6.94 N 6.27.

***N*-[(2,5-Dimethoxy-1-phenyl)methoxy]acetamide (11a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white solid (yield: 59%) mp 59 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.82 (s, 3H), 3.74–3.76 (2s, 6H), 4.85 (s, 2H), 6.81–6.98 (m, 3H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.48, 56.19, 56.64, 73.60, 113.02, 115.71, 117.61, 126.06, 153.58, 155.00, 169.97. Anal. ($C_{11}H_{15}NO_4$) calcd C 58.66 H 6.71 N 6.22; F. C 58.68 H 6.73 N 6.11.

***N* - [(2,5 - Dimethoxy - 1 - phenyl)methoxy]propionamide (11b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white solid (yield: 61%) mp 74 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.09 (t, J = 7.6 Hz, 3H), 2.05 (q, J = 7.6 Hz, 2H), 3.74–3.76 (2s, 6H), 4.85 (s, 2H), 6.81–6.97 (m, 3H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.29, 27.4, 56.21, 56.65, 73.55, 113.03, 115.73, 117.69, 126.09, 153. 61, 154.98, 173.80. Anal. ($C_{12}H_{17}NO_4$) calcd C 60.24 H 7.16 N 5.85; F. C 60.13 H 7.18 N 5.83.

***N*-[(2,5-Dimethoxy-1-phenyl)methoxy]butyramide (11c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white solid (yield: 66%) mp 71 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.90 (t, J = 7.3 Hz, 3H), 2.05 (sx, J = 7.3 Hz, 2H), 3.74–3.77 (2s, 6H), 4.86 (s, 2H), 6.81–6.98 (m, 3H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.88, 20.10, 35.72, 56.19, 56.62, 73.58, 112.99, 115.72, 117.63, 126.08, 153. 62, 154.98, 172.64. Anal. ($C_{13}H_{19}NO_4$) calcd C 61.64 H 7.56 N 5.53 F. C 61.64 H 7.61 N 5.45.

***N* - [(2,5 - Dimethoxy - 1 - phenyl)methoxy]chloracetamide (11e).** It was prepared according to the previous method described for **10a** with chloroacetyl chloride. The compound was isolated as a white solid (yield: 30%) mp 72 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm), 3.74–3.77 (2s, 6H), 3.91 (s, 2H), 4.89 (s, 2H), 6.87–6.97 (m, 3H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 40.89, 56.22, 56.66, 73.68, 113.08, 116.01, 117.79, 125.70, 153. 68, 154.99, 166.75. Anal. ($C_{11}H_{14}NO_4Cl$) calcd C 50.88 H 5.43 N 5.39; F. C 50.84 H 5.46 N 5.19.

***N* - [(2,5 - Dimethoxy - 1 - phenyl)methoxy]cyclopropylcarboxamide (11f).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a white solid (yield: 84%) mp 83 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.67–0.90 (m, 4H), 1.33–1.43 (m, 1H), 3.74–3.77 (2s, 6H), 4.85 (s, 2H), 6.82–6.97

(m, 3H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 7.05, 12.15, 56.19, 56.64, 73.64, 113.01, 115.69, 117.60, 126.57, 154.61, 155.00, 174.54. Anal. ($C_{13}H_{17}NO_4$) calcd C 62.14 H 6.82 N 5.57; F. C 62.17 H 6.88 N 5.57.

***N*-[1-(3-Methoxyphenyl)ethoxy]acetamide (12a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white foam (yield: 50%) mp 93 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.48 (d, J = 6.5 Hz, 3H), 1.75 (s, 3H), 3.79 (s, 6H), 4.89 (q, J = 6.5 Hz, 1H), 6.83–6.94 (m, 3H), 7.25 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.39, 21.50, 55.78, 84. 47, 113.30, 114.97, 120.26, 130.61, 144.61, 161.42, 174.33. Anal. ($C_{11}H_{15}NO_3$) calcd C 63.14 H 7.22 N 6.69; F. C 63.16 H 7.27 N 6.60.

***N*-[1-(3-Methoxyphenyl)ethoxy]propionamide (12b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white foam (yield: 72%) mp 84 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.03 (t, J = 7.6 Hz), 1.48 (d, J = 6.5 Hz, 3H), 1.98 (q, J = 7.6 Hz, 2H), 3.79 (s, 6H), 4.89 (q, J = 6.6 Hz, 1H), 6.83–6.94 (m, 3H), 7.25 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.35, 21.36, 27.07, 55.72, 84. 30, 113.33, 114.93, 120.29, 130.53, 144.26, 161.35, 173.78. Anal. ($C_{12}H_{17}NO_3$) calcd C 64.55 H 7.67 N 6.27; F. C 64.42 H 7.76 N 6.12.

***N*-[1-(3-Methoxyphenyl)ethoxy]butyramide (12c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white foam (yield: 81%) mp 82 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.82 (t, J = 7.3 Hz, 3H), 1.46–1.59 (m, 5H), 1.95 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 4.90 (q, J = 6.5 Hz, 1H), 6.83–6.94 (m, 3H), 7.24 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.79, 35.64, 55.73, 84. 37, 113.32, 114.97, 120.30, 130.53, 144.79, 161.84, 174.61. Anal. ($C_{13}H_{19}NO_3$) calcd C 65.80 H 8.07 N 5.92; F. C 65.64 H 8.08 N 5.85.

***N*-[1-(3-Methoxyphenyl)ethoxy]chloracetamide (12d).** It was prepared according to the previous method described for **10a** with chloroacetyl chloride. The compound was isolated as a white foam (yield: 48%) mp 100 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.50 (d, J = 6.5 Hz, 3H), 3.79 (s, 3H), 3.84 (s, 2H), 4.95 (q, J = 6.5 Hz, 1H), 6.83–6.96 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 21.23, 40.72, 55.67, 84. 54, 113.27, 115.07, 120.22, 130.55, 143.80, 161.34, 166.31. Anal. ($C_{11}H_{14}NO_3Cl$) calcd C 54.22 H 5.79 N 5.75; F. C 54.31 H 5.83 N 5.75.

***N*-[1-(3-Methoxyphenyl)ethoxy]cyclopropylcarboxamide (12e).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white foam after recrystallisation in an AcOEt/Hexane mixture (yield: 86%) mp 126 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.66–0.86 (m, 4H), 1.28–1.38 (m, 1H), 1.48 (d, J = 6.5 Hz, 3H), 3.79 (s, 3H), 4.88 (q, J = 6.5 Hz, 1H), 6.83–6.95 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 12.03, 21.42, 55.71, 84. 42, 113.27, 114.87, 120.21, 130.54, 161.37, 173.89. Anal. ($C_{13}H_{17}NO_3$) calcd C 66.36 H 7.28 N 5.95; F. C 66.23 H 7.39 N 5.94.

***N*-[(3-Methoxyphenethyl)oxy]acetamide (13a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a colourless oil (yield: 70%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.84 (s, 3H), 2.90 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 4.01 (t, J = 7.0 Hz, 2H), 6.71–6.81 (m, 3H), 7.17 (t, J = 8.2 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.48, 35.52, 55.64, 77.95, 112.95, 115.64, 122.27, 130.46, 140.94, 161.33, 170.16. Anal. ($C_{11}H_{15}NO_3$) calcd C 63.14 H 7.22 N 6.69; F. C 62.89 H 7.35 N 6.57.

***N*-[(3-Methoxyphenethyl)oxy]propionamide (13b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a colourless oil (yield: 85%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.11 (t, J = 7.6 Hz), 2.08 (q, J = 7.6 Hz), 2.90 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 4.01 (t, J = 7.1 Hz, 2H), 6.71–6.82 (m, 3H), 7.17 (t, J = 8.1 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.24, 27.18, 35.61, 55.69, 77.98, 112.99, 115.70, 122.32, 130.51, 141.03, 161.37, 173.98. Anal. ($C_{12}H_{17}NO_3$) calcd C 64.55 H 7.67 N 6.27; F. C 64.60 H 7.70 N 6.20.

***N*-[2-(3-Methoxyphenethyl)oxy]butyramide (13c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a colourless oil (yield: 88%). ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.98 (t, J = 7.4 Hz), 1.62 (sx, J = 7.3 Hz, 2H), 2.04 (t, J = 7.3 Hz, 2H), 2.90 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 4.01 (t, J = 7.1 Hz, 2H), 6.71–6.82 (m, 3H), 7.16 (t, J = 8.1 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.90, 20.07, 35.57, 35.73, 55.64, 77.98, 112.94, 115.65, 122.27, 130.47, 161.33, 172.90. Anal. ($C_{13}H_{19}NO_3$) calcd C 65.80 H 8.07 N 5.90; F. C 65.67 H 8.10 N 5.80.

***N*-[(3-Methoxyphenethyl)oxy]chloracetamide (13d).** It was prepared according to the previous method described for **10a** with chloracetyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 59%) mp 62 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 2.92 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 3.95 (s, 2H), 4.01 (t, J = 7.1 Hz, 2H), 6.72–6.83 (m, 3H), 7.17 (t, J = 7.9 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 35.52, 40.97, 55.71, 77.99, 113.04, 115.68, 122.31, 130.54, 161.32, 166.40. Anal. ($C_{11}H_{14}NO_3Cl$) calcd C 54.22 H 5.79 N 5.75; F. C 54.36 H 5.98 N 5.64.

***N* - [(3 - Methoxyphenethyl)oxy]cyclopropylcarboxamide (13e).** It was prepared according to the previous method described for **10a** with cyclopropanecarbonyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 69%) mp 86 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.72–0.91 (m, 4H), 1.39–1.42 (m, 1H), 2.90 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 4.01 (t, J = 7.1 Hz, 2H), 6.71–6.82 (m, 3H), 7.17 (t, J = 7.9 Hz, 1H). ^{13}C NMR

(200 MHz, CD_3OD) δ (ppm) 7.26, 12.29, 35.61, 55.69, 78.09, 112.96, 115.70, 122.33, 130.51, 141.01, 161.32, 174.10. Anal. ($C_{11}H_{17}NO_3$) calcd C 66.36 H 7.28 N 5.95; F. C 66.24 H 7.38 N 5.92.

***N*-[(7-Methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)oxy]-acetamide (14a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 53%) mp 70 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.69–2.77 (m, 6H), 1.88 (s, 3H), 3.76 (s, 3H), 4.80 (t, J = 3.7 Hz, br s, 2H), 6.79 (dd, J = 8.4 Hz, J = 2.7 Hz, 1H), 6.99 (d, J = 8.4.7 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 20.63, 29.17, 30.38, 56.78, 83.26, 117.11, 117.40, 131.79, 136.51, 160.13, 171.25. Anal. ($C_{13}H_{17}NO_3$) Calc. C 66.36 H 7.28 N 5.95; F. C 66.19 H 7.36 N 5.88.

***N*-[(7-Methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)oxy]-propionamide (14b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 77%) mp 113 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.15 (t, J = 7.6 Hz, 3H), 1.70–2.24 (m, 4H), 2.13 (q, J = 7.6 Hz, 2H), 2.53–2.79 (m, 2H), 3.77(s, 3H), 4.81 (t, J = 3.7 Hz, 2H), 6.79 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.60, 27.26, 28.15, 29.36, 55.74, 82.19, 116.10, 116.38, 130.75, 131.55, 135.59, 159.10, 173.07. Anal. ($C_{14}H_{19}NO_3$) calcd C 67.45 H 7.68 N 5.62; F. C 67.24 H 7.76 N 5.73.

***N*-[(7-Methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)oxy]-butyramide (14c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/Hexane mixture (yield: 32%) mp 82 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.95 (t, J = 7.2 Hz, 2H), 1.6 (sx, J = 7.4 Hz, 2H), 1.56–2.26 (m, 4H), 2.09 (t, J = 7.2 Hz, 2H), 2.52–2.81 (m, 2H), 3.77(s, 3H), 4.81 (t, J = 3.7 Hz, 2H), 6.79 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 6.99 (d, J = 8.45 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.62, 20.17, 28.16, 29.38, 35.90, 55.76, 82.23, 116.10, 116.408, 130.76, 131.55, 135.59, 159.11, 173.06. Anal. ($C_{15}H_{21}NO_3$) calc. C 68.42 H 8.04 N 5.32; F. C 68.23 H 7.98 N 5.52.

***N*-[(7-Methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)oxy]-chloracetamide (14d).** It was prepared according to the previous method described for **10a** with chloroacetyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/Hexane mixture (yield: 21%) mp 91 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.70–2.27 (m, 4H), 2.61–2.79 (m, 2H), 3.77(s, 3H), 3.97 (s, 2H), 4.84 (t, J = 3.7 Hz, 2H), 6.80 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.55, 28.15, 29.33, 41.05, 55.79, 82.50, 116.07, 116.58, 130.83, 131.61, 135.19, 159.13, 166.58. Anal. ($C_{13}H_{161}NO_3Cl$) calcd C 57.89 H 5.98 N 5.19; F. C 58.08 H 6.10 N 5.03.

***N*-[(7-Methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)oxy]-cyclopropylcarboxamide (14e).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 68%) mp 160 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.76–0.91 (m, 4H), 1.32–1.51(m, 1H), 1.70–2.25 (m, 4H), 2.54–2.79 (m, 2H), 3.77(s, 3H), 4.80 (t, J = 3.7 Hz, 2H), 6.79 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 7.00 (d, J = 8.45 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 7.03, 12.25, 19.61, 28.14, 29.38, 35.90, 55.76, 82.21, 116.09, 116.47, 130.78, 131.58, 135.65, 159.14, 174.36. Anal. ($C_{15}H_{19}NO_3$) calcd C 68.94 H 7.31 N 5.36; F. C 68.75 H 7.38 N 5.32.

***N*-[7-Methoxy-1-naphthyl)methoxy]acetamide (15a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white solid after recrystallisation in an Et_2O/CH_2Cl_2 mixture (yield: 90%) mp 125 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.85 (s, 3H), 3.95 (2s, 3H), 5.30 (s, 2H), 7.10–7.80 (m, 6H), 8.45 (s, 1H). Anal. ($C_{14}H_{15}NO_3$) calcd C 68.57 H 6.17 N 5.72; F. C 68.48 H 6.29 N 5.68.

***N*-[7-Methoxy-1-naphthyl)methoxy]butyramide (15c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white solid after recrystallisation in an Et_2O/CH_2Cl_2 mixture (yield: 90%) mp 98 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.95 (t, J = 7 Hz, 3H), 1.75 (m, 2H), 2.10 (m, 2H), 4.00 (s, 3H), 7.15–7.85 (m, 6H), 8.20 (s, 1H). Anal. ($C_{16}H_{19}NO_3$) calcd C 70.33 H 7.01 N 5.13; F. C 70.33 H 7.10 N 5.08.

***N*-[7-Methoxy-1-naphthyl)methoxy]cyclopropylcarboxamide (15e).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a white solid after recrystallisation in cyclohexane (yield: 90%) mp 125 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.65–1.20 (m, 5H), 3.95 (s, 3H), 5.30 (s, 2H), 7.15–7.80 (m, 5H), 8.40 (s, 1H). Anal. ($C_{16}H_{17}NO_3$) calcd C 70.83 H 76.32 N 5.16; F. C 70.76 H 6.47 N 5.11.

***N*-[2-Methoxy-1-naphthyl)methoxy]acetamide (16a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white solid after recrystallisation in an Et_2O/CH_2Cl_2 mixture (yield: 39%) mp 112 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.9 (s, 3H), 3.95 (s, 3H), 5.45 (s, 2H), 7.10–8.40 (m, 6H), 8.50 (s, 1H). Anal. ($C_{14}H_{15}NO_3$) calcd C 68.57 H 6.17 N 5.72; F. C 68.41 H 6.27 N 5.73.

***N*-[2-Methoxy-1-naphthyl)methoxy]propionamide (16b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white solid after recrystallisation in Et_2O (yield: 39%) mp: 118 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.15 (t, 3H), 1.9–2.5 (m, 2H), 3.90 (s, 3H), 5.50 (s, 2H), 7.10–8.40 (m, 6H), 8.80

(s, 1H). Anal. ($C_{15}H_{17}NO_3$) calcd C 69.47 H 6.62 N 5.40; F. C 69.25 H 6.71 N 5.34.

***N*-[2-Methoxy-1-naphthyl)methoxy]cyclopropylcarboxamide (16e).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a white solid after recrystallisation in Et_2O (yield: 39%) mp 145 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.51–1.30 (m, 5H), 3.95 (s, 3H), 5.50 (s, 2H), 7.10–8.20 (m, 6H), 8.40 (s, 1H). Anal. ($C_{16}H_{17}NO_3$) calcd C 70.82 H 6.32 N 5.16; F. C 70.98 H 6.52 N 5.11.

***N*-[2,7-Dimethoxy-1-naphthyl)methoxy]acetamide (17a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a beige solid after recrystallisation in an AcOEt/hexane mixture (yield: 39%) mp 143 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.85 (s, 3H), 3.93–3.95 (2s, 6H), 5.38 (s, 2H), 6.96 (dd, $J=8.9$ Hz, $J=2.4$ Hz, 1H), 7.19 (d, $J=9.0$ Hz, 1H), 7.66 (d, $J=8.8$ Hz, 1H), 7.73 (d, $J=2.3$ Hz, 1H), 7.80 (d, $J=9.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.59, 56.07, 57.09, 62.73, 103.42, 111.52, 117.66, 130.74, 132.12, 125.96, 136.60, 137.25, 158.61, 160.35, 170.13. Anal. ($C_{15}H_{17}NO_4$) calcd C 65.44 H 6.22 N 5.09; F. C 65.10 H 6.28 N 4.80.

***N*-[2,7-Dimethoxy-1-naphthyl)methoxy]propionamide (17b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a beige solid after recrystallisation in an AcOEt/hexane mixture (yield: 60%) mp 121 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.12 (t, $J=7.6$ Hz, 3H), 2.07 (q, $J=7.6$ Hz, 2H), 3.92–3.95 (2s, 6H), 5.37 (s, 2H), 6.97 (dd, $J=8.9$ Hz, $J=2.4$ Hz, 1H), 7.18 (d, $J=9.0$ Hz, 1H), 7.65 (d, $J=9.0$ Hz, 1H), 7.70 (d, $J=2.2$ Hz, 1H), 7.79 (d, $J=9.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.33, 27.29, 56.05, 57.04, 69.04, 103.49, 111.49, 116.02, 117.61, 130.76, 132.10, 125.97, 137.12, 158.61, 160.33, 174.52. Anal. ($C_{16}H_{19}NO_4$) calcd C 66.42 H 6.62 N 4.84; F. C 66.38 H 6.67 N 4.76.

***N*-[2,7-Dimethoxy-1-naphthyl)methoxy]butyramide (17c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 61%) mp 86 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm), 0.93 (t, $J=7.3$ Hz, 3H), 1.62 (sx, $J=7.3$ Hz, 2H), 2.03 (t, $J=7.3$ Hz, 2H), 3.88–3.94 (2s, 6H), 5.34 (s, 2H), 6.95 (dd, $J=8.9$ Hz, $J=2.3$ Hz, 1H), 7.13 (d, $J=9.0$ Hz, 1H), 7.62 (d, $J=9.0$ Hz, 1H), 7.68 (d, $J=2.1$ Hz, 1H), 7.75 (d, $J=9.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.96, 20.18, 35.93, 56.07, 57.02, 69.17, 103.52, 111.45, 115.99, 117.61, 125.95, 130.75, 132.09, 125.97, 137.10, 158.55, 160.32, 172.91. Anal. ($C_{17}H_{21}NO_4$) calcd C 67.31 H 6.98 N 4.62; F. C 67.02 H 7.00 N 4.55.

***N*-[2,7-Dimethoxy-1-naphthyl)methoxy]chloracetamide (17d).** It was prepared according to the previous method described for **10a** with chloroacetyl chloride. The compound was isolated as a beige solid after recrystallisation in an AcOEt/hexane mixture (yield: 67%) mp 122 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm), 3.92–3.94 (2s, 6H), 3.96 (s, 2H), 5.41 (s, 2H), 6.96 (dd, $J=8.9$ Hz, $J=2.4$ Hz, 1H), 7.18 (d, $J=9.0$ Hz, 1H), 7.65 (d, $J=8.9$ Hz, 1H), 7.73 (d, $J=2.0$ Hz, 1H), 7.79 (d, $J=9.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 56.11, 57.05, 69.25, 103.40, 111.45,115.62, 117.71, 125.94, 130.76, 132.26, 137.11, 158.67, 160.43, 166.45. Anal. ($C_{15}H_{16}NO_4Cl$) calcd C 58.17 H 5.21 N 4.52; F. C 58.23 H 5.23 N 4.48.

***N*-[2,7-Dimethoxy-1-naphthyl)methoxy]cyclopropylcarboxamide (17e).** It was prepared according to the previous method described for **10a** with cyclopropylcarbonyl chloride. The compound was isolated as a beige solid after recrystallisation in an AcOEt/hexane mixture (yield: 67%) mp 149 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 0.72–0.79 (m, 2H), 1.32–1.42 (m, 1H), 3.91–3.93 (2s, 6H), 5.36 (s, 2H), 6.96 (dd, $J=9.0$ Hz, $J=2.4$ Hz, 1H), 7.16 (d, $J=9.0$ Hz, 1H), 7.62–7.67 (m, 2H), 7.77 (d, $J=9.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 5.09, 7.00, 12.27, 56.01, 57.09, 69.14, 103.45, 111.56, 116.14, 117.56, 125.99, 130.76, 132.07, 137.06, 158.78, 160.32, 173.99. Anal. ($C_{17}H_{19}NO_4$) calcd C 67.76 H 6.35 N 4.65; F. C 67.65 H 6.42 N 4.62.

***N*-[1,2-Dihydro-1-acenaphthylenyloxy)acetamide (18a).** It was prepared according to the previous method described for **10a** with acetyl chloride. The compound was isolated as a white foam after recrystallisation in an AcOEt/hexane mixture (yield: 71%) mp 125 °C. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.87 (s, 3H), 3.45 (d, $J=17$ Hz, 1H), 3.66 (dd, $J=17.7$ Hz, $J=6.8$ Hz, 1H), 5.89 (d, $J=5.1$ Hz), 7.30 (d, $J=6.8$ Hz, 1H), 7.43–7.67 (m, 4H), 7.78 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 19.59, 38.01, 87.44, 120.88, 123.26, 123.81, 126.75, 128.86, 129.25, 132.77, 139.49, 142.26, 142.70, 170.69. Anal. ($C_{14}H_{13}NO_2$) calcd C 73.99 H 5.76 N 6.16; F. C 73.81 H 5.92 N 6.08.

***N*-[1,2-Dihydro-1-acenaphthylenyloxy)propionamide (18b).** It was prepared according to the previous method described for **10a** with propionyl chloride. The compound was isolated as a white foam after recrystallisation in an AcOEt/hexane mixture (yield: 81%) mp 137 °C ^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 1.08 (t, $J=7.6$ Hz, 3H), 2.08 (q, $J=7.6$ Hz), 3.44 (d, $J=17.8$ Hz, 1H), 3.44 (d, $J=17.8$ Hz, 1H), 3.60 (dd, $J=18.2$ Hz, $J=6.6$ Hz, 1H), 5.84 (d, $J=4.9$ Hz, 1H), 7.27 (d, $J=6.7$ Hz, 1H), 7.40–7.64 (m, 4H), 7.76 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 10.27, 27.22, 38.03, 87.42, 120.87, 123.29, 123.80, 126.74, 128.84, 129.24, 132.74, 139.51, 142.27, 142.73, 174.48. Anal. ($C_{15}H_{15}NO_2$) calcd C 74.67 H 6.27 N 5.80; F. C 74.53 H 6.41 N 5.75.

***N*-[1,2-Dihydro-1-acenaphthylenyloxy)butyramide (18c).** It was prepared according to the previous method described for **10a** with butyryl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 63%) mp 105 °C. ^{1}H

NMR (200 MHz, CD_3OD) δ (ppm) 0.88 (t, $J=7.4$ Hz, 3H), 1.59 (sx, $J=7.3$ Hz, 2H), 2.05 (t, $J=7.3$ Hz, 2H), 3.46 (d, $J=17.8$ Hz, 1H), 3.446 (d, $J=17.8$ Hz, 1H), 3.65 (dd, $J=18.3$ Hz, $J=6.7$ Hz, 1H), 5.89 (d, $J=4.9$ Hz, 1H), 7.30 (d, $J=6.4$ Hz, 1H), 7.43–7.66 (m, 4H), 7.78 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 13.89, 20.12, 35.81, 38.03, 87.42, 120.87, 123.29, 123.79, 126.74, 128.85, 129.23, 132.46, 139.21, 142.33, 143.01, 173.32. Anal. ($C_{16}H_{17}NO_2$) calc. C 75.27 H 6.71 N 5.48; F. C 75.25 H 6.80 N 5.40.

***N*-[1,2-dihydro-1-acenaphthylenyloxy)chloracetamide (18d).** It was prepared according to the previous method described for **10a** with chloroacetyl chloride. The compound was isolated as a white solid after recrystallisation in an AcOEt/hexane mixture (yield: 72%) mp: 132 °C. ^1H NMR (200 MHz, CD_3OD) δ (ppm) 3.47 (d, $J=17.8$ Hz, 1H), 3.68 (dd, $J=178.2$ Hz, $J=6.7$ Hz, 1H), 3.3.98 (s, 2H), 5.93 (d, $J=6.1$ Hz, 1H), 7.32 (d, $J=6.9$ Hz, 1H), 7.44–7.68 (m, 4H), 7.80 (d, $J=8.1$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 38.01, 40.96, 87.62, 120.95, 123.38, 123.85, 126.85, 128.84, 129.28, 132.81, 140.01, 142.62, 145.01, 162.50. Anal. ($C_{14}H_{12}NO_2Cl$) calc. C 64.25 H 4.62 N 5.35; F. C 64.17 H 4.77 N 5.26.

***N*-[1,2-Dihydro-1-acenaphthylenyloxy)cyclopropylcarboxamide (18e).** It was prepared according to the previous method described for **10a** with cyclopropanecarbonyl chloride. The compound was isolated as a white powder after recrystallisation in an AcOEt/hexane mixture (yield: 59%) mp: 126 °C. ^1H NMR (200 MHz, CD_3OD) δ (ppm) 0.77–0.89 (m, 4H), 3.47 (d, $J=17.7$ Hz, 1H), 3.67 (dd, $J=18.3$ Hz, $J=6.5$ Hz, 1H), 5.88 (d, $J=6.3$ Hz, 1H), 7.32 (d, $J=6.6$ Hz, 1H), 7.44–7.67 (m, 4H), 7.79 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (200 MHz, CD_3OD) δ (ppm) 7.18, 12.19, 37.89, 87.38, 120.80, 123.19, 123.70, 126.62, 128.74, 129.14, 132.59, 139.37, 142.14, 142.61, 174.64. Anal. ($C_{16}H_{15}NO_2$) calcd C 75.87 H 5.97 N 5.53; F. C 75.67 H 6.14 N 5.45.

Melatonin receptor binding assay in chicken brain membranes. Chickens (*Redbrook*, male or female, 4 months (3–4 kg); Cellubio, France) were decapitated at 12 am. The brains were quickly removed and stored at −80 °C.

The brains were homogenized (Polytron) in 10 vol 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 vol of the same buffer to a final concentration of 5 or 6 mg of protein/mL as determined by the method of Lowry. 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 2-iodomelatonin and represented 10% of the total binding. K_i values were determined using the Cheng–Prussof equation.

Melatonin receptor binding assay with human MT_1 and MT_2 receptors. Competitive inhibition curves were performed according to the methods already described[22] with the receptors expressed in HEK-293 cells with [^{125}I]iodomelatonin as the radioligand. 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 nM 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 γ counter (TopCount). Non-specific binding was defined with 10 μM melatonin. K_i values were calculated as above.

Melanophore contraction in *X. laevis* tadpoles. The *X. laevis* tadpoles (stage 41) used in this study were obtained from the Laboratoire de Biologie Cellulaire et Reproduction CNRS (Rennes, France). They were maintained in an aquarium in the laboratory at 22 °C under natural illumination for 8 days and fed daily with powdered fish food. 18 h before the bioassay, tadpoles of uniform stage, size, and color, were selected, removed from the aquarium, and placed in groups of 5 in 100 mL beakers on a dark background and filled with 45 mL of pool water. They were illuminated with artificial light (60 W) for 3 h before the experiments which were performed at midday. The compound under test was dissolved in a DMF and water mixture in a final volume of 5 mL and added to the liquid in the beaker (45 mL) to achieve the final selected concentration. After 15 min, the experiment was terminated by the addition of a 37% formaldehyde solution. The degree of the melanophore response in each tadpole was determined by examination of the melanophore configuration under a microscope (Leitz, magnification ×4) and evaluated according to the melanophore index scale (1–5) of Hogben and Slome.[25] The data are the results of the sum of the determinations of the melanophore index on the body and the dorsal surface of the tadpole. EC_{50} values for the compounds were determined from the concentration-response curves obtained with 5 concentrations in the range of 0.1–100×the K_i values for chicken brain receptors. The mean of the control data (animals treated with vehicle) represented 100%. The results ($n=2$) were calculated using the PRISM program (Graphpad).

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