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Substituted Oxygenated Heterocycles and Thio-Analogues: Synthesis and Biological Evaluation as Melatonin Ligands

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Abstract—A new series of substituted oxygenated heterocycles and thio-analogues were synthesized and evaluated as melatonin receptor ligands. The replacement of the indolic moiety of melatonin by heterocyclic skeleton such as 1,4-benzodioxin, 2,3-dihydro-1,4-benzodioxin, chroman, 2,3-dihydro-1,4-benzoxathiin, thiochroman, carrying the amidic chain on the aromatic ring, leads to compounds showing a weak affinity for melatonin receptors, except for the compounds **1cb** and **1hb**.

Introduction

Since melatonin was isolated and identified as *N*-acetyl-5-methoxytryptamine by Lerner in 1958,[1] the interest in this hormone has been steadily growing. In vertebrates this hormone has its primary sites of production in the pineal gland and the photoreceptor cells of the retina, where it is synthesized from serotonin via a two-steps biochemical pathway.[2,3] Melatonin plays a fundamental role in a number of related actions. Its activity, mediated through high-affinity-G-protein-coupled receptors, is mainly related to the regulation of the photoperiodic responses,[4] the entrainment of the mammalian circadian-rhythms,[5] the induction of sleep in humans,[6] and retinal physiology.[7] Recently, the antitumoral properties of melatonin, its implication in the responsiveness of the immune system,[8] and its free radical scavenger properties have also been described.[9] Despite its potential involvement in the regulation in many possible physiological processes, two problems limit its therapeutic use at the present time. Firstly, its very short biological half-life (15–30 min), due to its rapid catabolism to 6-hydroxymelatonin and *N*-acetylkynurenamines. Secondly, the lack of selectivity of melatonin at its target sites, mt_1, MT_2, and MT_3,[10] although the physiological role of the last two receptors is still unclear.[11,12] Therefore, research on new molecules capable of mimicking or antagonizing responses to melatonin has been considerably developed. Such compounds represent important tools for the understanding of the physiological roles of melatonin. Thus, several indolic analogues[13–20] of melatonin have been found to act as ligands and many papers reported the synthesis of several non-indolic bioisosteres.[21–31]

It is well known that some structural requirements are in favor of a good affinity for the melatonin receptors. For example in phenylethyl amide series, the *ortho* and *meta* positions of the methoxy group on the phenyl ring are more optimal than the *para* positions.[22,25,29] Moreover, the variable length of the side chain is able to provide a good relative position to the methoxy group and the *N*-acyl group of the ligands.[29]

Therefore, we decided to examine if these assessments could be confirmed in a series of heterocyclic compounds, whose structure represents a conformational restriction of the (2- or 3-methoxyphenyl)alkyl amides.

In order to mimic compounds described by Garratt et al.[29] and Langlois et al.,[25] which possess methoxy group in *ortho* or *meta* position, we have synthesized 2,3-dihydro-1,4-benzodioxinic and 2,3-dihydro-1,4-benzoxathiinic

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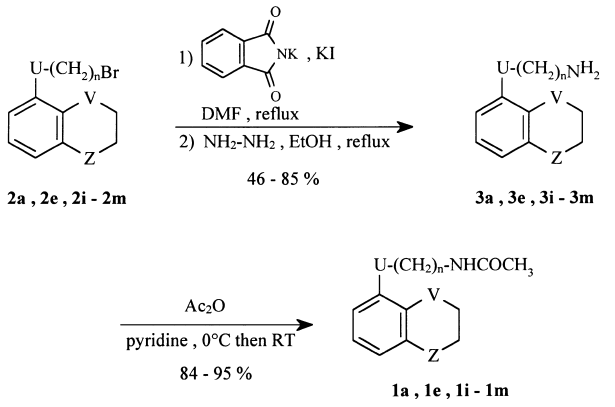
structural families with variable *N*-acylalkyl side chain on the aromatic ring, in *ortho* position of the oxygen or sulfur atom of the heterocycle. 2,3-Insaturated analogues were also prepared and, in the same way, 2,3-dihydro-1,4-benzodioxinic, chromanic and thiochromanic compounds, where an oxygen atom is intercalated between the aromatic ring and the *N*-alkanamido side chain.

In this paper, we report our results on the synthesis and the biological evaluation of those new non-indolic melatonin-ligands (Fig. 1).

Chemistry

The synthesis of amides **1a**, **1e**, **1i**–**1m** required access to a number of different bromo derivatives **2a**, **2e**, **2i**–**2m**. Compound **2a** was obtained by radical bromination of 5-methyl-2,3-dihydro-1,4-benzodioxin. Compounds **2i**–**2m** were generated by treatment of corresponding phenols with appropriate dibromoalkanes in basic medium. Bromo derivative **2e** was prepared by heating of *N*-[2-(3,4-dihydro-2*H*-1-benzothiopyran-8-yloxy)]-bromoethane **2m** in anhydrous acetonitrile. Bromides **2a**, **2e**, **2i**–**2m** were smoothly substituted by potassium phthalimide in *N,N*-dimethylformamide at reflux in the presence of potassium iodide to provide the corresponding phthalimido compounds. The latter products were cleaved by hydrazine hydrate in refluxing ethanol leading to amides **3a**, **3e**, **3i**–**3m** in satisfactorily global yields. The acetylation of these amines with acetic anhydride in pyridine gave amides **1a**, **1e**, **1i**–**1m** in very good yields (Scheme 1).

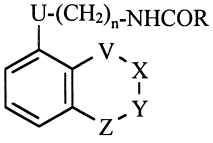


	U	V	Z	n
2a , 3a , 1a	CH_2	O	O	0
2e , 3e , 1e	CH_2	S	O	2
2i , 3i , 1i	O	O	O	2
2j , 3j , 1j	O	O	O	3
2k , 3k , 1k	O	O	O	4
2l , 3l , 1l	O	O	CH_2	2
2m , 3m , 1m	O	S	CH_2	2

Scheme 1.

The syntheses of target compounds **1b**, **1d** and **1f** are depicted in Scheme 2. Treatment of either bromides **2a** and **2e** (vide infra) or tosylate **4**[32] with potassium cyanide in *N,N*-dimethylformamide gave required nitriles **5b**, **5d** and **5f**. Reduction of these compounds was carried out with lithium aluminum hydride in diethyl ether, and the resulting amines **3b**, **3d** and **3f** acylated with acetic anhydride in pyridine to supply amides **1b**, **1d**, **1f** in good overall yield.

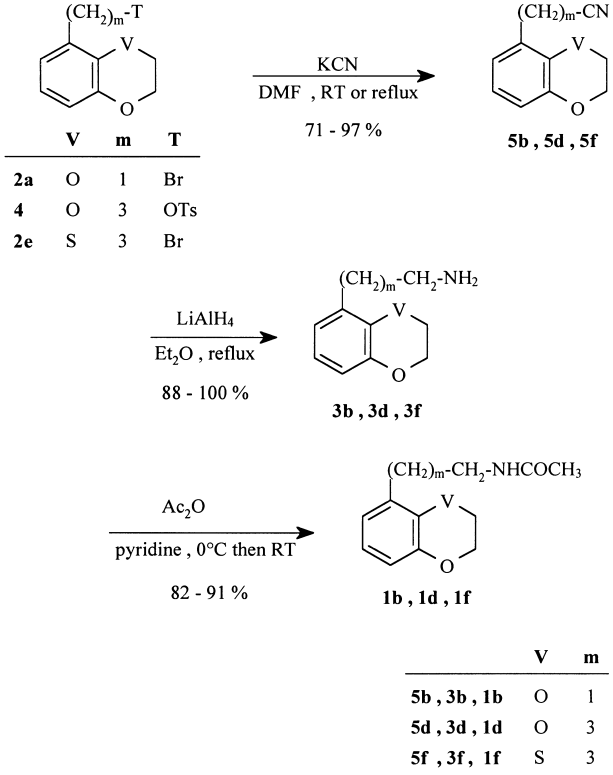
The synthesis of the new amino derivatives **1c** and **1h** is outlined in Scheme 3. The aldehyde **6** was synthesized



Compound	U	V	Z	X-Y	n	R
1a	CH_2	O	O	CH_2-CH_2	0	CH_3
1b	CH_2	O	O	CH_2-CH_2	1	CH_3
1ca	CH_2	O	O	CH_2-CH_2	2	CH_3
1cb	CH_2	O	O	CH_2-CH_2	2	*n*-Pr
1d	CH_2	O	O	CH_2-CH_2	3	CH_3
1e	CH_2	S	O	CH_2-CH_2	2	CH_3
1f	CH_2	S	O	CH_2-CH_2	3	CH_3
1g	CH_2	S	O	CH_2-CH_2	4	CH_3
1ha	CH_2	O	O	CH=CH	2	CH_3
1hb	CH_2	O	O	CH=CH	2	*n*-Pr
1i	O	O	O	CH_2-CH_2	2	CH_3
1j	O	O	O	CH_2-CH_2	3	CH_3
1k	O	O	O	CH_2-CH_2	4	CH_3
1l	O	O	CH_2	CH_2-CH_2	2	CH_3
1m	O	S	CH_2	CH_2-CH_2	2	CH_3

Figure 1. Compounds **1a**–**m** synthesized.

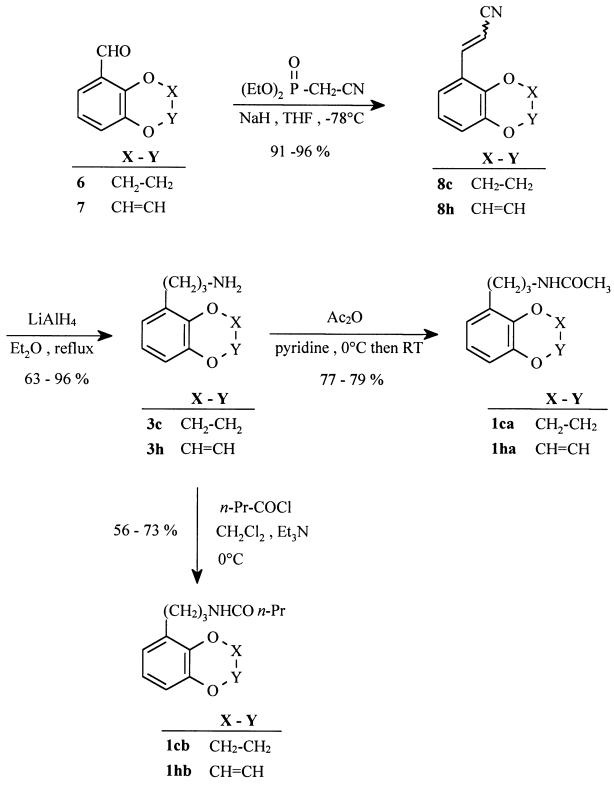
via route developed in our laboratories.[33] The carbonyl derivative **7** was obtained from 5-carboxy-1,4-benzodioxin.[34] Using the Horner–Emmons modification of the Wittig reaction, compounds **6** and **7** were converted to propenenitriles **8c** and **8h**, which were reduced in amines **3c** and **3b** by treatment with lithium aluminum hydride. The acetylation of these amines with acetic anhydride in pyridine gave acetamides **1ca** and **1ha** whereas its condensation with butyryl chloride in the presence of triethylamine in anhydrous methylene chloride afforded butyramides **1cb** and **1hb**.



	V	m	T
2a	O	1	Br
4	O	3	OTs
2e	S	3	Br

	V	m
5b , 3b , 1b	O	1
5d , 3d , 1d	O	3
5f , 3f , 1f	S	3

Scheme 2.



X - Y	
6	CH_2-CH_2
7	CH=CH

X - Y	
8c	CH_2-CH_2
8h	CH=CH

X - Y	
3c	CH_2-CH_2
3h	CH=CH

X - Y	
1ca	CH_2-CH_2
1ha	CH=CH

X - Y	
1cb	CH_2-CH_2
1hb	CH=CH

Scheme 3.

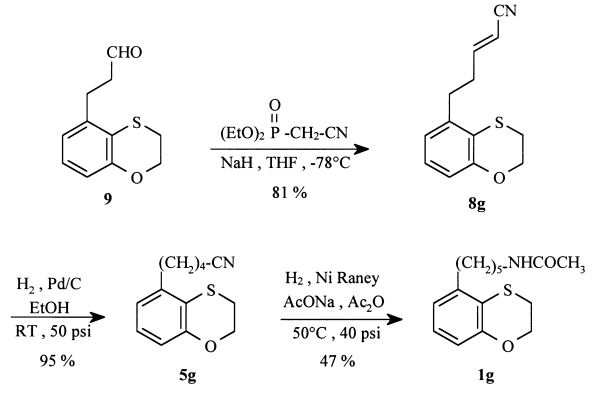
Biological Results and Discussion

The affinities of these new heterocyclic compounds for melatonin binding sites were evaluated in vitro, on ovine pars tuberalis membranes. The binding values are summarized in Table 1. The best compounds were evaluated on chicken brain membranes (Table 2) in order to confirm the affinity in another model, and to compare with data published previously.

In addition to the binding data, bioassays are carried out to characterize the activity of the reported compounds on forskolin stimulated cAMP production, according to the methodology described by Howell et al.[35] Indeed, melatonin at 1 nM inhibits (typically 80%) this forskolin stimulated production of cAMP.

In each experiment the cAMP responses are normalized against the response induced by forskolin (F) 10 μM alone, which is taken as the 100% effect. The effect of 10 μM drug alone (D), with forskolin (F/D), and with forskolin and melatonin (F/M/D) is compared to the effect of forskolin and melatonin (F/M).

The indexed activity of melatonin (M) is defined from the normalized response ratio $[F-F/M]/[F-F/M]=1$ and the indexed activity of the various treatments are



Scheme 4.

Table 1. Pharmacological evaluation on ovine pars tuberalis membranes of compounds **1**

	Binding	Activity	
	Ovine pars tuberalis $-\text{Log } K_i \pm \text{SD}$ ($n=3$)	Agonist index F/D ± SD ($n=3$)	Antagonist index F/M/D ± SD ($n=3$)
Melatonin	9.52 ± 0.10	1	
1a	3.70 ± 0.34	0.13 ± 0.08	1.01 ± 0.08
1b	6.62 ± 0.07	0.45 ± 0.14	0.86 ± 0.07
1ca	7.11 ± 0.01	0.85 ± 0.21	0.94 ± 0.25
1cb	7.46 ± 0.03	0.71 ± 0.01	0.76 ± 0.02
1d	7.12 ± 0.01	0.28 ± 0.13	0.66 ± 0.08
1e	7.02 ± 0.07	0.43 ± 0.12	0.88 ± 0.24
1f	7.14 ± 0.04	0.31 ± 0.19	0.82 ± 0.19
1g	6.66 ± 0.04	−0.13 ± 0.1	0.61 ± 0.11
1ha	7.20 ± 0.09	0.39 ± 0.11	0.81 ± 0.05
1hb	7.48 ± 0.35	0.66 ± 0.29	0.97 ± 0.33
1i	5.60 ± 0.03	0.29 ± 0.17	0.98 ± 0.16
1j	6.45 ± 0.05	0.42 ± 0.09	1.00 ± 0.08
1k	6.05 ± 0.04	0.29 ± 0.17	0.93 ± 0.03
1l	4.68 ± 0.01	−0.17 ± 0.18	0.94 ± 0.13
1m	<4.0	ND	ND

Table 2. Pharmacological evaluaton on chicken brain membranes of compounds **1cb** and **1hb**

	$-\text{Log } K_i$ Chicken brain ± SD ($n=3$)
Melatonin	10.0 ± 0.16
1cb	8.62 ± 0.36
1hb	8.15 ± 0.14

calculated as the ratio [F−treatment]/[F−F/M], where treatments are: basal response melatonin alone, drug alone, forskolin/drug (F/D, agonist index) or forskolin/melatonin/drug (F/M/D, antagonist index) at final concentrations indicated above. The criteria used to categorize the biological properties of the compounds are as follows:

Agonist index (F/D)	Antagonist index (F/M/D)	
F/D > 0.8	F/M/D > 0.8	Full agonist
0.4 < F/D < 0.8	F/M/D > 0.8	Weak agonist
0.4 < F/D < 0.8	0.2 < F/M/D < 0.8	Partial agonist/antagonist
F/D < 0.4	F/M/D < 0.2	Antagonist
F/D < 0.4	F/M/D > 0.8	No activity

The results are summarized in Table 1.

The binding results obtained in the 2,3-dihydro-1,4-benzodioxinic, 2,3-dihydro-1,4-benzoxathiinic, and 1,4-benzodioxinic series are in good agreement with those of Garratt et al.[29] Indeed in the (alkoxyphenyl)alkyl amide series, when the alkoxy position is fixed, especially in *meta* position of the side chain, there is a significant increase in affinity if this chain becomes longer. This is the case for the series in this study, with compounds containing oxygen atoms at fixed positions. (e.g. **1a** $K_i = 2.0\times10^{-4}$ M, **1d** $K_i = 7.6\times10^{-8}$ M).

If we compare compounds **1b**, **1ca**, **1d**, **1e**, **1f**, **1g**, **1ha**, which possess variable alkyl acetamide side chains, we can notice that ethanamide **1b** and pentanamide **1g** have comparable affinities which are 2.5- to 3.5-fold lower than those of propanamides (**1ca**, **1c**, **1ha**) and butanamides (**1d**, **1f**).

A methanamide side chain (**1a**) and to a lesser extent ethanamide (**1b**), is precluding a simultaneous favorable interaction between the *N*-acyl group and the heteroatoms of the molecule, and the main amino acid residues of the transmembrane domains, thus playing a role in establishment of a binding interaction as shown on ovine melatonin receptor by Conway et al.,[36] Navajas et al.,[37] and Sugden et al.[38] This is the same case with too much flexibility of pentanamide side chain **1g**.

Moreover, **1g** is the only compound of this series which displays an antagonist activity. The NH group of the amidic function can not take place with such a long side chain in order to provide a hydrogen bond for full functional activation of the receptor response. All the other compounds have at least a partial agonist activity and the best activation of the receptor occurs with compound **1ca**, which is a full agonist.

The results obtained for compound **1d**, have helped to determine which of the two oxygen atoms plays a predominant role in the affinity. Indeed the K_i value of **1d** ($K_i = 7.6\times10^{-8}$ M) and the K_i value published for the *N*-acetyl 3-(3-methoxyphenyl)-propanamine[29] ($K_i = 6.3\times10^{-8}$ M) are of the same rank of order, whereas there is a large difference with the value of K_i for the *N*-acetyl-3-(2-methoxyphenyl)propanamine ($K_i = 1.1\times10^{-6}$ M).

Therefore, one of the interactions that occur between the heterocyclic compounds and the receptor, concerns preferentially the oxygen atom in *meta* position of the side chain rather than the oxygen, or sulfur atom, in the ortho position. It was already the case with tricyclic compounds published by Leclerc et al.,[26] where it was shown that the electronic interaction between oxygen and receptor was optimal when the lone pairs of electrons were appropriately oriented.

Globally, the different heterocyclic skeletons do not lead to important variations of the binding affinities, from a structural family to another (on the one hand, 2,3-dihydro-1,4-benzodioxin **1ca**, 2,3-dihydro-1,4-benzoxathiin **1e**, 1,4-benzodioxin **1ha**, and on the other hand, 2,3-dihydro-1,4-benzodioxin **1d**, 2,3-dihydro-1,4-benzoxathiin **1f**), as long as the presence of the oxygen atom in meta position of the side chain is respected.

However, inside an homogeneous heterocyclic family, differences appear when the nature of the *N*-acyl group is modified. Indeed among the best compounds such as **1ca** and **1ha** ($K_i = 7.7\times10^{-8}$ M and 6.3×10^{-8} M, respectively), the replacement of the acetyl group by a butanoyl group leads to an improvement of the affinity (**1cb** $K_i = 3.5\times10^{-8}$ M, **1hb** $K_i = 3.3\times10^{-8}$ M). This result is not surprising, according to former publications in other melatoninergic series.[15,16,21,23,29]

Another type of bioisosteric pharmacomodulations concerns the intercalation of an oxygen atom between the aromatic cycle and the alkyl side chain, in 2,3-dihydro-1,4-benzodioxin, chroman, thiochroman series, which leads to a significant loss of affinity (**1j** $K_i = 3.5\times10^{-7}$ M compared to **1d** $K_i = 7.6\times10^{-8}$ M). In that case, it is obvious that the oxygen atom plays an unfavorable role since there is a loss of affinity (≈4.5-fold).

These results correlate with previous results, although not provided on the same membrane preparation, where the incidence of a such oxygen atom is similar, and where the same structural analogy exists between these described compounds and our compounds. Indeed, on one hand the sequence *N*-acetyl-2-(3-alkoxyphenyloxy)ethanamine can be identified both in **1j** ($K_i = 3.5\times10^{-7}$ M) and in the *N*-acetyl-3-amino-5-methoxychroman[23] which also displays a poor binding affinity ($K_i = 8.4\times10^{-6}$ M). On the other hand, the sequence *N*-acetyl-3-(3-alkoxyphenyl)propanamine is contained both in **1d** ($K_i = 7.6\times10^{-8}$ M) and in the 2-acetamido-8-methoxytetralin ($K_i = 4.6\times10^{-8}$ M).[22]

In that series with alkoxy acetamidic side chain, the particularly very poor binding obtained for compounds **1l** and **1m** can be explained by the absence of oxygen atom in *meta* position. However, **1i** displays a better affinity which confirms the respective roles of the heteroatoms contained in these heterocyclic structures.

The two best compounds in this study are **1cb** and **1hb**. Their binding affinities have been evaluated on chicken brain membranes (Table 2) in order to be compared with the values obtained on ovine pars tuberalis membranes (Table 1). Chicken binding experiments provide similar binding affinity values to ovine binding experiments and confirm the possible comparison between the ovine binding model and the chicken binding model. The affinities of these compounds are in the nanomolar range (**1cb** $K_i = 2.4\times10^{-9}$ M, **1hb** $K_i = 7.0\times10^{-9}$ M) and are quite similar to those of the *N*-butanoyl-3-(3-methoxyphenyl) propanamine described by Garratt et al.,[29] ($K_i = 5.5\times10^{-9}$ M) on chicken brain too.

These results confirm the interaction of the *N*-acyl group and heteroatom for conformational restricted compounds **1cb** and **1hb**, previously described for methoxyphenylalkylamides compounds.[29] In these two families of compounds, the interacting groups are retained in the appropriate relative position and provide to the compounds significant binding affinities for the melatonin receptor.

Conclusion

In conclusion, these results show the interest of the new 2,3-dihydro-1,4-benzodioxin or 1,4-benzodioxin derivatives as non-indolic melatoninergic agents. This study confirms the hypothesis that compounds with conformational restriction are melatoninergic ligands.

Experimental Protocols

Chemistry

Melting points were determined on a Köfler hot-stage and are uncorrected. Proton NMR were recorded on a Bruker 300 spectrometer. The coupling constants are recorded in hertz (Hz) and the chemical shifts are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Infrared spectra were obtained with Perkin–Elmer spectrophotometers 297 and Paragon 1000 PC version 2. Mass spectra were recorded on a R 10-10 C Nermag (70 eV) apparatus. Organic solvents were purified when necessary according to literature methods[39] or purchased from Aldrich Chimie. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Buchi rotatory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F_{254}), and spots were visualized with UV light or an alcohol solution of ammonium cerium (IV) nitrate. Column chromatography was performed with Kieselgel 60 (70–230 mesh) silica gel (Merck) for gravity columns and Kieselgel 60 (230–400 mesh) silica gel (Merck) for flash columns. When analyses are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon. The column chromatography solvents employed were distilled and solvent mixtures were reported as volume to volume ratios.

The compound **2a** was prepared from 2-methylresorcinol by heating in acetone in the presence of 1,2-dibromoethane and potassium carbonate followed by treatment of the obtained compound with *N*-bromosuccinimide in the presence of 2,2′-azobisisobutyronitrile in carbon tetrachloride at reflux (global yield: 67%).

The compounds **2i**–**2m** were obtained by treatment of appropriate phenols with 1,*n*-dibromoalkanes in the presence of potassium carbonate in acetone at reflux (yields: 40–74%).

The compound **2e** was synthesized by heating of *N*-[2-(3,4-dihydro-2*H*-1-benzothiopyran-8-yloxy)]-bromoethane **2m** in anhydrous acetonitrile at reflux for 48 h (yield: 80%).

General procedure for the synthesis of the amines 3a, 3e, 3i–3m

The appropriate bromo derivatives **2** (6 mmol) and potassium phthalimide 1.67 g, (9.03 mmol) were stirred in the presence of catalytic amount of potassium iodide (700 mg, 0.42 mmol) in *N,N*-dimethylformamide (10 mL) at reflux for 3 h under inert atmosphere. After cooling at room temperature, the insoluble salts were eliminated by filtration and the mixture was diluted with water. The solid precipitate was filtered, washed with water and dried in a vacuum dessicator over phosphorous pentoxide to give the desired phthalimido compounds which were used without further purification.

To a solution of compounds obtained above (6 mmol) in ethanol (20 mL) was added, at reflux, hydrazine hydrate (0.58 mL, 12 mmol). After refluxing for 5 h and cooling of the reaction mixture, the volatiles were evaporated under reduced pressure to give a dark brown oil which is dissolved in a cold solution of methylene chloride in order to precipitate the phthalylhydrazine. This one was filtered off and the solvent was evaporated under reduced pressure to provide the pure amino derivatives **3a**, **3e** and **3i**–**3m**.

***N*-[(2,3-Dihydro-1,4-benzodioxin-5-yl]-methanamine 3a.** Yellow oil; yield: 62%. IR (neat) ν 3370–3280, 1205, 1070 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.80 (br s, 2H, NH_2), 3.73 (s, 2H, CH_2N), 4.18–4.24 (m, 4H, H_2 and H_3), 6.72 (s, 3H, H_{arom}).

***N*-[3-(2,3-Dihydro-1,4-benzoxathiin-5-yl)]-propanamine 3e.** Yellow oil; yield: 60%; IR (neat) ν 3370–3290, 1258, 1084 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.74 (q, 2H, $J=7.4$, CH_2), 1.96 (br s, 2H, NH_2), 2.61 (t, 2H, $J=7.4$, $ArCH_2$), 2.76 (t, 2H, $J=7.4$, CH_2N), 3.11 (t, 2H, $J=4.7$, H_3), 4.36 (t, 2H, $J=7.4$, H_2), 6.68–6.76 (m, 2H, H_6 and H_8), 6.68–7.82 (m, 1H, H_7).

***N*-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)]ethanamine 3i.** Orange solid; mp 64–65 °C; yield: 75%; IR (KBr) ν 3560–3360, 1207, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (br s, 2H, NH_2), 3.04 (t, 2H, $J=5.2$, CH_2N), 3.97 (t, 2H, $J=5.2$, OCH_2), 4.17–4.25 (m, 4H, H_2 and H_3), 6.42–6.48 (m, 2H, H_6 and H_8), 6.67 (t, 1H, $J=8.3$, H_7).

***N*-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy]-propanamine 3j.** White solid; mp 133–134 °C, yield: 69%; IR (KBr) 3560–3400, 1209, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (br s, 2H, NH_2), 1.90 (q, 2H, $J=6.4$, CH_2), 2.85 (t, 2H, $J=6.4$, CH_2N), 4.03 (t, 2H, $J=6.4$, OCH_2), 4.17–4.23 (m, 4H, H_2 and H_3), 6.41–6.45 (m, 2H, H_6 and H_8), 6.66 (t, 1H, $J=8.2$, H_7).

***N*-[4-2(2,3-Dihydro-1,4-benzodioxin-5-yloxy]-butanamine 3k.** Yellow oil; yield: 85%; IR (neat) ν 3370–3300, 1215, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (br s, 2H, NH_2), 1,59 (q, 2H, $J=6.6$, CH_2), 1.85 (q, 2H, $J=6.6$, CH_2), 2.74 (t, 2H, $J=6.6$, CH_2N), 4.00 (t, 2H, $J=6.6$, OCH_2), 4.21–4.29 (m, 4H, H_2 and H_3), 6.44–6.50 (m, 2H, H_6 and H_8), 6.71 (t, 1H, $J=8.3$, H_7).

***N*-[2-(3,4-Dihydro-2*H*-1-benzopyran-8-yloxy)]-ethanamine 3l.** Yellow oil; yield: 46%; IR (neat) ν 3410–3320, 1206 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (br s, 2H, NH_2), 1.95 (q, 2H, $J=6.0$, H_3), 2.75 (t, 2H, $J=6.0$, H_4), 3.04 (t, 2H, $J=5.4$, CH_2N), 4.18–4.27 (m, 4H, H_2 and OCH_2), 6.70–6.77 (m, 3H, H_{arom}).

***N*-[2-(3,4-Dihydro-2*H*-1-benzothiopyran-8-yloxy)]-ethanamine 3m.** White solid; mp 44–45 °C; yield: 64%; IR (neat) 3390–3300, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (br s, 2H, NH_2), 2.06 (q, 2H, $J=6.6$, H_3), 2.79 (t, 2H, $J=6.6$, H_2 or H_4), 2.97 (t, 2H, $J=6.6$, H_2 or H_4), 3.06 (t, 2H, $J=5.9$, CH_2N), 4.08 (t, 2H, $J=5.9$, OCH_2), 6.74 (t, 2H, $J=8.1$, H_5 and H_7), 6.90 (t, 1H, $J=8.1$, H_6).

General procedure for the synthesis of the cyano derivatives 5b and 5f

To a stirred mixture of bromo derivatives **2c** (200 mg, 0.87 mmol) or **2e** (200 mg, 0.73 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added potassium cyanide (1.1 equiv) under inert atmosphere. The reaction mixture was stirred at room temperature for 12 h, then potassium cyanide (1.1 equiv) was added again. After this addition, the reaction mixture was allowed to stir at room temperature for supplementary 12 h. The solvent was removed at reduced pressure and the residue was taken up with dichloromethane and water. The aqueous phase was extracted with dichloromethane and the collected organic layers were washed with water and then dried ($MgSO_4$).

After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (eluent: petroleum ether:AcOEt, 9:1 for **5b** and petroleum ether:AcOEt, 7:3 for **5f**).

5-Cyanomethyl-2,3-dihydro-1,4-benzodioxin 5b. White solid; mp 46–47 °C; yield: 71%, IR (KBr) ν 2365, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 2H, CH_2), 4.21–4.27 (m, 4H, H_2 and H_3), 6.78–6.86 (m, 3H, H_6, H_7 and H_8), anal $C_{10}H_9NO_2$ (C,H,N).

5-(3-Cyano propyl)-2,3-dihydro-1,4-benzoxathiin 5f. Colorless oil; yield: 97%; IR (neat) ν 2234, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (q, 2H, $J=7.2$, CH_2), 2.36 (t, 2H, $J=7.2$, CH_2), 2.74 (t, 2H, $J=7.2$, CH_2), 3.13 (t, 2H, $J=4.6$, H_3), 4.37 (t, 2H, $J=4.6$, H_2), 6.71 6.76 (m, 2H, H_6 and H_8), 6.95 (t, 1H, $J=7.9$, H_7), anal $C_{12}H_{13}NOS$ (C,H,N).

5-(3-Cyanopropyl)-2,3-dihydro-1,4-benzodioxin 5d. A mixture of tosylate **4** (2 g, 5.74 mmol) and potassium cyanide (448 mg, 6.89 mmol) in *N,N*-dimethylformamide (20 mL) was stirred for 5 h 30 min at 100 °C under inert atmosphere. After cooling, the solvent was removed at reduced pressure and the mixture was taken up with dichloromethane and water. The aqueous phase was extracted three times with dichloromethane and the organic extract was washed with water, then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by column chromatography (eluent: petroleum ether:AcOEt, 7:3) to obtain the desired compound **5d** as a yellowish oil; yield: 77%; IR (neat) ν 2250, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (q, 2H, $J=7.4$, CH_2), 2.30 (t, 2H, $J=7.4$, CH_2), 2.71 (t, 2H, $J=7.4$, CH_2), 4.20–4.26 (m, 4H, H_2 and H_3), 6.65–6.75 (m, 3H, H_{arom}), anal $C_{12}H_{13}NO_2$ (C,H,N).

General procedure for the synthesis of the amines 3b, 3d and 3f

To a stirred suspension of lithium aluminum hydride (173 mg, 4.5 mmol) in anhydrous ether (10 mL) under an Ar atmosphere and at 0 °C was added dropwise a solution of cyano compounds **4b**, **4d** or **4f** (2.3 mmol) in ether (5 mL). After the addition, the reaction mixture was heated at reflux for 4 h. After cooling, water

(0.17 mL), 15% NaOH solution (0.17 mL) and water (0.52 mL) were successively added. The mixture was filtered, and the filtrate was dried over $MgSO_4$. The solvent was evaporated in vacuo to afford the pure amines **3b**, **3d** and **3f**.

***N*-[2-(2,3-Dihydro-1,4-benzodioxin-5-yl]ethanamine 3b.** Yellowish oil; yield: 100%; IR (neat) ν 3600–3140, 1283, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (br s, 2H, NH_2), 2.64–2.68 (m, 2H, CH_2), 2.84–2.88 (m, 2H, CH_2), 4.16–4.20 (m, 4H, H_2 and H_3), 6.62–6.70 (m, 3H, H_{arom}).

***N*-[4-(2,3-Dihydro-1,4-benzodioxin-5-yl]-butanamine 3d.** Colorless oil; yield: 97%; IR (neat) ν 3620–3160; 1290, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (br s, 2H, NH_2), 1.58–1.70 (m, 4H, CH_2), 2.61 (t, 2H, $J=7.4$, $ArCH_2$), 2.71 (m, 2H, CH_2N), 4.18–4.23 (m, 4H, H_2 and H_3), 6.66–6.74 (m, 3H, H_{arom}).

***N*-[4-(2,3-Dihydro-1,4-benzoxathiin-5-yl]-butanamine 3f.** Yellowish oil; yield: 88%; IR (neat) ν 3680–3140, 1302, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (br s, 2H, NH_2), 1.47–1.70 (m, 4H, CH_2), 2.58 (t, 2H, $J=7.4$, $ArCH_2$), 2.73 (t, 2H, $J=6.6$, CH_2N), 3.13 (t, 2H, $J=4.4$, H_3), 4.38 (t, 2H, $J=4.4$, H_2), 6.67–6.75 (m, 2H, H_6 and H_8), 6.92 (t, 2H, $J=8.1$, H_7).

General procedure for the synthesis of propenenitrile derivatives 8c and 8h

To a stirred suspension of sodium hydride (1.15 equiv, 60% dispersion in mineral oil) in tetrahydrofuran (20 mL), at 0 °C, was added diethyl cyanomethylphosphonate (1.1 equiv) under inert atmosphere. After stirring for 10 min at 0 °C, the reaction mixture was cooled at −78 °C, then was dropwise added a solution of the aldehyde **6** (984 mg, 6 mmol) or **7** (988 mg, 6.1 mmol) in THF (20 mL). Stirring was maintained at −78 °C for 90 min. The reaction mixture was warmed at room temperature and quenched with saturated sodium hydrogenocarbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated to leave a residue which was chromatographed on silica gel (eluent: petroleum:AcOEt, 7:3) to furnish the cyano derivatives **8c** and **8h**.

3-(2,3-Dihydro-1,4-benzodioxin-5-yl)-2-propenenitrile 8c. White solid; the mixture of two isomers *Z* and *E* was obtained (*Z*/*E*:3/1), yield 91%; IR (KBr) ν 2208, 1300, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37–4.28 (m, 4H, H_2 and H_3), 5.55 (d, 1H, $J=12.0$, CHCN *Z* isomer), 6.05 (d, 1H, $J=16.0$, CHCN *E* isomer), 6.85–6.95 (m, 3H, H_{arom}), 7.45 (d, 1H, $J=12.0$, ArCH *Z* isomer), 7.55 (d, 1H, $J=16.0$, ArCH *E* isomer), anal $C_{11}H_9NO_2$ (C,H,N).

3-(1,4-Benzodioxin-5-yl)-2-propenenitrile 8h. White solid; the mixture of two isomers *Z* and *E* was obtained (*Z*/*E*:1/1), yield 96%; IR (KBr) ν 2210, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (d, 1H, $J=12.0$, CHCN *Z* isomer), 5.93–6.02 (m, 3H, OCH and CHCN *E* isomer), 6.70–6.99 (m, 3H, H_{arom}), 7.14 (d, 1H, $J=12.0$, ArCH *Z* isomer), 7.33 (d, 1H, $J=17.0$, ArCH *E* isomer), anal $C_{11}H_7NO_2$ (C,H,N).

General procedure for the synthesis of the amino compounds 3c and 3h

To a solution of the propenenitriles **8c** or **8h** (5 mmol) in anhydrous diethyl ether (40 mL) was added portionwise lithium aluminum hydride (20 mmol) at room temperature under inert atmosphere and the mixture was stirred at reflux for 5 h. After cooling at room temperature, water was added dropwise to destroy the excess hydride, the mixture was filtered on Celite and the filtrate was concentrated in vacuo to give the pure amines **3c** or **3h**.

3-(2,3-Dihydro-1,4-benzodioxin-5-yl)-propanamine 3c. Yellowish oil; yield 63%; IR (neat) ν 3390–3150, 1282, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (br s, 2H, NH_2), 1.79 (q, 2H, $J=7.8$, CH_2), 2.62 (t, 2H, $J=7.8$, CH_2), 2.72 (t, 2H, $J=7.8$, CH_2), 4.22–4.29 (m, 4H, H_2 and H_3), 6.68–6.79 (m, 3H, H_{arom}).

3-(1,4-Benzodioxin-5-yl)-propanamine 3h. Yellow oil; yield 96%; IR (neat) ν 3390–3250, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.75 (m, 4H, CH_2 and NH_2), 2.54 (t, 2H, $J=7.5$, CH_2), 2.78 (t, 2H, $J=7.0$, CH_2), 5.92 (d, 1H, $J=3.5$, H_2 or H_3), 5.97 (d, 1H, $J=3.5$, H_2 or H_3), 6.52 (dd, 1H, $J=7.5$, 2.0, H_{arom}), 6.71–6.88 (m, 2H, H_{arom}).

5-(4-Cyanobut-3-ene)-2,3-dihydro-1,4-benzoxathiin 8g. Compound **8g** was prepared starting from the aldehyde **9** (500 mg, 2.4 mmol) according to the general procedure described above and purified by column chromatography (eluent: petroleum ether:AcOEt, 7:3) to afford the pure compound **8g** (*E* isomer) as yellowish oil; yield: 81%; IR (neat) ν 2208, 1305, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (td, 2H, $J=6.0$, 2.0, CH_2), 2.75 (t, 2H, $J=6.0$, $ArCH_2$), 3.13 (t, 2H, $J=5.0$, H_3), 4.38 (t, 2H, $J=5.0$, H_2), 5.35 (td, 1H, $J=17.0$, 2.0, CH=C), 6.69–6.80 (m, 3H, CHCN, H_6 and H_8), 6.95 (t, 1H, $J=7.7$, H_7), anal $C_{13}H_{13}NOS$ (C,H,N).

5-(4-Cyanobutyl)-2,3-dihydro-1,4-benzoxathiin 5g. The unsaturated nitrile **8g** (400 mg, 1.71 mmol) was dissolved in anhydrous ethanol (20 mL), (10% in mass). Pd-C catalyst was added, and the reaction mixture was treated in a Parr hydrogenation flask for 12 h at room temperature under a hydrogen pressure of 50 psi. After filtering off of the catalyst, the volatiles were removed under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether: AcOEt, 7:3) to afford **5g** in 95% yield as a colorless oil; IR (neat) ν 2244, 1302, 1078 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (t, 4H, $J=7.3$, CH_2), 2.35 (t, 2H, $J=7.3$, CH_2CN), 2.68 (t, 2H, $J=7.3$, $ArCH_2$), 3.08 (t, 2H, $J=4.4$, H_3), 4.32 (t, 2H, $J=4.4$, H_2), 6.60–6.80 (m, 2H, H_6 and H_8), 6.95 (t, 1H, $J=7.9$, H_7), anal $C_{13}H_{15}NOS$ (C,H,N).

General procedure for the synthesis of the acetamides 1a, 1b, 1ca, 1d–1f, 1ha, 1i–1m

To a stirred solution of amines **3** (3 mmol) in anhydrous pyridine (5 mL) under an Ar atmosphere and at 0 °C was

added dropwise acetic anhydride (0.34 mL, 3.6 mmol). After the addition, the reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in dichloromethane. The combined organic extracts were washed with water and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (eluent: $CHCl_3$:AcOEt, 70:30) to yield **1a**, **1b**, **1ca**, **1d**–**1f**, **1ha**, **1i**–**1m**.

***N*-[2,3-Dihydro-1,4-benzodioxin-5-yl)methyl]-acetamide 1a.** Yield 85%. White solid; mp 117–118 °C; IR (KBr) ν 3300, 1638, 1099 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.92 (s, 3H, CH_2), 4.18–4.25 (m, 4H, H_2 and H_3), 4.34 (s, 2H, CH_2N), 6.70–6.85 (m, 3H, H_{arom}), MS (CI with NH_3) *m*/*z* 208 (M + 1), anal $C_{11}H_{13}NO_3$ (C,H,N).

***N*-[2-(2,3-Dihydro-1,4-benzodioxin-5-yl)ethyl]-acetamide 1b.** Yield 91%. White solid; mp 56–57 °C; IR (KBr) ν 3340, 1629, 1068 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.92 (s, 3H, CH_3), 2.77 (t, 2H, $J = 6.6$, $ArCH_2$), 3.45 (t, 2H, $J = 6.6$, NCH_2), 4.20–4.26 (m, 4H, H_2 and H_3), 6.65–6.75 (m, 3H, H_{arom}), MS (CI with NH_3) *m*/*z* 222 (M + 1), anal $C_{12}H_{15}NO_3$ (C,H,N).

***N*-[3-(2.3-Dihydro-1,4-benzodioxin-5-yl)propyl]-acetamide 1ca.** Yield 77%. Yellowish oil; IR (neat) ν 3291, 1672, 1109 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.71 (q, 2H, $J = 7.4$, CH_2), 1.88 (s, 3H, CH_3), 2.53 (t, 2H, $J = 7.4$, $ArCH_2$), 3.17 (t, 2H, $J = 7.4$, CH_2N), 4.13–4.23 (m, 4H, H_2 and H_3), 6.59–6.68 (m, 3H, H_{arom}), MS (CI with NH_3) *m*/*z* 236 (M + 1), anal $C_{13}H_{17}NO_3$ (C,H,N).

***N*-[4-(2,3-Dihydro-1,4-benzodioxin-5-yl)butyl]-acetamide 1d.** Yield 82%. Yellow gum; IR (neat) ν 3308, 1672, 1076 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.49–1.66 (m, 4H, CH_2), 1.95 (s, 3H, CH_3), 2.58 (t, 2H, $J = 7.3$, $ArCH_2$), 3.25 (t, 2H, $J = 6.9$, CH_2N), 4.22–4.26 (m, 4H, H_2 and H_3), 6.65–6.75 (m, 3H, H_{arom}), MS (CI with NH_3) *m*/*z* 250 (M + 1), anal $C_{14}H_{19}NO_3$ (C,H,N).

***N*-[3-(2,3-Dihydro-1,4-benzoxathiin-5-yl)propyl]-acetamide 1e.** Yield 86%. Yellow gum; IR (neat) ν 3308, 1656, 1075 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.77 (q, 2H, $J = 7.3$, CH_2), 1.96 (s, 3H, CH_3), 2.58 (t, 2H, $J = 7.3$, $ArCH_2$), 3.13 (t, 2H, $J = 4.7$, H_3), 3.27 (t, 2H, $J = 7.3$, CH_2N), 4.38 (t, 2H, $J = 4.7$, H_2), 6.68–6.74 (m, 2H, H_6 and H_8), 6.92 (t, 1H, $J = 7.8$, H_7), MS (CI with NH_3) *m*/*z* 252 (M + 1), anal $C_{13}H_{17}NO_2S$ (C,H,N).

***N*-[4-(2,3-Dihydro-1,4-benzoxathiin-5-yl)butyl]-acetamide 1f.** Yield 90%. Yellow gum; IR (neat) ν 3300, 1646, 1075 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.56–1.70 (m, 4H, CH_2), 1.96 (s, 3H, CH_3), 2.59 (t, 2H, $J = 7.3$, $ArCH_2$), 3.13 (t, 2H, $J = 4.7$, H_3), 3.28 (t, 2H, $J = 6.9$, CH_2N), 4.38 (t, 2H, $J = 4.7$, H_2), 6.65–6.74 (m, 2H, H_6 and H_8), 6.93 (t, 1H, $J = 7.8$, H_7), MS (CI with NH_3) *m*/*z* 266 (M + 1), anal $C_{14}H_{19}NO_2S$ (C,H,N).

***N*-[3-(1,4-Benzodioxin-5-yl)propyl]-acetamide 1ha.** Yield 79%. Yellowish oil; IR (neat) ν 3420–3240, 1670, 1225 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.76–1.84 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.54 (t, 2H, $J = 7.2$, $ArCH_2$), 3.31 (t, 2H, $J = 7.2$, CH_2N), 5.93 (d, 1H, $J = 3.5$, OCH), 5.96 (d, 1H, $J = 3.5$, OCH), 6.53 (dd, 1H, $J = 2.0$, 8.0, H_6 or H_8), 6.72 (dd, 1H, $J = 2.0$, 8.0, H_6 or H_8), 6.79 (t, 1H, $J = 8.0$, H_7), MS (CI with NH_3) *m*/*z* 234 (M + 1), anal $C_{13}H_{15}NO_3$ (C,H,N).

***N*-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)ethyl]-acetamide 1i.** Yield 90%. White solid; mp 93–94 °C; IR (KBr) ν 3274, 1640, 1112 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.95 (s, 3H, CH_3), 3.66 (t, 2H, $J = 5.0$, CH_2N), 4.08 (t, 2H, $J = 5.0$, OCH_2), 4.26–4.32 (m, 4H, H_2 and H_3), 6.50 (d, 1H, $J = 8.3$, H_6 or H_8), 6.57 (d, 1H, $J = 8.3$, H_6 or H_8), 6.76 (t, 1H, $J = 8.3$, H_7), MS (CI with NH_3) *m*/*z* 238 (M + 1), anal $C_{12}H_{15}NO_4$ (C,H,N).

***N*-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)propyl]-acetamide 1j.** Yield 89%. White solid; mp 95–96 °C; IR (KBr) ν 3268, 1641, 1111 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.92–1.97 (m, 5H, CH_2 and CH_3), 3.42 (t, 2H, $J = 5.9$, CH_2N), 4.06 (t, 2H, $J = 5.9$, CH_2O), 4.22–4.24 (m, 4H, H_2 and H_3), 6.40–6.50 (m, 2H, H_6 and H_8), 6.70 (t, 1H, $J = 8.1$, H_7), MS (CI with NH_3) *m*/*z* 252 (M + 1), anal $C_{13}H_{17}NO_4$ (C,H,N).

***N*-[4-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)butyl]-acetamide 1k.** Yield 85%. White solid; mp 90–91 °C; IR (KBr) ν 3276, 1635, 1114 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.69 (q, 2H, $J = 6.6$, CH_2), 1.85 (q, 2H, $J = 6.6$, CH_2), 1.93 (s, 3H, CH_3), 3.29 (t, 2H, $J = 6.6$, CH_2N), 4.00 (t, 2H, $J = 6.6$, OCH_2), 4.23–4.28 (m, 4H, H_2 and H_3), 6.40–6.50 (m, 2H, H_6 and H_8), 6.73 (t, 1H, $J = 8.1$, H_7), MS (CI with NH_3) *m*/*z* 266 (M + 1), anal $C_{14}H_{19}NO_4$ (C,H,N).

***N*-[2-(3,4-Dihydro-2*H*-1-benzopyran-8-yloxy)ethyl]-acetamide 1l.** Yield 84%. White solid; mp 110–111 °C; IR (KBr) ν 3338, 1636, 1094 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 2.00–2.07 (m, 5H, H_3 and CH_3), 2.80 (t, 2H, $J = 5.8$, H_4), 3.64 (t, 2H, $J = 4.8$, CH_2N), 4.07 (t, 2H, $J = 4.8$, OCH_2), 4.26 (t, 2H, $J = 5.8$, H_2), 6.72–6.80 (m, 3H, H_{arom}), MS (CI with NH_3) *m*/*z* 236 (M + 1), anal $C_{13}H_{17}NO_3$ (C,H,N).

***N*-[2-3,4-Dihydro-2*H*-1-benzothiopyran-8-yloxy)ethyl]-acetamide 1m.** Yield 95% White solid; mp 116–117 °C; IR (KBr) ν 3234, 1636, 1084 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 2.00 (s, 3H, CH_3), 2.10 (q, 2H, $J = 6.0$, H_3), 2.83 (t, 2H, $J = 6.0$, H_2 or H_4), 3.02 (t, 2H, $J = 6.0$, H_2 or H_4), 3.65 (t, 2H, $J = 5.0$, CH_2N), 4.08 (t, 2H, $J = 5.0$, OCH_2), 6.66 (d, 1H, $J = 7.9$, H_5 or H_7), 6.71 (d, 1H, $J = 7.9$, H_5 or H_7), 6.95 (t, 1H, $J = 7.9$, H_6), MS (CI with NH_3) *m*/*z* 252 (M + 1), anal $C_{13}H_{17}NO_2S$ (C,H,N).

***N*-[4-(2,3-Dihydro-1,4-benzoxathiin-5-yl)pentyl]-acetamide 1g.** To a suspension of Raney nickel (48 mg) in acetic anhydride (10 mL) were added the nitrile **5g** (400 mg, 1.71 mmol) and sodium acetate (211 mg, 2.57 mmol). The mixture was treated in a Parr hydrogenation flask for 12 h at 50 °C under a hydrogen pressure of 40 psi. After cooling, the salts were filtered and then the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and the organic layer was

washed with saturated sodium hydrogenocarbonate solution. After drying over magnesium sulfate and removal of the solvent in vacuo, the resulting oil was submitted to column chromatography (eluent: $CHCl_3$:AcOEt, 70:30) to afford the compound **1g** in 47% yield as a white solid; mp 92–93 °C; IR (KBr) ν 3268, 1634, 1298, 1075 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.33–1.71 (m, 6H, CH_2), 1.96 (s, 3H, CH_3), 2.53–2.59 (m, 2H, $ArCH_2$), 3.13 (t, 2H, $J = 4.4$, H_3), 3.21–3.28 (m, 2H, CH_2N), 4.38 (t, 2H, $J = 4.4$, H_2), 6.68–6.75 (m, 2H, H_6 and H_8), 6.93 (t, 1H, $J = 7.9$, H_7), SM (CI with NH_3) m/z 280 (M + 1), anal $C_{15}H_{21}NO_2S$ (C,H,N).

General procedure for the synthesis of the butyramides 1cb and 1hb

To a well-stirred solution of the amine **3c** or **3h** (5.23 mmol) in dichloromethane (20 mL) were successively added, at 0 °C, butyryl chloride (0.78 g, 7.32 mmol) then triethylamine (1.58 g, 15.7 mmol). After 30 min of stirring under inert atmosphere at 0 °C and after addition of HCl 1 N to pH 1, the phases were separated and the aqueous layer was extracted with dichloromethane. Subsequently, the organic layers were combined and dried over $MgSO_4$. After evaporation under reduced pressure, the residue was chromatographed on silica gel (eluent: petroleum ether:AcOEt, 8:2 for **1cb** and petroleum ether:AcOEt, 1:1 for **1hb**).

***N*-[3-(2,3-Dihydro-1,4-benzodioxin-5-yl)propyl]-*n*-butyramide 1cb.** Yield 56%. Colorless oil; IR (neat) ν 3295, 1644, 1283, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, $J = 7.4$, CH_3), 1.64 (sext., 2H, $J = 7.4$, CH_2), 1.79 (q, 2H, $J = 7.2$, CH_2), 2.12 (q, 2H, $J = 7.2$, $COCH_2$), 2.62 (t, 2H, $J = 7.2$, $ArCH_2$), 3.27 (q, 2H, $J = 7.2$, CH_2N), 4.21–4.29 (m, 4H, H_2 and H_3), 5.56 (br s, 1H, NH), 6.67–6.79 (m, 3H, H_{arom}). MS (CI with NH_3) m/z 264 (M + 1), anal $C_{15}H_{21}NO_3$ (C,H,N).

***N*-[3-(1,4-Benzodioxin-5-yl)propyl]-*n*-butyramide 1hb.** Yield 73%. Colorless oil; IR (neat) ν 3410–3255, 1670, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, $J = 7.4$, CH_3), 1.57–1.79 (m, 4H, CH_2), 2.13 (t, 2H, $J = 7.5$, $COCH_2$), 2.47 (t, 2H, $J = 7.5$, $ArCH_2$), 3.26 (q, 2H, $J = 6.9$, CH_2N), 5.65 (br s, 1H, NH), 5.86 (d, 1H, $J = 3.5$, H_2 or H_3), 5.89 (d, 1H, $J = 3.5$, H_2 or H_3), 6.47 (dd, 1H, $J = 7.6$, 1.9, H_6 or H_8), 6.66 (dd, 1H, $J = 7.6$, 1.9, H_6 or H_8), 6.73 (t, 1H, $J = 7.6$, H_7), MS (CI with NH_3) m/z 262 (M + 1), anal $C_{15}H_{19}NO_3$ (C,H,N).

Pharmacology

Melatonin receptor binding assays. The affinity of the compounds has been assessed on ovine pars tuberalis membranes and for the most potent compounds on chicken brain membranes.

- Fresh ovine pars tuberalis tissue was obtained at a local abattoir from animals of mixed sex and age. Preparation of membranes and primary culture of pars tuberalis cells were prepared according to the method described by Morgan et al.[40,41] For competitive binding experiments membranes were incubated with 50 pM 2-[^{125}I]-iodomelatonin and 11 concentrations of competing ligand for 2 h at 37 °C. Melatonin was tested as reference. Individual compounds were assayed in triplicate and the values expressed in $-\text{Log}K_i \pm \text{SD}$.
- Chickens (*Gallus domesticus*), 12 days old, were sacrificed at 1 pm. The brains were quickly removed, prepared at 4 °C and stored at −80 °C. Membranes were prepared according to the method described by Yuan and Pang.[42] Membranes aliquots were incubated at 25 °C for 60 min with 50 pM 2-[^{125}I]-iodomelatonin and ligands were evaluated at 10 concentrations in triplicate. Melatonin was tested in the same conditions as reference. Results are expressed in $-\text{Log}\ K_i \pm \text{SD}$.

Non specific binding was defined with 1 μM melatonin.

Cyclic AMP studies. The compounds (10 μM) were tested alone and were compared to melatonin (1 nM) for their inhibition of forskolin (10 μM) stimulated cAMP production. These experiments were carried out in triplicate. The compounds were tested for their antagonist activity at 10 μM with melatonin 1 nM. In this case an antagonist will prevent the cAMP inhibition induced by melatonin.

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