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Synthesis of 5-Substituted-2,3-dihydro-1,4-benzoxathiins: Biological Evaluation as Melatonin Receptors Ligands

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The synthesis of benzoxathiins bearing a retroamide function is described from 8-hydroxythiochroman, the key step involving the synthesis of the benzoxathiin ring through a sulfonium salt. These new melatonin analogues were evaluated on human receptors MT_1 and MT_2 and have a similar affinity to that of melatonin itself.

Keywords: Melatonin ligands, Benzoxathiins, Sulfonium salt

INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine, Figure 1) is a neurohormone principally synthesised by the pineal gland and secreted into the general circulation during the night.[1] Tryptophan is taken up by the pinealocyte and transformed to serotonin which is then converted into melatonin *via* a two-step biochemical pathway.[2] Melatonin appears to play a central role in the control of circadian rhythms in humans. It is involved in sleep regulation as well as in various endocrine and immune functions.[3] In addition, melatonin might exert protective effects on the cardiovascular system.[4] These numerous effects suggest potential therapeutic applications for melatonin such as sleep disorders (jet lag, shift work syndrome, blindness, aging) and seasonal affective disorders.[5] However, two problems limit the use of melatonin as a drug; firstly, its very short biological half-life (15–30 min), secondly, the lack of selectivity of melatonin at its target sites, MT_1, MT_2 and MT_3,[6] although the physiological role of the latter two receptors is still unclear.[7,8] To solve these problems, the design, synthesis and pharmacological studies of new agonist and antagonist melatoninergic ligands have been considerably developed. Thus, several indolic analogues[9–16] of melatonin have been synthesized as ligands and many reports have described the synthesis of several nonindolic bioisosteres.[17–30]

In parallel with studies done by Copinga *et al.*,[18] Garratt *et al.*, [25] Langlois *et al.*,[21] and Lesieur *et al.*,[28,29] our group was interested in the synthesis and the biological evaluation of new non-indolic melatonin receptor-ligands. Recently, we described the synthesis of a new series of substituted oxygenated heterocycles and thio-analogues and evaluated them as melatonin receptor ligands.[30] The replacement of the indole moiety of melatonin by a heterocyclic skeleton carrying the amidic chain led to compounds showing, *in vitro*, a weak affinity for melatonin receptors on ovine pituitary membranes.

Here, we report a new and unusual synthesis of 5-substituted-2,3-dihydro-1,4-benzoxathiins **1** bearing a retroamide function and the biological evaluation of these non-indolic melatonin receptor-ligands on human transfected receptors MT_1 and MT_2. Our choice was motivated by recent results from Lesieur *et al.*[31] which have shown that retroamide analogs have an antagonist activity.

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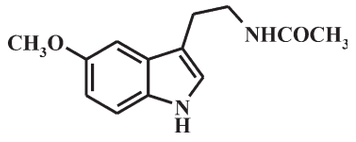


FIGURE 1 Melatonin.

MATERIALS AND METHODS

Chemistry

Instrumentation

Melting points were determined on a Köfler hot-stage and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 250 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) machine. Organic solvents were purified when necessary according to literature methods[32] or purchased from Aldrich Chimie. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi 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 alcoholic 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 elemental analyses are indicated by symbols for the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. The column chromatography solvents employed were distilled and solvent mixtures are reported as volume to volume ratios.

Synthesis

8-(2-Bromoethoxy)-2,3-dihydro-2*H*-1-benzothiopyran **3**

To a mixture of potassium carbonate (8.3 g, 60 mmol, 10 eq) in water (20 mL) were added thiochromanol **2**[33] (1 g, 6 mmol) and tetrabutylammonium bromide (97 mg, 0.3 mmol, 0.05 eq). The reaction mixture was heated to reflux and dibromoethane (4.13 mL, 48 mmol, 8 eq) was introduced. After 45 min at reflux, the mixture was cooled to room temperature and filtered. The product was extracted with dichloromethane, and the organic phase washed with a 5% sodium hydroxide solution and concentrated. The crude product was purified by flash chromatography (eluent: petroleum ether:CH_2Cl_2, 2:1) to yield **3** (85%) as a colorless oil. ν_{max} (KBr)/cm^{-1} 1253, 1075; δ_H(250 MHz, $CDCl_3$) 2.11 (q, 2H, $J = 5.9$, H_3), 2.82 (t, 2H, $J = 5.9$, H_2 or H_4), 3.00 (t, 2H, $J = 5.9$, H_2 or H_4), 3.66 (t, 2H, $J = 6.6$, CH_2), 4.20 (t, 2H, $J = 6.6$, CH_2), 6.63-6.72 (m, 2H, H_5 and H_7), 6.93 (t, 1H, $J = 7.8$, H_6); δ_C(62.5 MHz, $CDCl_3$) 153.5, 135.1, 124.6, 123.5, 123.8, 109.7, 69.6, 29.6, 28.9, 26.9, 22.3. MS(EI) m/z = 272/274 (M^+);

5-(3-Bromopropyl)-2,3-dihydro-1,4-benzoxathiin **4**

A decimolar solution of 8-(2-bromoethoxy)-2,3-dihydro-2*H*-1-benzothiopyran **3** (2 mmol) was stirred at reflux in acetonitrile for 48 h. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography (eluent: petroleum ether : CH_2Cl_2, 2:1) to yield **4** (81%) as a colourless oil. ν_{max} (film)/cm^{-1} 1308, 1245, 1075; δ_H(250 MHz, $CDCl_3$) 2.17 (q, 2H, $J = 6.6$, CH_2), 2.73 (t, 2H, $J = 6.6$, CH_2), 3.12 (t, 2H, $J = 4.6$, H_3), 3.41 (t, 2H, $J = 6.6$, CH_2), 4.37 (t, 2H, $J = 4.6$, H_2), 6.60–6.76 (m, 2H, H_6 and H_8), 6.93 (t, 1H, $J = 7.7$, H_7); δ_C(62.5 MHz, $CDCl_3$) 152.4, 138.3, 125.2, 122.7, 117.5, 116.9, 65.2, 33.8, 32.3, 32.0, 26.0; MS(IS) m/z = 273/275 $(M + H)^+$.

5-(3-Cyanopropyl)-2,3-dihydro-1,4-benzoxathiin **5**

To a stirred mixture of the bromo derivative **4** (200 mg, 0.73 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) was added potassium cyanide (52 mg, 0.8 mmol, 1.1 eq) under an inert atmosphere. The reaction mixture was stirred at room temperature for 12 h, then potassium cyanide (52 mg, 0.8 mmol, 1.1 eq) was added again. After this addition, the reaction mixture was allowed to stir at room temperature for an additional 12 h. The solvent was removed at reduced pressure and the residue was taken up in 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 7:3). A colourless oil was isolated in 97% yield.

ν_{max} (film)/cm^{-1} 2234, 1252, 1084, 1054; δ_H(250 MHz, $CDCl_3$) 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); δ_C(62.5 MHz, $CDCl_3$) 152.1, 137.5, 124.3, 121.7, 119.0, 116.2, 64.0, 31.3, 25.0, 24.1, 16.0. Anal $C_{12}H_{13}NOS$ (C,H,N).

4-(2,3-Dihydro-1,4-benzoxathiin-5-yl)-butanoic Acid **6**

To a stirred mixture of the cyano compound **5** (200 mg, 0.9 mmol) in ethanol (10 mL) was added a 10% solution of sodium hydroxide (5 eq). The reaction mixture was stirred at 60°C for 24 h. The ethanol was removed at reduced pressure and the aqueous phase was washed with ethyl acetate to remove organic residue. The acid **6** was precipitated by addition of 2N hydrochloric acid solution. The precipitate was filtered off and dried over P_2O_5 as a white solid (71% yield). mp = 93°C, ν_{max} (KBr)/cm^{-1} 3300–2790, 1712, 1040; δ_H(250 MHz, DMSO) 1.74 (t, 2H, $J = 7.5$, CH_2), 2.20 (t, 2H, $J = 7.5$, CH_2), 2.48 (t, 2H, $J = 7.5$, CH_2), 3.13 (t, 2H, $J = 4.8$, H_3), 4.27 (t, 2H, $J = 4.6$, H_2), 6.63 (d, 1H, $J = 7.1$, H_6 or H_8), 6.71 (d, 1H, $J = 7.1$, H_6 or H_8), 6.89 (t, 1H, $J = 7.1$, H_7), 12.00 (bs, 1H, COOH); δ_C(62.5 MHz, DMSO) 173.7, 151.2, 138.2, 124.1, 121.2, 116.4, 115.5, 64.0, 32.8, 31.3, 24.3, 23.6; MS(IS) m/z = 239 $(M + H)^+$.

N-Methyl-[4-(2,3-dihydro-1,4-benzoxathiin-5-yl)]-butanamide **1a**

To a stirred solution of the acid **6** (500 mg, 2.1 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) at 0°C were introduced HOBt (312 mg, 2.31 mmol, 1.1 eq) and EDCI (443 mg, 2.31 mmol, 1.1 eq). Then a 10% solution of methylamine in benzene (3.15 mmol, 1.5 eq) (CARE-carcinogen) was added. The temperature was slowly warmed to room temperature and the reaction mixture was stirred for 18 h. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane and water. The aqueous phase was extracted with dichloromethane and the collected organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: $CHCl_3$:AcOEt, 7:3) to provide the pure retroamide **1a** in 74% yield as a white solid. mp = 94°C, ν_{max} (KBr)/cm^{-1} 3265–3590, 1722, 1274, 1126, 1075; δ_H(250 MHz, $CDCl_3/D_2O$) 1.51–1.70 (m, 2H, CH_2), 1.96 (s, 3H, CH_3), 2.61 (t, 2H, $J = 7.5$, CH_2), 2.81 (t, 2H, $J = 7.5$, CH_2), 3.13 (t, 2H, $J = 4.7$, H_3), 4.38 (t, 2H, $J = 4.7$, H_2), 6.69-6.76 (m, 2H, H_6 and H_8), 6.93 (t, 1H, $J = 7.8$, H_7); MS(CI/NH_3) m/z = 252 (M + 1); Anal $C_{13}H_{17}NO_2S$ (C,H,N).

General Procedure for the Synthesis of the Retroamides **1b** and **1c**

To a stirred solution of ethylamine hydrochloride (1.1 eq) or *n*-propylamine hydrochloride (1.1 eq) in *N,N*-dimethylformamide (10 mL) at 0°C was added 4-dimethylaminopyridine (1.5 eq). The acid **6** (400 mg, 1.68 mmol) diluted in *N,N*-dimethylformamide (4 mL) then EDCI (1.1 eq) were added. The temperature was slowly warmed to room temperature and the reaction mixture was stirred for 12 h. The solvent was removed at reduced pressure and the residue was taken up with ethyl acetate. The organic phase was washed many times with water. The collected organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: $CHCl_3$:AcOEt, 7:3) to provide the pure retroamides **1b** or **1c** as white solids in 93% and 96% yield, respectively.

N-*Ethyl-[4-(2,3-dihydro-1,4-benzoxathiin-5-yl)]-butanamide* ***1b.*** mp = 86°C, ν_{max} (KBr)/cm^{-1} 3260-3590, 1672, 1270, 1116, 1080; δ_H(250 MHz, $CDCl_3/D_2O$) 1.16 (t, 2H, $J = 7.3$, CH_3), 1.99 (q, 2H, $J = 7.6$, CH_2), 2.24 (t, 2H, $J = 7.6$, CH_2), 2.64 (t, 2H, $J = 7.6$, CH_2), 3.15 (t, 2H, $J = 4.7$, H_3), 3.32 (t, 2H, $J = 7.3$, CH_2), 4.41 (t, 2H, $J = 4.7$, H_2), 6.71–6.79 (m, 2H, H_6 and H_8), 6.96 (t, 1H, $J = 7.8$, H_7); δ_C(62.5 MHz, $CDCl_3$) 171.8, 151.3, 138.2, 124.1, 121.5, 116.4, 115.6, 64.1, 35.5, 33.7, 31.8, 24.9, 24.5, 14.3; MS(EI) m/z = 265 (M^+); Anal $C_{14}H_{19}NO_2S$ (C,H,N).

N-*Propyl-[4-(2,3-dihydro-1,4-benzoxathiin-5-yl)]-butanamide* ***1c.*** mp = 93°C, ν_{max} (KBr)/cm^{-1} 3260–3590, 1668, 1274, 1120, 1075; δ_H(250 MHz, $CDCl_3/D_2O$) 0.93 (t, 2H, $J = 7.6$, CH_3), 1.54 (sextuplet, 2H, $J = 7.6$, CH_2), 1.98 (q, 2H, $J = 7.6$, CH_2), 2.23 (t, 2H, $J = 7.6$, CH_2), 2.62 (t, 2H, $J = 7.6$, CH_2), 3.14 (t, 2H, $J = 4.2$, H_3), 3.22 (t, 2H, $J = 7.6$, CH_2), 4.39 (t, 2H, $J = 4.2$, H_2), 6.69–6.77 (m, 2H, H_6 and H_8), 6.94 (t, 1H, $J = 8.1$, H_7); δ_C(62.5 MHz, $CDCl_3$) 174.9, 154.3, 141.3, 127.1, 124.5, 119.5, 118.7, 67.2, 43.6, 38.6, 34.9, 27.9, 27.5, 25.3, 13.8; MS(EI) m/z = 279 (M^+); Anal $C_{15}H_{21}NO_2S$ (C,H,N).

Pharmacology

Reagents and Chemicals

2-[^{125}I]Iodo-melatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma-Aldrich (Saint Quentin, France).

Cell Culture

HEK 293 cells (provided by A.D. Strosberg, Paris, France) stably expressing the human melatonin MT_1 or MT_2 receptor were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/ml penicillin, and 100 μg/ml streptomycin. Grown at confluence at 37°C (95% O_2/5% CO_2), they were harvested in PBS containing EDTA (2 mM) and centrifuged at 1000 × g for 5 min (4°C). The resulting pellet was suspended in TRIS (5 mM, pH 7.5), containing EDTA (2 mM), and homogenized using a Kinematica polytron. The homogenate was then centrifuged (95000 × g, 30 min, 4°C) and the resulting pellet suspended in

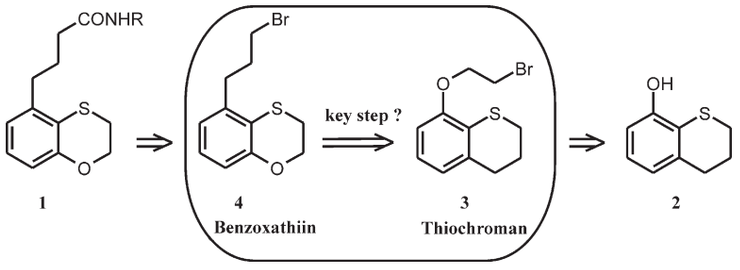


FIGURE 2 Retrosynthetic approach to benzoxathiin analogs.

75 mM TRIS (pH 7.5), 12.5 mM $MgCl_2$, and 2 mM EDTA. Aliquots of membrane preparations were stored at -80°C until use.

Binding Assays

Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK 293 cells (40 μg/mL) diluted in binding buffer (50 mM TRIS-HCl buffer, pH 7.4, containing 5 mM $MgCl_2$) to 2-[^{125}I] iodo-melatonin (0.025 and 0.2 nM, respectively, for MT_1 and MT_2 receptors) and the tested drug. Nonspecific binding was defined in the presence of 1 μM melatonin. After 60 min incubation at 37°C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. The filters were washed three times with 1 ml of ice-cold 50 mM TRIS-HCl buffer, pH 7.4.

Data were analysed using the program PRISM (Graph Pad Software Inc., San Diego, CA) and expressed as IC_{50} values (concentration resulting in 50% inhibition).

RESULTS

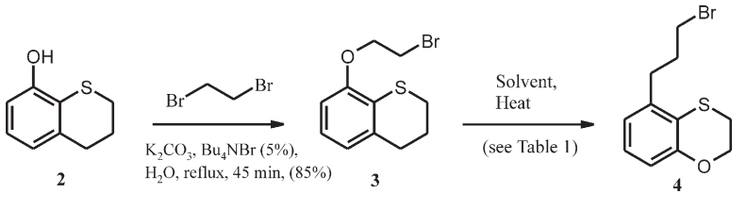
Our strategy to synthesise benzoxathiins **1** is shown in Figure 2. Starting from 8-hydroxythiochroman **2**,[33] the key step of our approach is the rearrangement of the 8-(2-bromoethoxy)-2,3-dihydro-2H-1-benzothiopyran **3** to the benzoxathiin unit **4**. This only intermediate **4** allows a rapid and efficient synthetic route to many retroamides **1**.

The synthesis of the benzoxathiin intermediate **4** is outlined in Scheme 1. The 8-(2-bromoethoxy)-2,3-dihydro-2H-1-benzothiopyran **3** was obtained by alkylation of 8-hydroxythiochroman **2** with dibromoethane (8 eq). The optimised reaction conditions use 10 equivalents of potassium carbonate with 5% molar *tetra*butylammonium bromide in refluxing water for 45 minutes (85% yield).[34]

Rearrangement of compound **3** was evaluated in different solvents at different temperatures (see Table I). All the attempts were made under the same experimental conditions and compound **3**/compound **4** ratios were based on NMR integration.

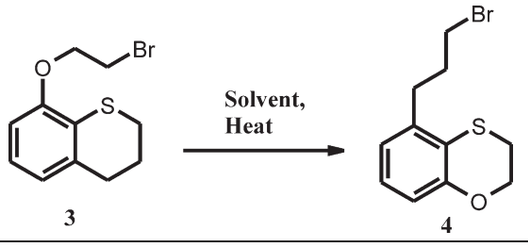
As in many nucleophilic substitutions, the formation of the rearranged product **4** was readily dependent on the solvent (see Table I). At 80°C, *N*,*N*-dimethylformamide seemed to be the best solvent, the optimum conversion rate being observed in 12 hours reaction (entry 7) contrary to 48 hours for acetonitrile (entry 3). Nevertheless, at 80°C, whatever the solvent used or even neat, we were never able to obtain more than 87% (NMR ratio) of compound **4** (entries 1, 2, 5, 6, 7, 8). If the reaction temperature was increased to 140°C in xylene some degradation was observed (entries 9, 10).

Completion of the synthesis of target retroamides **1a**, **1b** and **1c** is depicted in Scheme 2. Treatment of bromide **4** with potassium cyanide in *N*,*N*-dimethylformamide gave the required nitrile **5**. Hydrolysis of this compound with aqueous sodium hydroxide (10%) in refluxing ethanol followed by aqueous hydrochloric acid (2N) work up gave the carboxylic acid **6**. Compound **6** was then submitted to peptide coupling type reactions with different primary amines. Using hydroxybenzotriazole, EDCI and methylamine in *N*,*N*-dimethylformamide, the retroamide **1a** (R = Me) was isolated in 74% yield. Modified experimental conditions were used for



SCHEME 1 Synthesis of benzoxathiin intermediate **4**.

TABLE I Solvent and temperature effect on thiochroman **3** rearrangement



3 **4**

				NMR ratio		Yields (%)	
Entry	Solvent	Temperature (°C)	Time (h)	**3** (%)	**4** (%)	**3** (%)	**4** (%)
1	Neat	80	24	75	25	/	/
2			180	14	86	11	82
3	CH_3CN	40	48	88	12	/	/
4			96	76	24	73	22
5	CH_3CN	80	48	14	86	11	81
6			96	13	87	12	82
7	DMF	80	12	14	86	12	82
8			48	13	87	11	83
9	Xylene	140	48	17	83	9	44
10			96	3	97	Traces	45

the retroamides **1b** and **1c**; ethylamine hydrochloride and *n*-propylamine hydrochloride were reacted with the carboxylic acid intermediate **6** in the presence of DMAP and EDCI in *N,N*-dimethylformamide to give compounds **1b** and **1c** in 93% and 96% yield respectively.

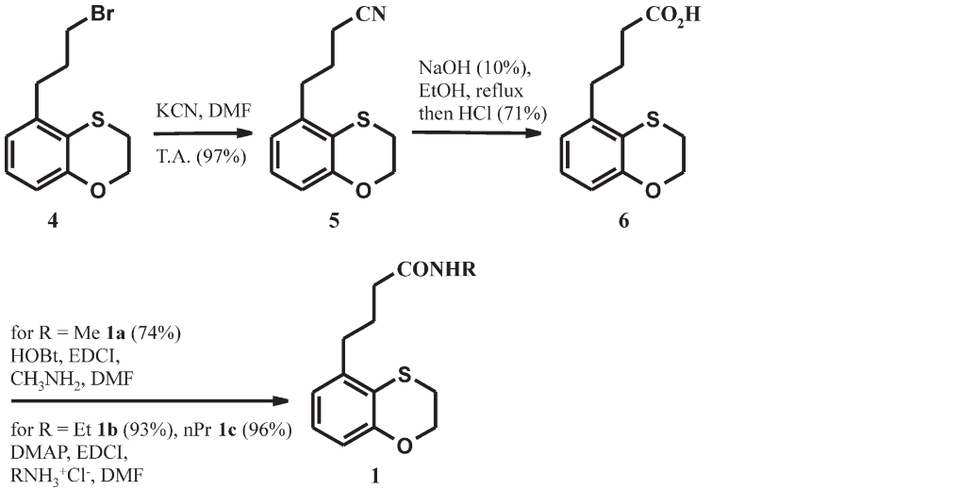
The affinities of these new heterocyclic compounds for melatonin binding sites were evaluated on human receptors MT_1 and MT_2.

DISCUSSION

Chemistry

We were interested in understanding the origin of the asymptotic value of 87% for the rearrangement. It is known that the sulfur of an alkyl sulfide can attack an electrophilic position to produce a sulfonium salt, which undergoes alkyl group removal via S_N2 displacement by nucleophiles present in the reaction mixture.[35–39]

Taking into account this consideration, we believe that the rearrangement of compound **3** could be explained via the sulfonium salt **A** (see Figure 3). At this point, the nucleophilic bromide ion present in the reaction mixture may attack on the carbon α to lead to the starting thiochroman **3** or on carbon α′ to give the desired benzoxathiin **4**. To explain the asymptotic ratio observed we considered that all the processes could be under equilibrium. This has been proved by heating pure benzoxathiin **4** in acetonitrile for 48 hours. The resulting crude reaction



4 **5** **6** **1**

SCHEME 2 Synthesis of benzoxathiin analogues.

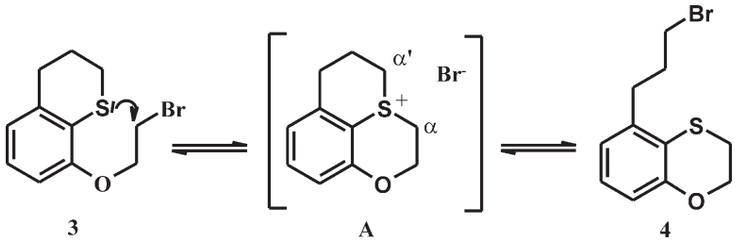


FIGURE 3 Mechanistic consideration on the rearrangement.

TABLE II Pharmacological evaluation of the retroamides **1a**, **1b** et **1c**

		Affinity		Selectivity
Entry	Compounds	IC_{50}(M) MT_1	IC_{50}(M) MT_2	MT_1/MT_2
1	Melatonin	2.0×10^{-10}	5.3×10^{-10}	0.4
2	**1a**	1.0×10^{-9}	9.7×10^{-9}	0.1
3	**1b**	1.5×10^{-9}	2.5×10^{-9}	0.6
4	**1c**	2.3×10^{-9}	6.7×10^{-9}	0.34

was a mixture of benzoxathiin **4** (88%) and the thiochroman **3** (12%) showing that at this ratio the thermodynamical equilibrium had been reached.

Pharmacology

Compounds **1a**, **1b** and **1c** were evaluated for their binding affinity for human MT_1 and MT_2 receptors stably transfected in human embryonic kidney (HEK 293) cells, using 2-[^{125}I]iodomelatonin as radioligand (see Table II). Compared with melatonin, all the compounds have a similar affinity for the human melatonin receptors as melatonin itself. Unfortunately, these retroamides were not selective for one of the human receptor subtypes. It is noteworthy that increasing the chain length of the amido group seems to improve the affinity for the MT_1 receptor subtype (entries 2, 3, 4).

In conclusion, the thiochroman rearrangement constitutes a new synthesis of the benzoxathiin ring. Benzoxathiin retroamide analogues of melatonin could constitute potential ligands of melatonin receptors. Further studies and pharmacomodulations are necessary to evaluate their pharmacological potential.

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