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5-Halobenzothiophene Analogues of Melatonin: Synthesis and Affinity for mt_1 and MT_2 Receptors in Man

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Abstract

A novel series of melatonin analogues based on the benzothiophene nucleus is described.

In these compounds the methoxy group was replaced by electron-attracting groups such halogens (Br and Cl) with the aim of supplementing structure–affinity relationships on melatoninergic ligands. Target derivatives were prepared from the corresponding 4-halothiophenol. Some of these derivatives had high affinity for mt_1 and MT_2 receptors, almost as high as that of melatonin.

These results prove that the methoxy group is not an essential requirement for binding to melatoninergic receptors.

Melatonin (*N*-acetyl-5-methoxytryptamine), a neurohormone synthesized during the night by the pineal gland (Lerner et al 1958), acts through the blood circulation as an internal synchronizer of circadian rhythms and informs the organism about the photoperiod. It is also essential in the regulation of some physiological (endocrinal and neuronal) processes. The biological activity of melatonin acts through specific receptors, for example the mt_1 and MT_2 receptors; these receptors in man were recently cloned (Reppert et al 1994, 1995, 1996; Conway et al 1997). These two receptors subtypes are located in the central nervous system (suprachiasmatic nucleus, hypothalamus, hippocampus) and at the peripheral level (kidney, retina). Because this distribution of melatonin sites suggests that each receptor could play a specific physiological role, it is fundamental to conceive and synthesize new molecules which mimic or antagonize responses to melatonin and, if possible, selectively for one subtype, to enable determination of their respective functional role and to specify their therapeutic potential.

Many non-indole analogues of melatonin, for example the naphthalene, benzofuran and benzothiophene bioisosteres, have been designed and synthesized in our laboratory (Yous et al 1992; Depreux et al 1994). This work has enabled us to specify structure-affinity and -activity relationships towards melatonin receptors—in particular the indole nucleus can be replaced by another aromatic nucleus, for example, benzothiophene, without seriously affecting the affinity and the activity of the ligands. The benzothiophene bioisostere of melatonin is an agonist with lower affinity than melatonin but with the advantage of being metabolically more stable (Depreux et al 1994).

Because the methoxy group seems to be important for interaction with and activation of receptors, we decided to replace this group in the 5-position by electronically different substituents, with an equivalent molar volume, but without any possibility of hydrogen-bonding. This paper describes the synthesis and pharmacological evaluation of these benzothiophene compounds substituted by halogens (Br and Cl) in the 5 position (Figure 1).

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Material and Methods

Chemistry

Melting points were determined by means of a Büchi SMP-535 apparatus. Column chromatography was performed on silica gel 60 (70-230 mesh, ASTM; Merck) with an appropriate mobile phase. IR spectra were recorded on Perkin-Elmer

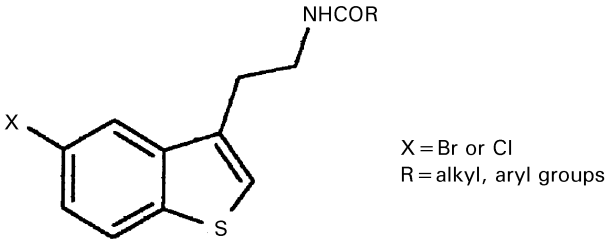


Figure 1. Structures of 5-halobenzothiophene compounds.

297 or Brücker Vector 22 spectrometers, using KBr tablets. ^{1}H NMR spectra were recorded on an AC 300 P (300 MHz) spectrometer with d_6-DMSO (dimethylsulphoxide) or $CDCl_3$ as solvent. Chemical shifts are expressed downfield from the internal standard tetramethylsilane. Coupling constants (J) are expressed in Hz. In the data below s = singlet, d = doublet, t = triplet, m = multiplet, b = broad. Elemental analysis (C, H, N) was performed by the CNRS Centre of Analysis (Vernaison, France) and agree with the proposed structures within 0·4% of the theoretical values.

*(4-Bromophenylthio)acetone (**1a**)*
Chloroacetone (5·35 g, 0·064 mol) was slowly added to a cold stirred solution of 4-bromothiophenol (10 g, 0·053 mol) and pyridine (17·36 g, 0·212 mol) in ether. The mixture was stirred for 3 h, then poured into ice-water and extracted with ether. The organic layer was separated, washed with 1 M HCl, then with water, dried over magnesium sulphate and evaporated under reduced pressure. The resulting solid was recrystallized from 95% ethanol to give a white powder (80% yield), mp 63–65°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2·28 (s, 3H, CH_3), 3·66 (s, 2H, CH_2), 7·20 (d, J = 6·6 Hz, 2H, H-2,2′), 7·41 (d, J = 6·6 Hz, 2H, H-3,3′). IR (KBr) ν 1700 cm^{-1}.

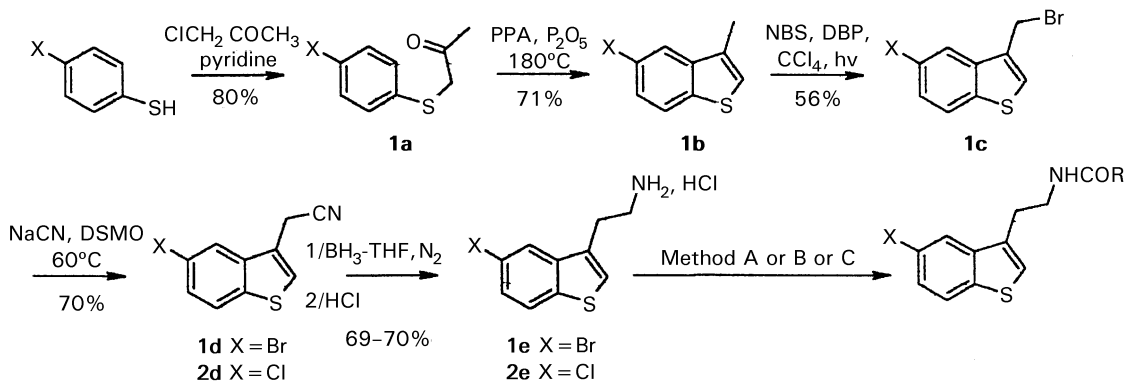
*5-Bromo-3-methylbenzo[b]thiophene (**1b**)*
1a (5 g, 0·020 mol) was added to a solution of phosphorus pentoxide (P_2O_5; 0·58 g, 0·002 mol) in polyphosphoric acid (PPA; 50 g). The mixture was heated slowly to 180°C with vigorous stirring, kept at this temperature for 3 h and, after cooling, poured into ice-water. After extraction with ether the organic layer was separated, washed with water, dried over magnesium sulphate and evaporated, yielding a residue that was purified by silica gel column chromatography, with light petroleum as eluent, to give a white powder (71% yield), mp 38–39°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2·37 (s, 3H, CH_3), 7·06 (s, 1H, H-2), 7·40 (dd, J = 8·7 and 1·8 Hz, 1H, H-6), 7·65 (d, J = 8·7 Hz, 1H, H-7), 7·81 (d, J = 1·8 Hz, 1H, H-4). IR (KBr) ν 3080–2840 cm^{-1}.

*5-Bromo-3-bromomethylbenzo[b]thiophene (**1c**)*
Dibenzoyl peroxide (DBP; 0·13 g, 0·001 mol) was added to a vigorously stirred solution of **1b** (3 g, 0·013
mol) in dry carbon tetrachloride (300 mL). *N*-bromosuccinimide (NBS; 2·35 g, 0·013 mol) was added in small portions to the boiling mixture which was then irradiated (500 W). The mixture was heated under reflux for 4 h, then cooled and filtered to remove the succinimide. The solvent was evaporated and **1c** was obtained as a solid by triturating with ether. The solid was recrystallized from toluene–cyclohexane (4 : 1) to give a yellow powder (56% yield), mp 127–129°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5·05 (s, 2H, CH_2), 7·58 (dd, J = 8·7 and 1·9 Hz, 1H, H-6), 8·02 (d, J = 8·7 Hz, 1H, H-7), 8·04 (s, 1H, H-2), 8·15 (d, J = 1·9 Hz, 1H, H-4).

*5-Bromo-3-cyanomethyl benzo[b]thiophene (**1d**)*
1c (2 g, 0·007 mol) was added to a solution of sodium cyanide (0·38 g, 0·008 mol) in dimethylsulphoxide (50 mL). The mixture was heated slowly to 60°C with vigorous stirring and kept at this temperature for 1 h. It was then cooled and poured into ice-water. The resulting precipitate was purified by recrystallization from 95% ethanol to give a brown powder (70% yield), mp 139–140°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3·88 (s, 2H, CH_2), 7·70–7·54 (m, 2H, H-2,6), 7·75 (d, J = 8·4 Hz, 1H, H-7), 7·84 (d, J = 1·9 Hz, 1H, H-4). IR (KBr) ν 2240 cm^{-1}.

*General procedure for preparation of the N-2-(5-halobenzo[b]thiophen-3-yl)ethylamine hydrochlorides (**1e** and **2e**) (Figure 2)*
The method adopted for the synthesis of *N*-2-(5-bromobenzo[*b*]thiophen-3-yl)ethylamine hydrochloride (**1e**) is described.

A solution of borane–tetrahydrofuran complex (24 mL, 0·024 mol; 1 M in tetrahydrofuran (THF) and **1d** (2·02 g, 0·008 mol) in tetrahydrofuran (50 mL) was heated under reflux for 3 h under nitrogen. Hydrochloric acid (6 M, 16 mL, 0·095 mol) was then added dropwise. Tetrahydrofuran was evaporated and the resulting precipitate was filtered and recrystallized from absolute ethanol affording **1e** as a white powder (70% yield), mp > 260°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3·00–3·19 (m, 4H, 2 CH_2), 7·55 (dd, J = 8·3 and 1·8 Hz, 1H, H-6), 7·69 (s, 1H, H-2),



X \ R	CH_3	$(CH_2)_2Cl$	CF_3		$CH{=}CH_2$	$CH_2CH{=}CH_2$	$CH{=}CHC_6H_5$	$CH_2CH{=}CHC_6H_5$	$C{\equiv}CH_3$		3,4-$Cl_2C_6H_3$	$CH_2C_6H_5$
Br	1f (A)		1h(C)	1i(A)		1k(B)	1l(B)	1m(B)		1o(A)	1p(A)	1q(A)
Cl	2f (A)	2g(A)	2h(C)	2i(A)	2j(A)	2k(B)	2l(B)	2m(B)	2n(A)	2o(A)		

Figure 2. Synthesis of *N*-2-(5-halobenzo[*b*]thiophen-3-yl)ethylaminehydrochlorides. Phosphroic acid (PPA); Phosphorus pentoxide (P_2O_5); *N*-bromosuccinimide (NBS); dibenzylperoxide (DBP); borane–tetrahydrofuran (BH_3-THF). A and B refer to the method used for preparation of the compounds.

7·99-8·02 (m, 4H, NH_3^+ and H-7), 8·12 (d, J = 1·8 Hz, 1H, H-4). IR (KBr) ν 3400–2990 cm^{-1}. Calculated for $C_{10}H_{11}BrClNS$: C, 41·04; H, 3·79; N, 4·79; found: C, 41·03; H, 3·99; N, 4·45.

General procedures for preparation of the N-acylated derivatives

*Method A, from acid chlorides (derivatives **1f**, **1i**, **1o–1q**, **2f**, **2g**, **2i**, **2j**, **2n**, **2o**).* The method adopted for the synthesis of *N*-2-(5-bromobenzo[*b*]thiophen-3-yl)ethyl acetamide (**1f**) is described.

Potassium carbonate (0·69 g, 0·005 mol) was added to a solution of *N*-2-(5-bromobenzo[*b*]-thiophen-3-yl)ethylamine hydrochloride (**1e**; 0·88 g, 0·003 mol) in water (40 mL) and dichloromethane (60 mL). The mixture was cooled to 0°C and acetyl chloride (0·35 mL, 0·005 mol) was added dropwise. The solution was then stirred at room temperature for 2 h. The organic layer was separated, washed with water, dried over magnesium sulphate and evaporated under reduced pressure yielding a residue that was recrystallized from toluene affording **1f** as a white powder (55% yield), mp 134–136°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1·80 (s, 3H, CH_3), 2·94 (t, J = 7·1 Hz, 2H, CH_2), 3·34 (m, 2H, CH_2-NH), 7·52 (dd, J = 8·6 and 2·0 Hz, 1H, H-6), 7·55 (s, 1H, H-2), 7·96 (d, J = 8·6 Hz, 1H, H-7), 8·04 (signal, 1H, NH), 8·06 (s, 1H, H-4). IR (KBr) ν 3230, 3050, 1625 cm^{-1}. Calculated for $C_{12}H_{12}BrNOS$: C, 48·33; H, 4·06; N, 4·70; found: C, 48·65; H, 4·14; N, 4·72.

*Method B, from acids (derivatives **1k–1m** and **2k–2m**).* The method adopted for the synthesis of *N*-[2-(5-chlorobenzo[*b*]thiophen-3-yl)ethyl] allylcarboxamide (**2k**) is described.

Potassium carbonate was added slowly to a solution of *N*-2-(5-chlorobenzo[*b*]thiophen-3-yl)-ethylamine hydrochloride (**2e**) (0·74 g, 0·003 mol) in water until pH 9. After stirring for 2 h the medium was extracted with ether and the organic layer dried over magnesium sulphate and evaporated to obtain the basic amine, which was dissolved in dichloromethane and cooled to −20°C. Vinylacetic acid (0·74 g, 0·006 mol) and 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (1·15 g, 0·006 mol) were dissolved in dichloromethane (30 mL); after 30 min the solution was cooled to −20°C. The previously obtained solution of the amine in dichloromethane was added dropwise to this solution and the reaction mixture was stirred for a further 30 min at −20°C and then overnight at room temperature. The dichloromethane was evaporated, the residue was taken up in ethyl acetate, and the solution was washed with 10% aqueous potassium carbonate and with water. The organic layer was dried over magnesium sulphate and evaporated, yielding a residue which was recrystallized from cyclohexane–toluene (4 : 1) affording **2k** as a white powder (37% yield), mp 76–77°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2·87 (d, J = 6·8 Hz, 2H, CH_2-CO), 2·94 (t, J = 7·2 Hz, 2H, CH_2), 3·35 (m, 2H, CH_2-NH), 5·05–5·12 (m, 2H, CH_2 = CH), 5·86 (m, 1H, CH_2 = C*H*), 7·41 (dd, J = 8·4 and 2·0 Hz, 1H, H-6), 7·57 (s, 1H, H-2), 7·94

(d, J = 2·0 Hz, 1H, H-4), 8·00–8·03 (m, 2H, H-7 and NH). IR (KBr) ν 3292, 3082, 1641 cm^{-1}. Calculated for $C_{14}H_{14}ClNOS$: C, 60·10; H, 5·04; N, 5·01; found: C, 60·04; H, 5·09; N, 5·00.

*Method C, from acid anhydrides (derivatives **1h** and **2h**).* The method adopted for the synthesis of *N*-[2-(5-bromobenzo[*b*]thiophen-3-yl)ethyl] trifluoroacetamide (**1h**) is described.

Trifluoroacetic anhydride (0·85 mL, 0·006 mol) was added to a solution of *N*-2-(5-bromobenzo[*b*]thiophen-3-yl)ethylamine hydrochloride (**1e**) (0·88 g, 0·003 mol) in pyridine (0·48 mL, 0·006 mol) and ether (20 mL). The reaction mixture was stirred at room temperature for 2 h, then acidified with 6 M HCl and extracted with ethyl acetate. The organic layer was washed, dried over magnesium sulphate and evaporated yielding a residue that was recrystallized from toluene affording **1h** as a white powder (70% yield), mp 144–146°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3·05 (t, J = 7·2 Hz, 2H, CH_2), 3·50 (m, 2H, CH_2-NH), 7·53 (dd, J = 8·6 and 1·6 Hz, 1H, H-6), 7·59 (s, 1H, H-2), 7·97 (d, J = 8·6 Hz, 1H, H-7), 8·09 (d, J = 1·6 Hz, 1H, H-4), 9·58 (t, J = 5·6 Hz, 1H, NH). IR (KBr) ν 3250, 3000, 1690 cm^{-1}. Calculated for $C_{12}H_9BrF_3NOS$: C, 40·93; H, 2·58; N, 3·98; found: C, 41·09; H, 2·66; N, 4·05.

Pharmacology

Cell Culture. Embryonic kidney cell line HEK293 from man (A. D. Strosberg, Paris, France), stably expressing mt_1 or MT_2 melatonin receptors, were grown as monolayers at 37°C (95% O_2–5% CO_2) in Dulbecco's modified Eagle's medium glutamax-1 (Gibco 31966-036; Gibco Laboratories, Grand Island, NY) supplemented with 10% foetal calf serum, penicillin, and streptomycin (1%) in the presence of the selection agent geneticin G-418 (4%) (Gibco 11811-031). The cells were then washed twice with phosphate-buffered saline (PBS), harvested in MatriSperse (Becton Dickinson, Le Pont-de-Claix, France), pelleted at 4°C at 1000 rev min^{-1}, and suspended in PBS. The cells were homogenized with a Polytron tissue disrupter, and the resulting homogenate was centrifuged at 20 000 *g* for 30 min. The pellet was suspended in buffer, and the protein concentration was measured by the method of Bradford (1976), with BSA as standard. The membranes were stored at −80°C at a concentration of 5 mg mL^{-1}.

Binding receptor assays. In saturation experiments, membrane suspensions of mt_1 (0·04 mg mL^{-1}) and MT_2 (0·04 mg mL^{-1}) were incubated for 2 h at 37°C in Tris–HCl (50 mM, final volume 0·25 mL) containing $MgCl_2$ (5 mM) at pH 7·40, with different concentrations of 2-[^{125}I]iodomelatonin (2200 Ci $mmol^{-1}$) from 0·005 to 1·5 nM for mt_1 and from 0·02 to 3 nM for MT_2 in the absence or presence of melatonin (10 μM), which determines the non-specific binding. Competition studies for 2-[^{125}I]iodomelatonin binding (radioligand concentration, 0·025 nM for mt_1 studies and 0·200 nM for MT_2 studies) were performed in the presence of reference substances to determine their affinity, expressed as IC50 (the dose (M) resulting in 50% inhibition), for the two melatonin receptors subtypes from man.

Results and Discussion

Chemistry

Key intermediates in the synthesis of the target compounds described here are the corresponding amine hydrochlorides (**1e** and **2e**) which were prepared by successive action of borane-tetrahydrofuran complex and hydrochloric acid (Brown et al 1970) on the synthesized nitrile **1d** or the commercially available nitrile **2d** (Figure 2).

The nitrile **1d** was obtained by the method described by Marshall et al (1969). Condensation of 4-bromothiophenol with chloroacetone in pyridine gave the ketone **1a**, which was cyclized in acidic medium (PPA and P_2O_5) at 180°C into 5-bromo-3-methyl benzo[*b*]thiophene (**1b**). Compound **1c** was obtained by bromination with *N*-bromosuccinimide (NBS) in the presence of dibenzoyl peroxide (DBP). Nucleophilic displacement of bromide with sodium cyanide in DMSO provided nitrile **1d**.

The *N*-acetylated derivatives (**1f**, **1h**–**1i**, **1k**–**1m**, **1o**–**1q**, **2f**–**2o**) were prepared (Figure 2) from appropriate amine hydrochlorides by treatment with the appropriate acid chloride in the presence of potassium carbonate as base in a biphasic medium (Method A; Yous et al 1992) according to a variant of the Schotten–Bauman procedure (Lindberg et al 1968) or with acids in the presence of 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride and potassium carbonate as base according to peptide synthesis (Method B) or with acid anhydrides in pyridine (Method C).

Pharmacology

Table 1 shows that replacement of the methoxy group by a halogen does not affect affinity—com-

Table 1. The physical properties and mt_1 and MT_2 receptor-binding affinity of the benzothiophene compounds.

Compound	X	R	Mp (°C)	Recrystallization solvent	IC50 mt_1 (M)	IC50 MT_2 (M)	Rate selectivity (mt_1/MT_2)
Melatonin	–	–	–	–	$2{\cdot}0 \times 10^{-10}$	$5{\cdot}3 \times 10^{-10}$	0·40
1f	Br	CH_3	134–136	Toluene	$2{\cdot}3 \times 10^{-09}$	$9{\cdot}3 \times 10^{-10}$	2·46
1h	Br	CF_3	144–146	Toluene	$1{\cdot}0 \times 10^{-08}$	$2{\cdot}0 \times 10^{-09}$	4·95
1i	Br	cyclopropyl	166–168	Toluene	–	–	–
1k	Br	$CH_2CH=CH_2$	90–91	Toluene	$2{\cdot}1 \times 10^{-09}$	$2{\cdot}1 \times 10^{-10}$	9·77
1l	Br	$CH=CHC_6H_5$	152–153	Toluene–cyclohexane[a]	$> \times 10^{-05}$	$9{\cdot}3 \times 10^{-06}$	1·10
1m	Br	$CH_2CH=CHC_6H_5$	130–131	Toluene–cyclohexane[a]	$2{\cdot}6 \times 10^{-06}$	$1{\cdot}3 \times 10^{-05}$	0·20
1o	Br	2-furyl	87–88	Toluene–cyclohexane[a]	$2{\cdot}1 \times 10^{-06}$	$1{\cdot}2 \times 10^{-06}$	1·74
1p	Br	$3,4\text{-}Cl_2C_6H_3$	144–146	Toluene	–	–	–
1q	Br	$CH_2C_6H_5$	147–148	Toluene	–	–	–
2f	Cl	CH_3	129–130	Toluene	$6{\cdot}5 \times 10^{-09}$	$1{\cdot}6 \times 10^{-09}$	4·00
2g	Cl	$(CH_2)_3Cl$	83–84	Cyclohexane	$1{\cdot}4 \times 10^{-08}$	$1{\cdot}2 \times 10^{-08}$	1·15
2h	Cl	CF_3	132–134	Toluene	$6{\cdot}3 \times 10^{-08}$	$1{\cdot}1 \times 10^{-08}$	5·90
2i	Cl	cyclopropyl	161–163	Toluene	$3{\cdot}8 \times 10^{-08}$	$2{\cdot}0 \times 10^{-08}$	1·89
2j	Cl	$CH=CH_2$	111–113	Toluene	$9{\cdot}8 \times 10^{-09}$	$4{\cdot}6 \times 10^{-09}$	2·13
2k	Cl	$CH_2CH=CH_2$	76–77	Toluene–cyclohexane[a]	$1{\cdot}6 \times 10^{-09}$	$3{\cdot}6 \times 10^{-10}$	4·47
2l	Cl	$CH=CHC_6H_5$	162–163	Toluene–cyclohexane[a]	$> \times 10^{-05}$	$> \times 10^{-05}$	1·00
2m	Cl	$CH_2CH=CHC_6H_5$	116–117	Cyclohexane	$3{\cdot}3 \times 10^{-06}$	$1{\cdot}0 \times 10^{-06}$	3·20
2n	Cl	$\equiv\text{-}CH_3$	79–80	Toluene–cyclohexane[a]	$2{\cdot}6 \times 10^{-07}$	$1{\cdot}1 \times 10^{-07}$	2·28
2o	Cl	2-furyl	70–71	Toluene–cyclohexane[a]	$2{\cdot}4 \times 10^{-06}$	$1{\cdot}9 \times 10^{-06}$	1·28

[a]In the proportions 4 : 1, respectively.

pounds **1f** and **2f**, which can be considered as the direct 5-halobenzothiophene analogues of melatonin, have slightly less affinity than melatonin. Furthermore, most of the 5-bromo compounds (**1f**, **1h**, **1k**–**1m**, **1o**) have similar affinity which is even higher than that of their 5-chloro analogues (**2f**, **2h**, **2k**–**2m**, **2o**).

Except for the allylic compounds (**1k**, **2k**), which in each series studied have the best affinity, replacement of the methyl group of the amidic group by another substituent results, overall, in a usually significant reduction of affinity according to the nature and steric hindrance of the substituents, especially when aromatic or conjugated aromatic groups are present (**1l**, **1m**, **1o**, **2l**, **2m**, **2o**).

With regard to selectivity, most of the 5-halobenzothiophene derivatives are slightly selective towards the MT_2 binding sites.

These results show that the methoxy group is not essential requirement for high affinity. This calls into question the suggestion that the methoxy group, which is likely to form a hydrogen-bond with a receptor residue, is responsible for the activity and affinity of melatonin.

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