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Synthesis and pharmacological evaluation of dual ligands for melatonin (MT₁/MT₂) and serotonin 5-HT_{2C} receptor subtypes (II)

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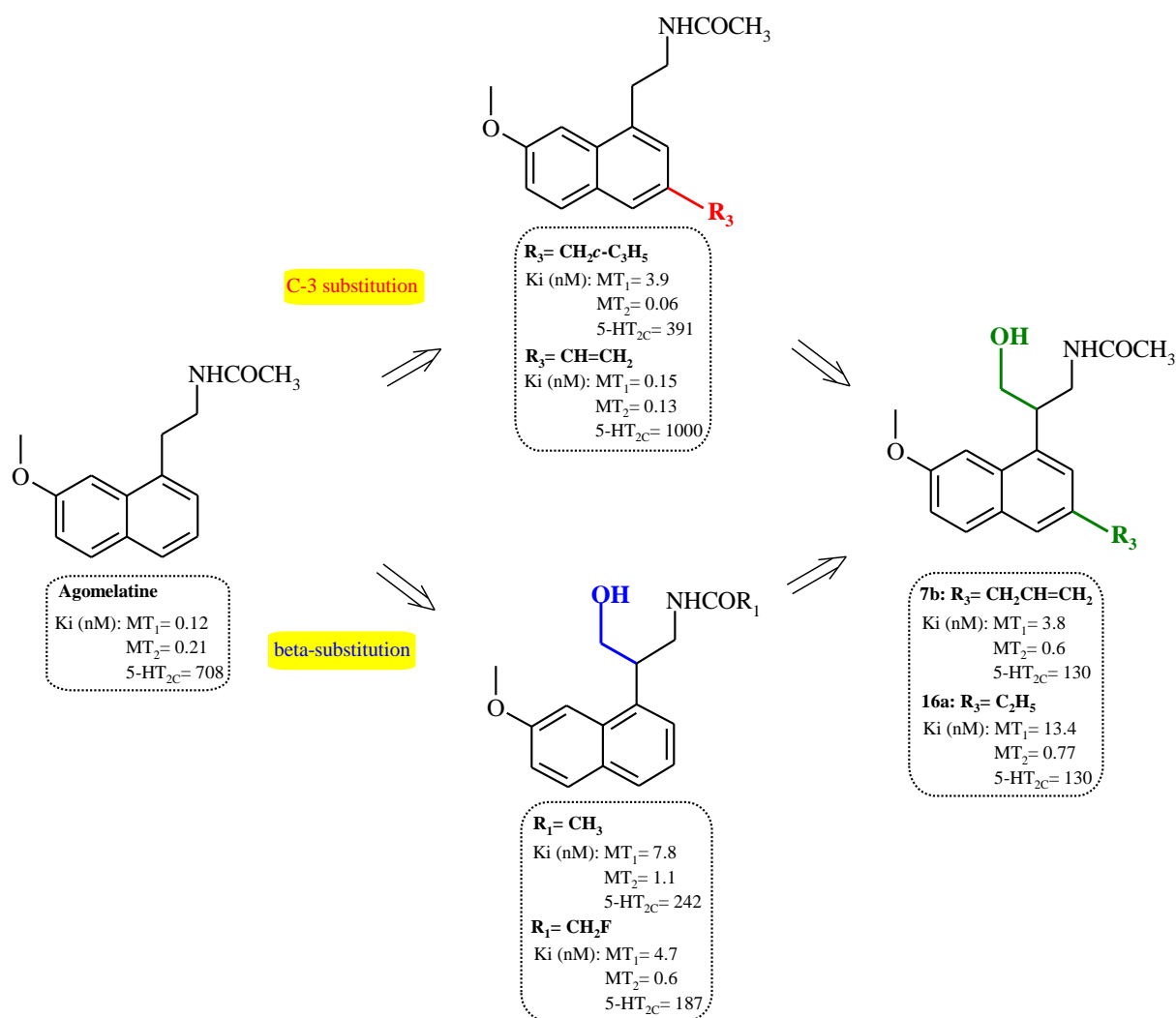
[⊥]*Both investigators equally contributed to this work*

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GRAPHICAL ABSTRACT



A new series of agomelatine analogues dual ligands for melatonin and serotonin were synthesized issued from combination of β - and C-3 modulations. Synthesized series conserved submicromolar melatonin binding affinities.

RESEARCH HIGHLIGHTS:

- New agomelatine analogues dual ligands for melatonin and serotonin were reported
- Combination of β - and C-3 modulations led to the improvement of serotonin binding affinity
- Synthesized series conserved melatonin binding affinities; The allyl **7b** and ethyl **16a** represented the more interesting compounds of this series.
- Methyl thiourea **12h** represent one of the highest MT₂ selective derivative nowadays reported

ABSTRACT

In the current paper we report the synthesis and biological results of new series of molecules issued from the investigation of agomelatine C-3 and β -acetamide positions. Accordingly, the introduction of a hydroxymethyl in the β -acetamide position and aliphatic groups in C-3 position produced a positive effect on both the melatonin (MT₁, MT₂) and serotonin (5-HT_{2C}) binding affinities. In particular, the allyl **7b** and ethyl **16a** represented the more interesting compounds of this series. The introduction of methyl cycloalkyl groups (compounds **12a**, **13a**) exhibited no change in both MT₂ and 5-HT_{2C} binding affinities while a decrease of MT₁ binding affinity occurred leading to MT₂ selectivity. Finally, the acetamide modulation has led to methyl thiourea **12h**, bearing one of the highest MT₂ selectivity nowadays reported.

Key words

Agomelatine, Melatonin receptors, MT₂-selectivity, Serotonin 5-HT_{2C} receptor.

Abbreviations used

MT₁, melatonin receptor subtype 1; MT₂, melatonin receptor subtype 2; 5-HT_{2C}, serotonin receptor subtype 2C; [³⁵S]GTPγS, [³⁵S]guanosine-5'-O-(3-thio-triphosphate).

1. Introduction

Melatonin or *N*-acetyl-5-methoxytryptamine is mainly produced and secreted by the pineal gland during the period of darkness following a circadian rhythm [1]. This neurohormone is the endogenous ligand for MT₁ and MT₂, two receptors belonging to the family of G protein-coupled receptors (GPCRs) and primarily expressed in the central nervous system (CNS) [2] and widely distributed in other tissues [3,4]. Melatonin interacts also with a low binding affinity site called MT₃ and characterized as the hamster homologue of the human enzyme quinone reductase 2 [5]. Once secreted, melatonin plays an important role in modulating various physiological processes upon activation of its binding sites [6-8].

Since its isolation, then characterization by Aaron Lerner in 1958 [9], melatonin was extensively studied during the 20th century in order to clarify its physiological and behavioural implications. Over the years were discovered and proved its biological implications. However, since the development of ramelteon and agomelatine (Chart 1) the interest of the scientific community is growing up significantly and special attention has been paid for the design and synthesis of selective ligands. The elucidation of the exact role of the two melatonin receptor subtypes remains a real challenge but may provide great potential in the comprehension of their biological functions and the development of specific ligands.

Melatonin was demonstrated to be involved in the regulation and re-establishment of circadian rhythms and sleep promoting [10]. Moreover, it is also suggested to be involved in a variety of other physiopathological processes. In fact, experimental evidence suggests its implication in type 2 diabetes [11], in depression [12-14], cancer [15], in Alzheimer and Parkinson diseases [16-17]. Furthermore, other studies showed the involvement of this

neurohormone in the modulation of immunity, cardiovascular responses and in blood pressure control [18].

Our research group started working, two decades ago, on the discovery of new tools for the study of the melatonergic system. Hence, a multicomponent research program was initiated and consisted in the synthesis of new ligands selective or not for one or the other of the melatonin binding sites MT_1 , MT_2 and MT_3 . A substantial work was done in terms of SAR and many interesting ligands were discovered [19-22]. In one of the investigated areas, the aim was to design and synthesize new molecules with a similar receptorial profile as agomelatine, a melatonin MT_1/MT_2 agonist and serotonin 5-HT_{2C} antagonist. To hit this objective, we previously described the synthesis of new analogues issued from the modulation of different sites of agomelatine [23,24]. Accordingly, the modulation of the C-3 position of the naphthalene ring [23] and the β -position of the amide side chain [24] have been shown to possess positive effects on binding affinities at both (MT_1 , MT_2) and 5-HT_{2C}. In the current work, we describe the synthesis and pharmacological results of compounds issued from the combination of these two modulations of agomelatine using β -hydroxymethyl-agomelatine as a lead.

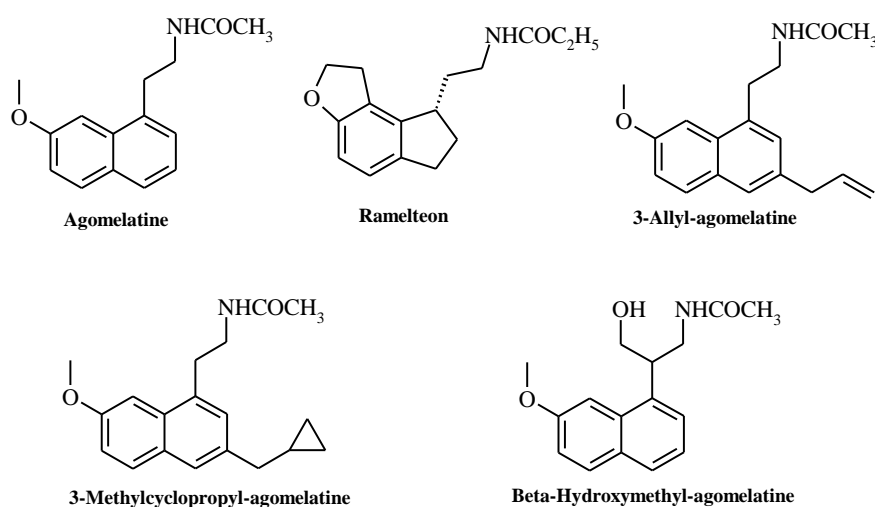
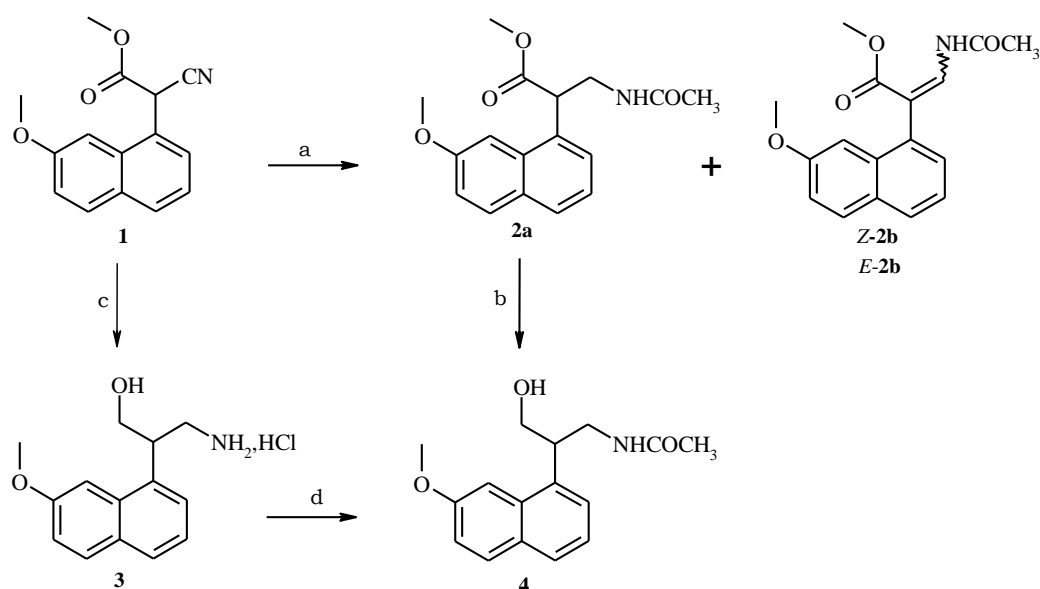


Chart 1. Melatonin and some of its analogues.

2. Results and Discussion

2.1. Chemistry. Synthetic routes to the designed compounds are depicted in Schemes 1-4. The acetamide **4** was resynthesized from cyanoester **1** [24] through two synthetic routes (Scheme 1). First, by a catalytic hydrogenation over Raney nickel in acetic anhydride [25] leading to the desired amidoester **2a** and two unsaturated isomers (*E,Z*)-**2b**. The treatment of compound **2a** with a mixture of lithium aluminum hydride furnished the desired compound **4** in a global yield of 56% [26]; The structures of isomers *E*-**2b** and *Z*-**2b** were determined by analytical studies using ^1H , ^{13}C and ROESY 1D NMR analyses. *Z*-**2b** identification was based on the presence of dipolar interactions between the ethylenic proton of the lateral chain and the naphthalenic proton H_8 (see supporting information).

Scheme 1. Synthesis of compound **4**

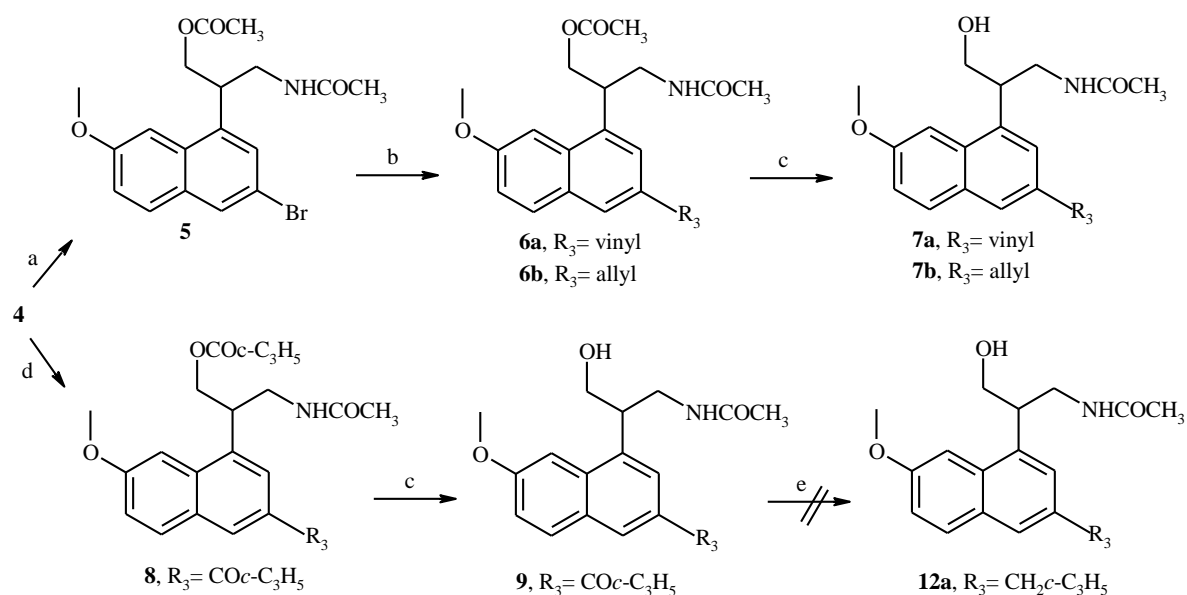


^aReagents: a) Ac_2O , H_2 , Ni-Raney, 60°C ; b) LiAlH_4 , THF, 0°C ; c) (i) LiAlH_4 , AlCl_3 , Et_2O , 0°C (ii) HCl_g , Et_2O ; d) K_2CO_3 , $\text{EtOAc}/\text{H}_2\text{O}$, CH_3COCl , 0°C -rt.

The first strategy gave only access to acetamide derivative while the second method allowed preparation of different amides and areas as was previously described by us [24]. This later method was realized in two steps, a one-pot reduction of nitrile and ester by treatment with a mixture of $\text{LiAlH}_4/\text{AlCl}_3$ followed by *N*-acylation of the resulting primary amine into the desired acetamide **4**.

After preparation of lead compound **4**, we moved to the synthesis of compounds issued from C-3 modulation. First, the access to vinyl and allyl derivatives **7a** and **7b** was achieved by C-3 selective bromination of compound **4** in acetic acid at 70 °C. The obtained ester **5** was then submitted to Stille cross-coupling reaction in the presence of vinyl and allyl tin derivatives to afford prodrugs **6a** and **6b** [27]. Finally, saponification of these later esters by sodium hydroxide in a hydro-alcoholic mixture furnished the desired compounds **7a** and **7b** in good yields (Scheme 2).

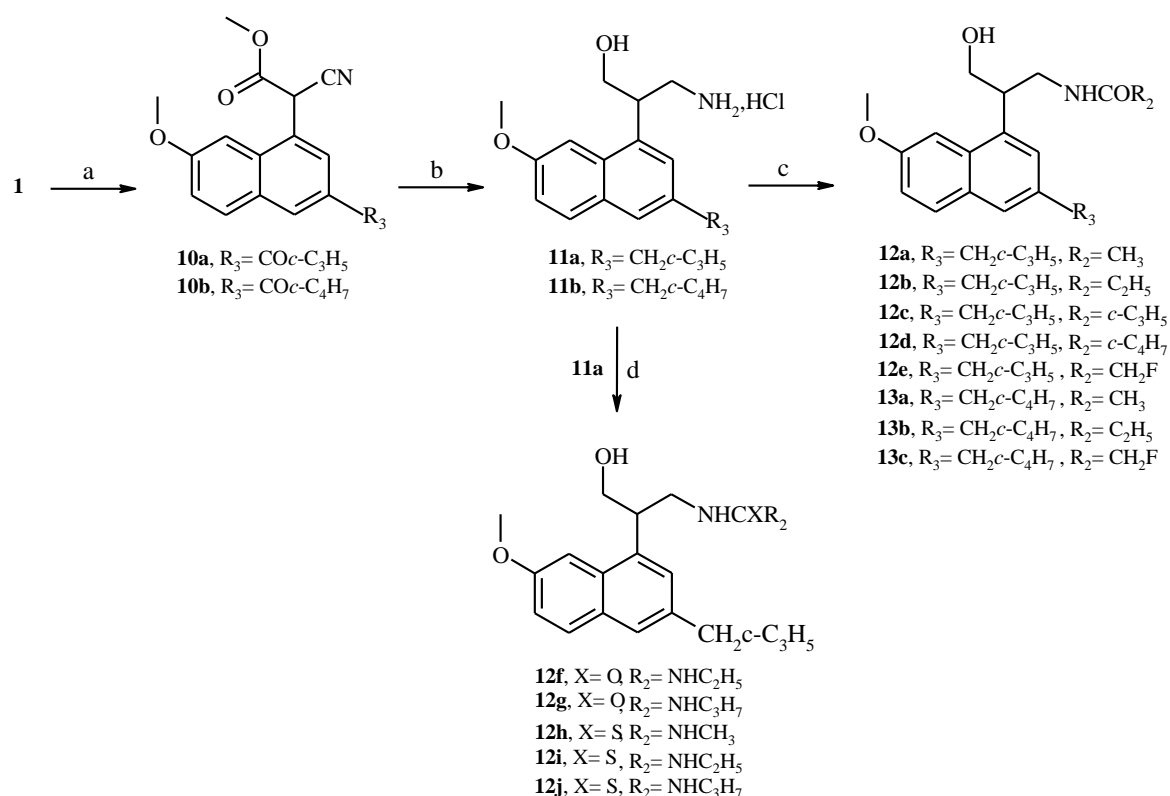
Scheme 2. Synthesis of compounds **7a-b** and **9**



^aReagents: a) Br_2 , AcOH, 70°C; b) $\text{Pd}(\text{PPh}_3)_4$, Bu_3SnR_3 , toluene, 110°C; c) $\text{NaOH}_{(\text{aq})}$, MeOH; d) $\text{H}_5\text{C}_3\text{c-COCl}$, AlCl_3 , DCM, 0°C; e) Et_3SiH , TFA, rt.

To prepare methylcyclopropyl **12a** we have adopted a strategy based on direct acylation of compound **4** (Scheme 2). By using Friedel-Crafts acylation conditions and cyclopropanoyl chloride, we obtained the intermediate ester **8** in a low yield (15%). Saponification of this later in methanol in the presence of sodium hydroxide furnished quantitatively acetamidoalcohol **9**. Next, attempts to selectively reduce the ketone group onto methylene (compound **12a**) using triethylsilane [28] were unsuccessful. This method figures out the difficulty of access to the desired compound by direct acylation of the amidolalcohol **4**. To overcome this synthetic difficulty, we developed a new strategy permitting also the access to different amides and ureas (**12a-j** and **13a-c**) and depicted in Scheme 3. This strategy consists in direct acylation of cyanoester **1** under Friedel-crafts conditions followed by one-step reduction of nitrile, ketone and ester functions using a mixture of LiAlH₄ and AlCl₃ in dry diethyl ether. The formed primary amines **11a** and **11b** were then *N*-acylated following the Schotten-Baumann conditions to afford compounds **12a-d** and **13a-b**. Otherwise, fluoroacetamides **12e** and **13c** were prepared from amine bases **11a** and **11b** as previously described by us using ethyl fluoroacetate in 2,2,2-trifluoroethanol. Finally, ureas and thioureas (**12f-j**) were prepared from the amine hydrochloride **11a** by treatment with the corresponding isocyanates or isothiocyanates [29].

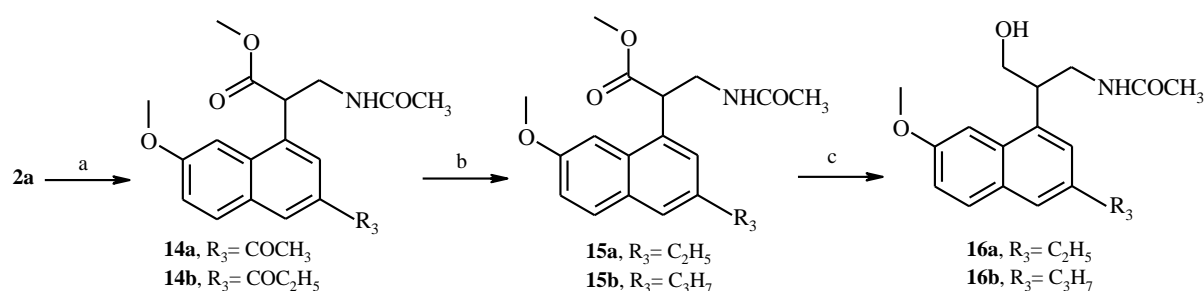
Scheme 3. Synthesis of compounds **12a-j** and **13a-c**



^aReagents: a) $R_3\text{Cl}$, AlCl_3 , DCM , 0°C ; b) (i) LiAlH_4 , AlCl_3 , Et_2O , 0°C , (ii) $\text{HCl}_{(\text{g})}$, Et_2O ; c) K_2CO_3 , $\text{EtOAc}/\text{H}_2\text{O}$ then (i) R_2COCl , 0°C -rt for **12a-d**, **13a-b**, (ii) $\text{FCH}_2\text{CO}_2\text{Et}$, TFE , reflux for **12e** and **13c**; d) Et_3N , R_2CX , DCM , 0°C .

Finally, C-3 alkylated derivatives (**16a-16b**) were prepared from intermediate **2a** previously described in Scheme 1. Direct acylation of compound **2a** in the presence of aluminum chloride and acetyl or propanoyl chloride provided intermediates **14a-b**. Selective reduction of the ketone with triethylsilane in TFA furnished C-3 alkylated derivatives **15a-b**. Finally, a selective chemical reduction of the methyl ester into hydroxymethyl using lithium aluminum hydride afforded the desired compounds **16a** and **16b** in good yields (Scheme 4). It is worth nothing that synthesis of compounds **16a-16b** starting from compounds **1** and **4** was tried and abandoned because of low yields.

Scheme 4. Synthesis of compounds **16a-16b**



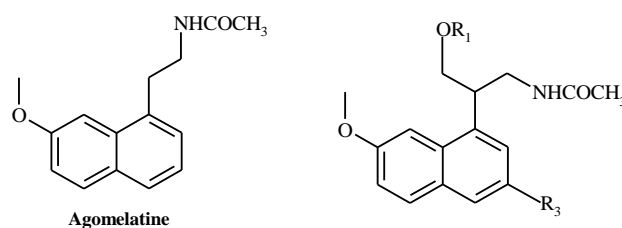
^aReagents: a) AlCl₃, DCM/DMF, R₃Cl, 0°C; b) Et₃SiH, TFA, rt; c) LiAlH₄, THF, 0°C.

Biological Results. Newly synthesized compounds were assayed at human MT₁ and MT₂ receptors stably transfected in Chinese Hamster Ovarian (CHO) cells, using 2-[¹²⁵I]iodomelatonin as radioligand [31]. Serotonergic 5-HT_{2C} binding affinity was performed using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human 5-HT_{2C} receptors. Tables 1-3 report the chemical structures, melatonin (MT₁, MT₂) and serotonin 5-HT_{2C} binding affinities of these compounds.

As was previously stated, the introduction of a hydroxymethyl group in the β-position of the acetamide lateral chain and the modulation of C-3 position of agomelatine improved both the melatonergic and serotonergic 5-HT_{2C} binding affinities [23,24]. Hence, compound **4** was chosen as a lead for new modulations in order to prepare new "dual" ligands for melatonin and serotonin receptors. In the current study we report the synthesis and biological results of a new series of derivatives issued from C-3 position modulation of **4**. Accordingly, the introduction of aliphatic chains such as vinyl (**7a**), allyl (**7b**), ethyl (**16a**) and propyl (**16b**) showed in general a positive effect on serotonergic 5-HT_{2C} binding affinity and the conservation of melatonergic binding affinities (Tables 1-2). This observation was in agreement with our previous findings. In fact, the insertion of an allyl (**7b**) or an ethyl group (**16a**) produced an improvement of binding affinities at both melatonin (MT₁, MT₂) and

serotonin 5-HT_{2C} receptor subtypes. These two compounds represented the more interesting ligands of this series. Besides, the vinyl **7a** exhibited a good binding affinity at melatonin receptor subtypes but a lower binding affinity at 5-HT_{2C}. On contrary, the propyl **16b** showed the conservation of both serotonin 5-HT_{2C} and melatonin MT₂ affinities with a decrease of the MT₁ binding affinity.

Table 1. Binding affinities of compounds **4-7b**

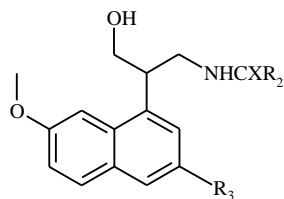


Compound	R ₁	R ₃	K _i (nM) MT ₁ [I95] (n)	K _i (nM) MT ₂ [I95] (n)	K _i (nM) 5-HT _{2C} [I95] (n)
Agomelatine	-	-	0.12 [0.12;0.12] (2)	0.21 [0.08;0.57] (2)	708 [674;752] (2)
4	H	H	7.8 [7.2;8.3] (2)	1.1 [0.7;1.5] (2)	242 [164;323] (2)
5	COCH ₃	Br	6.8 [6.1;7.7] (2)	0.74 [0.72;0.76] (2)	> 10000 (2)
6b	COCH ₃	allyl	33.0 [25.3;43.1] (2)	2.9 [2.6;3.4] (2)	> 10000 (2)
7a	H	vinyl	6.6 [5.9;7.5] (2)	1.7 [1.2;2.4] (2)	1040 [920;1190](4)
7b	H	allyl	3.8 [2.6;5.4] (2)	0.60 [0.04;1.0](2)	130 [90;190](4)

K_i (nM) values are geometric mean values (with 95% confidence limits shown in brackets) of at least n separate experiments performed in duplicate.

The introduction, in the C-3 position of naphthalene cycle, of a methyl cyclopropyl (**12a**) or a methyl cyclobutyl (**13a**), had no change in MT₂ and 5-HT_{2C} binding affinities in comparison with the parent ligand (Table 2). However, we noticed a decrease in the MT₁ binding affinity resulting in an MT₂ selectivity of about 79-fold for **12a** and 19-fold for **13a**, respectively. Otherwise, the acetamide functions of **12a** and **13a** were substituted with other amides (**12b-12d** and **13b-13c**), fluoroacetamide (**12e**) or ureas and thioureas (**12f-12j**). The acetamide **12a** replacement by a propylamide (**12b**) or a cyclopropylamide (**12c**) has

produced a decrease of melatonin MT₁ and serotonin 5-HT_{2C} binding affinities. In addition, the MT₂ selectivity was fallen by 55 and 27-fold respectively in comparison with **12a**. Furthermore, the bulky cyclobutanamide **12d** displayed a selectivity of 91-fold toward the MT₂ receptor subtype while the fluoroacetamide **12e** conserved the same good binding affinity towards MT₂ and 5-HT_{2C} receptors as the lead compound **4** and displayed a MT₂ selectivity of about 153-fold.

Table 2. Binding affinities of compounds **9-16b**

<i>Compd.</i>	<i>R</i> ₂	<i>R</i> ₃	<i>X</i>	<i>K</i> _i (nM) <i>MT</i> ₁ [I95] (<i>n</i>)	<i>K</i> _i (nM) <i>MT</i> ₂ [I95] (<i>n</i>)	<i>K</i> _i (nM) 5- <i>HT</i> _{2c} [I95] (<i>n</i>)
9	CH ₃	COc-C ₃ H ₅	O	116 [53;254] (2)	81 [61;108] (2)	> 10000 (2)
12a	CH ₃	CH ₂ c-C ₃ H ₅	O	174 [81;376] (3)	2.2[1.3;3.6] (2)	220 [100;500](2)
12b	C ₂ H ₅	CH ₂ c-C ₃ H ₅	O	100 [46;215] (3)	1.8 [1.4;2.3](2)	670 [340;1300] (2)
12c	<i>c</i> -C ₃ H ₅	CH ₂ c-C ₃ H ₅	O	217 [173;273] (2)	8.1 [4.6;14] (2)	1060 [1060;1060](2)
12d	<i>c</i> -C ₄ H ₇	CH ₂ c-C ₃ H ₅	O	1040 [724;1490](2)	11.4 [6.3;20.7](3)	990 [480;2020] (2)
12e	CH ₂ F	CH ₂ c-C ₃ H ₅	O	338 [210;544] (2)	2.2[2.0;2.5](2)	300 [150;620] (3)
12f	NHC ₂ H ₅	CH ₂ c-C ₃ H ₅	O	763 [69;84] (2)	15.9 [13.7;18.3] (2)	790 [460;1370] (3)
12g	NHC ₃ H ₇	CH ₂ c-C ₃ H ₅	O	2360 (1)	25.5 [19.5;33.2] (2)	990 [440;2250] (2)
12h	NHCH ₃	CH ₂ c-C ₃ H ₅	S	867 [45;169] (2)	0.48 [39.6;57.5] (2)	260 [110;610] (3)
12i	NHC ₂ H ₅	CH ₂ c-C ₃ H ₅	S	2800 (1)	70.5 [51.5;96.4] (2)	350 [170;750] (3)
12j	NHC ₃ H ₇	CH ₂ c-C ₃ H ₅	S	4870 (1)	143 [69;298](2)	160 [110;230] (2)
13a	CH ₃	CH ₂ c-C ₄ H ₇	O	199 [189;209] (2)	10.2 [6.1;16.9] (2)	1110 [520;2250](2)
13b	C ₂ H ₅	CH ₂ c-C ₄ H ₇	O	163 [126;211] (2)	0.81 [0.65;1.01] (2)	1000 [670;1480](2)
13c	CH ₂ F	CH ₂ c-C ₄ H ₇	O	229 [131;398] (2)	> 10000 (2)	580 [390;870] (2)
16a	CH ₃	C ₂ H ₅	O	13.4 [5.8;31.2] (3)	0.77 [0.47;1.29] (2)	130 [120;150] (2)
16b	CH ₃	C ₃ H ₇	O	59 [31;112](3)	1.1 [0.6;2.0](2)	210 [160;280](2)

*K*_i (nM) values are geometric mean values (with 95% confidence limits shown in brackets) of at least *n* separate experiments performed in duplicate.

With regard to the encouraging results obtained by the past with ureas and thioureas, the acetamide was then substituted by ureas (**12f-12g**) and thioureas (**12h-12j**). Hence, this modulation has led to a decrease of melatonin and serotonin 5-HT_{2C} binding affinities (Table 2). The same effect was observed with thioureas but the methyl thiourea **12h** who exhibited one of the highest MT₂ selectivity nowadays reported. Furthermore, propyl thiourea **12j** displayed one of the good serotonin 5-HT_{2C} binding affinities of this series. Finally, the acetamide function of compound **13a** was also submitted to modulation. Even its replacement by a propylamide (**13b**) had shown no noticed evolution, its substitution with a fluoroacetamide (**13c**) produced a lost of the MT₂ affinity and a decrease of both MT₁ and 5-HT_{2C} binding affinities.

Table 3. Functional activities of synthesized compounds

Compound	<i>h</i> -MT ₁		<i>h</i> -MT ₂	
	<i>EC</i> ₅₀ (nM) I95 (n)	<i>E</i> _{max} (%)±ESM(n)	<i>EC</i> ₅₀ (nM) [I95] (n)	<i>E</i> _{max} (%) ± ESM (n)
Agomelatine	1.56 [1.12;2.00] (4)	99 ± 6 (4)	0.21 [0.13;0.30] (3)	91 ± 7 (3)
4	72 [64;81] (2)	69 ± 5 (2)	144 [100;208] (2)	48 ± 6 (2)
5	> 10000 (2)	nd	1.4 [1.3;1.5] (2)	17 ± 3 (2)
6b	> 10000 (2)	nd	>10000 (2)	nd
7a	63 [43;91] (2)	63 ± 4 (2)	0.54 [0.27;1.1] (2)	98 ± 1 (2)
7b	41 [31;55] (2)	69 ± 6 (2)	0.53 [0.45;0.61](2)	87 ± 14 (2)
9	216 (1)	36 (1)	> 10000 (2)	nd
12a	1180 [1070;1300] (2)	75 ± 10 (2)	7.6 [7.5;7.7] (2)	102 ± 11 (2)
12b	1260 [999;1590](2)	56 ± 10 (2)	4.7 [4.5;5.0] (2)	107 ± 4 (2)
12c	> 10000 (2)	nd	26 [19;36] (2)	93 ± 12 (2)
12d	nd	nd	52 [31;89] (2)	86 ± 0 (2)
12e	> 10000 (4)	nd	3.2 [1.5;6.7] (2)	94 ± 8 (2)
12f	nd	nd	21 [16;27] (2)	155 ± 42 (2)
12g	nd	nd	77 [37;161] (2)	98 ± 6 (2)
12h	nd	nd	37 [31;45] (2)	55 ± 2 (2)
12i	nd	nd	632 [412;971] (2)	51 ± 11 (2)
13a	nd	nd	4.1 [3.3;5.0] (3)	116 ± 7 (3)
13b	1340 [1140;1570] (2)	87 ± 4 (2)	3.1 [2.4;4.1] (3)	129 ± 6 (3)
13c	nd	nd	5.9 [3.6;9.7] (3)	126 ± 8 (3)
16a	31 [11;94] (2)	46 ± 12 (2)	0.89 [0.60;1.31] (2)	99 ± 5 (2)
16b	198 [74;532] (3)	34 ± 3 (3)	0.85 [0.36;2.0](2)	58 ± 6 (2)

nd: not determined.

*EC*₅₀ values are geometric mean values of (n) experiments.

*E*_{max} values are arithmetic mean ± S.E.M.

Regarding the intrinsic activity, we investigated the *EC*₅₀ and *E*_{max} at melatonin MT₁ and MT₂ receptor subtypes of synthesized compounds. The obtained results are illustrated in

Table 3 and revealed the obtention of compounds with different pharmacological profiles. In fact, several compounds showed a partial agonist activity profile at MT₁ and MT₂ receptors (compounds **7b**, **12c**, **12d**, **12i**, **12j**, and **16b**) while other compounds (**7a**, **12a**, **12b**, **12f**, **13a-c**, and **16a**) behaved as partial agonist at MT₁ and full agonist at MT₂ receptor subtype.

Conclusions

We report in this paper the design and synthesis of a series of agomelatine analogues. The current strategy issued from the modulation of agomelatine β -acetamide position and C-3 position of the naphthalene ring led to compounds with different pharmacological profiles. In fact, insertion of aliphatic chains produced a positive effect on serotonin 5-HT_{2C} binding affinity and the conservation of melatonin binding affinities. The allyl **7b** and ethyl **16a** exhibited the most interesting results of this series. However, the introduction of sterically hindered groups (methyl cycloalkyls) resulted in a decrease of MT₁ binding affinity leading to an MT₂ selectivity and confirming the findings previously obtained with C-3 modulation. At melatonin receptors, all the synthesized compounds showed a partial agonist activity at MT₁ and full or partial agonist activities at MT₂.

Experimental Section

Chemistry: Melting points were determined on a Büchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Vector 22 Bruker spectrometer. ¹H and ¹³C NMR spectra were recorded on an AC300 Bruker spectrometer. Chemical shifts are reported in ppm units (parts per million) relative to (CH₃)₄Si. Elemental analyses for new compounds were performed by CNRS Laboratories (Vernaison, France) and the obtained results were within 0.4% of the theoretical values. Compounds purities were verified with analytical HPLC method and established to be > 95%.

Methyl 3-Acetylamino-2-(7-methoxy-naphthalen-1-yl) propanoate (2a).

Compound **1** (4.0 g, 39.2 mmol) was dissolved in acetic anhydride (200 mL) and the mixture was hydrogenated over Raney Ni (4.0 g) under pressure (30 bars) at 60 °C for 3 h. After filtration on celite, the solvent was concentrated and the residue was dissolved in water (100 mL) then extracted with ethyl ether. The organic phase was washed with a solution of sodium hydrogenocarbonate (1 M), dried over MgSO₄, and evaporated under reduced pressure to give **2a** as a white solid after recrystallization from isopropyl ether (70% yield). Mp 118-120 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 302.16; ¹H NMR (CDCl₃): δ 2.01 (s, 3H), 3.50 (m, 1H), 3.75 (s, 3H), 3.90 (m, 1H), 4.05 (s, 3H), 4.76 (m, 1H), 6.05 (br s, 1H), 7.13-7.34 (m, 3H), 7.66-7.82 (m, 3H); IR (neat, cm⁻¹): 3285 (NH), 1731 (C=O), 1655 (C=O).

Methyl (Z/E) 3-Acetylamino-2-(7-methoxy-naphthalen-1-yl) acrylate (2b).

After compound **2** recrystallisation, the filtrate was purified on a silica gel column eluted with a mixture acetone-cyclohexane (3:7) and gave the two isomers *Z*-**2b** and *E*-**2b** as white solids (8% yield). *Z*-**2b**: Mp 154-156 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 300.14; ¹H NMR (CDCl₃): δ 1.92 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 6.91 (d, 1H, *J* = 2.0), 6.93 (br s, 1H), 7.21 (dd, 1H, *J* = 2.0, *J* = 8.9), 7.32 (m, 1H), 7.42 (m, 1H), 7.80 (d, 1H, *J* = 8.9), 7.86 (m, 1H), 8.52 (d, 1H, *J* = 12.2); ¹³C NMR (CDCl₃): δ 23.5, 52.0, 55.4, 102.9, 112.1, 119.1, 123.5, 128.6, 128.8, 128.9, 129.5, 130.2, 132.8, 134.2, 158.4, 167.6, 167.7; IR (neat, cm⁻¹): 3286 (NH), 1718 (C=O), 1636 (C=O).

E-**2b**: Mp 161-163 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 300.14; ¹H NMR (CDCl₃): δ 1.91 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 6.92 (d, 1H, *J* = 2.0), 7.21 (dd, 1H, *J* = 2.0, *J* = 8.9), 7.32 (m, 1H), 7.44 (m, 1H), 7.71 (d, 1H, *J* = 11.0), 7.80 (d, 1H, *J* = 8.9), 7.87 (m, 1H), 10.83 (d, 1H, *J* = 11.0); ¹³C NMR (CDCl₃): δ 23.9, 52.8, 55.3, 104.0, 109.1, 118.3, 123.1, 128.2, 128.8, 129.0, 129.9, 132.3, 134.3, 138.6, 157.8, 168.4, 169.8; IR (neat, cm⁻¹): 3336 (NH), 1723 (C=O), 1683 (C=O).

3-Hydroxy-2-(7-methoxy-naphthalen-1-yl)propylamine hydrochloride (3).

To a suspension of LiAlH₄ (3.04 g, 80 mmol) in dry diethyl ether (300 mL) at 0 °C, was added dropwise a solution of AlCl₃ (10.6 g, 80 mmol) in dry diethyl ether (200 mL). After 10 mn under stirring, a solution of **1** (5.1 g, 20 mmol) in dry diethyl ether (200 mL) was added. The reaction mixture was stirred for additional 30 mn, and hydrolyzed with a solution of NaOH (10 g, 250 mmol). After filtration and evaporation of the filtrate, the residue was dissolved in water and extracted with dichloromethane. The organic phase was washed with water, dried over MgSO₄, filtered and evaporated under reduced pressure. The oily residue was then treated with HCl gas and recrystallized from acetonitrile. White solid (65% yield); Mp 164-166 °C. MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 232.14; ¹H NMR (DMSO-*d*₆): δ 3.20 (m, 1H), 3.41 (m, 1H), 3.69-3.72 (m, 2H), 3.92-4.02 (m, 4H), 5.31 (br s, 1H), 7.22 (dd, 1H, *J* = 2.0, *J* = 9.1), 7.33 (m, 1H), 7.46 (m, 1H), 7.51 (d, 1H, *J* = 2.0), 7.68 (m, 1H), 7.88 (d, 1H, *J* = 9.1), 7.99 (br s, 3H); IR (neat, cm⁻¹): 3330-2800; Anal. (C₁₄H₁₈ClNO₂) C, H, N.

***N*-[3-Hydroxy-2-(7-methoxy-naphthalen-1-yl)propyl]acetamide (4). Route 1:** Compound **2a** (6.02 g, 20 mmol) was dissolved in dry tetrahydrofuran (65 mL) and cooled at 0 °C in an ice-bath, then aluminum lithium hydride (1 g, 26 mmol) was added portionwise. After 1 h stirring, the reaction mixture was hydrolyzed with 1 mL of water, 1 mL of an aqueous solution of NaOH (15%) and 3 mL of water. The mineral formed was filtered and the filtrate was washed, dried over MgSO₄ and evaporated under reduced pressure to lead to a white solid after recrystallization from acetonitrile (80% yield).

Route 2. To a suspension of **3** (5.35 g, 20 mmol) in 100 mL of a mixture of H₂O/AcOEt (1:1) was added potassium carbonate (8.28 g, 60 mmol) and the reaction mixture was cooled to 0 °C in an ice-bath. Acetyl chloride (1.85 mL, 26 mmol) was added and the mixture stirred for 15 mn. The two phases were separated and the organic layer was washed with a solution of HCl (1 M) and water, dried over MgSO₄, filtered and evaporated under reduced pressure. The

desired product was collected as a white solid after recrystallization from acetonitrile (80% yield). Mp 136-138 °C; MS (APCI, pos. 30 V) m/z : $[M+H]^+$, 274.16; $^1\text{H NMR}$ (DMSO- d_6): δ 1.76 (s, 3H), 3.33-7.37 (m, 2H), 3.65-3.85 (m, 3H), 3.96 (s, 3H), 4.73 (br s, 1H), 7.17 (dd, 1H, $J = 2.0, J = 9.1$), 7.32 (m, 1H), 7.46 (m, 1H), 7.62 (d, 1H, $J = 2.0$), 7.71 (m, 1H), 7.83 (d, 1H, $J = 9.1$), 7.96 (br s, 1H); IR (neat, cm^{-1}): 3280 (NH), 3199 (OH), 1645 (C=O); Anal. ($\text{C}_{16}\text{H}_{19}\text{NO}_3$) C, H, N.

3-Acetylamino-2-(3-bromo-7-methoxy-naphthalen-1-yl)propyle acetate (5). To a heated solution of **4** (2.73 g, 10 mmol) in glacial acetic acid (40 mL) at 70 °C, was added dropwise dibromine (0.55 mL, 11 mmol). The reaction mixture was stirred for 4 h at this temperature then poured into water (80 mL) and extracted twice with 100 mL of diethyl ether. The organic phase was washed with NaHCO_3 (1 M) and water, dried over MgSO_4 , filtered and evaporated under reduced pressure to furnish the desired product as a white solid (60% yield), after recrystallization from toluene. Mp 150-152 °C; $^1\text{H NMR}$ (DMSO- d_6): δ 1.76 (s, 3H), 1.96 (s, 3H), 3.28 (m, 1H), 3.50 (m, 1H), 3.88-4.10 (m, 4H), 4.40-4.43 (m, 2H), 7.24 (dd, 1H, $J = 2.0, J = 9.1$), 7.53 (d, 1H, $J = 2.0$), 7.69 (s, 1H), 7.83 (d, 1H, $J = 9.1$), 8.04 (s, 1H), 8.12 (br s, 1H); IR (neat, cm^{-1}): 3395 (NH), 1718 (C=O), 1673 (C=O); Anal. ($\text{C}_{18}\text{H}_{20}\text{BrNO}_4$) C, H, N.

3-Acetylamino-2-(7-methoxy-3-vinyl-naphthalen-1-yl)propyle acetate (6a). Compound **5** (1.5 g, 3.8 mmol) and triphenylphosphine palladium tetrakis (0.219 g, 0.19 mmol) were dissolved in 22 mL of dry toluene under argon atmosphere, then vinyltributyltin (5.7 mmol) was added dropwise cautiously and the mixture was refluxed for 2 h. After cooling, the mixture was poured into 50 mL of an aqueous solution of KF 10% and the solid formed was filtered and washed with ethyl acetate. The organic phase was washed, dried over MgSO_4 and evaporated under reduced pressure to give the desired product as a white solid after purification on silica gel column eluted with a mixture of ethyl acetate/cyclohexane (8:2). Recrystallized from toluene (30% yield); Mp 122-124 °C; MS (APCI, pos. 30 V) m/z :

[M+H]⁺, 342.19; ¹H NMR (DMSO-*d*₆): δ 1.80 (s, 3H), 1.97 (s, 3H), 3.31 (m, 1H), 3.54 (m, 1H), 3.79-4.10 (m, 4H), 4.38 (dd, 1H, *J* = 6.2, *J* = 11.0), 4.52 (dd, 1H, *J* = 7.2, *J* = 11.0), 5.31 (d, 1H, *J* = 11.3), 5.95 (d, 1H, *J* = 17.6), 6.85 (dd, 1H, *J* = 11.3, *J* = 17.6), 7.16 (dd, 1H, *J* = 9.0, *J* = 2.4), 7.63 (m, 1H), 7.68 (d, 1H, *J* = 2.4), 7.54 (m, 1H), 7.77 (d, 1H, *J* = 9.0), 7.98 (br s, 1H); IR (neat, cm⁻¹): 3232 (NH), 1726 (C=O), 1626 (C=O); Anal. (C₂₀H₂₃NO₄) C, H, N.

3-Acetylamino-2-(3-allyl-7-methoxy-naphthalen-1-yl)propyle acetate (6b). This compound was prepared from compound **5** and tributylvinyltin according to the procedure described above for **6a**. The obtained compound was recrystallized from toluene; White solid (50% yield); Mp 78-80 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 356.20; ¹H NMR (DMSO-*d*₆): δ 1.80 (s, 3H), 1.97 (s, 3H), 3.16 (m, 1H), 3.40-3.65 (m, 3H), 3.85-4.18 (m, 4H), 4.38-3.42 (m, 2H), 5.10-5.15 (m, 2H), 6.04 (ddt, 1H, *J* = 6.8, *J* = 10.0, *J* = 17.1), 7.16 (dd, 1H, *J* = 9.0, *J* = 2.4), 7.28 (m, 1H), 7.53 (d, 1H, *J* = 2.4), 7.66 (m, 1H), 7.78 (d, 1H, *J* = 9.0), 8.09 (br s, 1H); IR (neat, cm⁻¹): 3238 (NH), 1725 (C=O), 1633 (C=O); Anal. (C₂₁H₂₅NO₄) C, H, N.

***N*-[3-Hydroxy-2-(7-methoxy-3-vinyl-naphthalen-1-yl)propyl]acetamide (7a).** To a solution of compound **6a** (5.0 mmol) in methanol (30 mL) was added sodium hydroxide (0.6 g, 15.0 mmol) in solution 30 mL of water. The reaction mixture was heated at 50 °C for 30 minutes then acidified with an aqueous solution of HCl (1 M). The mixture was extracted twice with 30 mL of ethyl acetate and the organic phase was washed with water, dried over MgSO₄ and evaporated under reduced pressure to give the desired product after recrystallization from acetonitrile as a white solid (80% yield). mp 109-111 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 300.18; ¹H NMR (DMSO-*d*₆): δ 1.80 (s, 3H), 3.33-3.38 (m, 2H), 3.60-3.85 (m, 3H), 3.93 (s, 3H), 4.56 (br s, 1H), 5.32 (d, 1H, *J* = 11.3), 5.94 (d, 1H, *J* = 17.6), 6.83 (dd, 1H, *J* = 11.3, *J* = 17.6), 7.16 (dd, 1H, *J* = 9.0, *J* = 2.4), 7.61 (m, 1H), 7.68 (d, 1H, *J* = 2.4), 7.55 (m, 1H), 7.78 (d, 1H, *J* = 9.0), 7.98 (br s, 1H); ¹³C NMR (CDCl₃): δ 23.1, 41.6,

42.3, 55.7, 63.1, 103.1, 113.9, 118.5, 122.1, 125.2, 129.4, 130.8, 132.3, 133.7, 137.1, 137.5, 158.0, 170.1; IR (neat, cm^{-1}): 3279, 3210, 1650; Anal. ($\text{C}_{18}\text{H}_{21}\text{NO}_3$) C, H, N.

***N*-[3-Hydroxy-2-(3-allyl-7-methoxy-naphthalen-1-yl)propyl]acetamide (7b).** This compound was prepared from compound **6b** according to the procedure described for **7a**. Recrystallized from acetonitrile as a white solid (80% yield); Mp 142-144 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 314.18; ^1H NMR ($\text{DMSO-}d_6$): δ 1.80 (s, 3H), 3.38-3.44 (m, 2H), 3.50 (d, 2H, $J = 6.7$), 3.62-3.85 (m, 3H), 3.93 (s, 3H), 4.72 (br s, 1H), 5.10-5.14 (m, 2H), 6.03 (ddt, 1H, $J = 6.7$, $J = 10.0$, $J = 17.1$), 7.16 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.32 (m, 1H), 7.48 (d, 1H, $J = 2.4$), 7.55 (m, 1H), 7.77 (d, 1H, $J = 9.0$), 7.95 (br s, 1H); ^{13}C NMR (CDCl_3): δ 23.1, 40.1, 41.6, 42.2, 55.6, 63.1, 102.8, 116.3, 118.2, 125.4, 126.2, 129.6, 130.2, 132.3, 134.7, 136.9, 138.1, 157.5, 170.1; IR (neat, cm^{-1}): 3254 (NH), 3172 (C=O), 1636 (C=O); Anal. ($\text{C}_{19}\text{H}_{23}\text{NO}_3$) C, H, N.

Preparation of compound 8. To a solution of compound **4** (3.0 g, 11.0 mmol) in 50 mL of dry dichloromethane at 0 °C, was added cautiously aluminum chloride (8.8 g, 66.0 mmol) then cyclopropanoyle chloride (3.3 mL, 36.4 mmol). The reaction mixture was stirred at room temperature for 1 h, poured into water (100 mL) and the organic phase was washed with brine, dried over MgSO_4 and evaporated under reduced pressure. The yellow oil obtained was then purified on a silica gel column eluted with a mixture of acetone-cyclohexane (3:7) to lead to compound **8**.

***N*-[3-Acetylamino-2-(3-cyclopropanecarbonyl-7-methoxy-naphthalen-1-yl)propyl]-cyclopropanoate ester (8).** Recrystallized from acetonitrile as a white solid (15% yield); Mp 108-110 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 410.25; ^1H NMR ($\text{DMSO-}d_6$): δ 0.72-0.78 (m, 8H), 1.46-1.54 (m, 2H), 1.78 (s, 3H), 3.30 (m, 1H), 3.50 (m, 1H), 3.95 (s, 3H), 3.99 (m, 1H), 4.35 (m, 1H), 4.46 (m, 1H), 7.16 (dd, 1H, $J = 9.0$, $J = 2.0$), 7.33 (m, 1H), 7.44 (m, 1H),

7.68 (d, 1H, $J = 2.0$), 7.76 (m, 1H), 7.86 (d, 1H, $J = 9.0$), 8.08 (br s, 1H); IR (neat, cm^{-1}): 3341 (NH), 1717 (C=O), 1653 (C=O), 1643 (C=O); Anal. ($\text{C}_{24}\text{H}_{27}\text{NO}_5$) C, H, N.

***N*-[2-(3-Cyclopropanecarbonyl-7-methoxy-naphthalen-1-yl)-3-hydroxy-propyl]-**

acetamide (9). The amidoester **8** (0.4 g, 1.0 mmol) was dissolved in methanol (10 mL) then 5 mL of an aqueous solution of NaOH (2 N) was added. The mixture was stirred at room temperature for 48 h, concentrated under reduced pressure, poured into water (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO_4 and evaporated under reduced pressure to give the desired product after recrystallisation from acetonitrile; White solid (61% yield); Mp 158-160 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 342.18; ^1H NMR ($\text{DMSO-}d_6$): δ 1.02-1.07 (m, 4H), 1.78 (s, 3H), 3.04 (m, 1H), 3.38-3.44 (m, 2H), 3.77-3.83 (m, 3H), 3.98 (s, 3H), 4.75 (br s, 1H), 7.25 (dd, 1H, $J = 9.0$, $J = 2.0$), 7.68 (d, 1H, $J = 2.0$), 7.91-7.95 (m, 1H), 8.00 (br s, 1H), 8.08 (d, 1H, $J = 9.0$), 8.63-8.66 (m, 1H); ^{13}C NMR ($\text{DMSO-}d_6$): δ 11.6 (2C), 16.8, 23.0, 41.7, 42.2, 55.9, 63.1, 103.1, 119.1, 122.4, 126.8, 128.5, 130.6, 132.5, 132.7, 137.5, 160.0, 170.2, 199.9; IR (neat, cm^{-1}): 3341-3199 (NH,OH), 1728 (C=O), 1643 (C=O); Anal. ($\text{C}_{20}\text{H}_{23}\text{NO}_4$) C, H, N.

Methyl 2-cyano-2-(3-cyclopropanecarbonyl-7-methoxy-naphthalen-1-yl)acetate (10a).

Prepared from **1** as described for **8a**; Recrystallized from ethanol as a yellow solid (86% yield); Mp 144-146 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 324.20; ^1H NMR ($\text{DMSO-}d_6$): δ 1.08-1.15 (m, 4H), 3.09 (m, 1H), 3.75 (s, 3H), 3.95 (s, 3H), 6.48 (s, 1H), 7.41-7.48 (m, 2H), 8.12 (d, 1H, $J = 2.4$), 8.21 (d, 1H, $J = 9.0$), 8.92 (m, 1H); IR (neat, cm^{-1}): 2242 (CN), 1747 (C=O), 1649 (C=O).

Methyl 2-cyano-2-(3-cyclobutanecarbonyl-7-methoxy-naphthalen-1-yl)acetate (10b).

Prepared from compound **1** according to procedure described for **8a**; Recrystallized from ethanol as a white solid (62% yield); Mp 132-134 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 338.21; ^1H NMR ($\text{DMSO-}d_6$): δ 1.82 (m, 1H), 2.08 (m, 1H), 2.26-2.33 (m, 4H), 3.74 (s,

3H), 3.92 (s, 3H), 4.27 (m, 1H), 6.48 (s, 1H), 7.36 (d, 1H, $J = 1.6$), 7.40 (dd, 1H, $J = 9.0$, $J = 2.4$), 8.09 (d, 1H, $J = 2.4$), 8.18 (d, 1H, $J = 9.0$), 8.59 (d, 1H, $J = 1.6$); IR (neat, cm^{-1}): 2242 (CN), 1748 (C=O), 1662 (C=O).

3-Hydroxy-2-(3-cyclopropylmethyl-7-methoxy-naphthalen-1-yl)propylamine hydrochloride (11a). This compound was prepared from **10a** according to the procedure described for **3**. Recrystallized from acetonitrile as a white solid (50% yield); Mp 174-176 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 322.12; ^1H NMR (DMSO- d_6): δ 0.20-0.25 (m, 2H), 0.46-0.50 (m, 2H), 1.05 (m, 1H), 2.60-2.63 (m, 2H), 3.18-3.21 (m, 2H), 3.70-3.74 (m, 2H), 3.93 (m, 1H), 3.90 (s, 3H), 5.31 (br s, 1H), 7.17 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.35 (d, 1H, $J = 2.0$), 7.47 (d, 1H, $J = 2.4$), 7.62 (d, 1H, $J = 2.0$), 7.80 (d, 1H, $J = 9.0$), 8.05 (br s, 3H); IR (neat, cm^{-1}): 3314-2827 (NH_2 , OH).

3-Hydroxy-2-(3-cyclobutylmethyl-7-methoxy-naphthalen-1-yl)propylamine hydrochloride (11b). Prepared from **10b** according to the procedure described for compound **3**; Recrystallized from acetonitrile as a white solid (52% yield); Mp 144-146 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 336.15; ^1H NMR (DMSO- d_6): δ 1.74-1.82 (m, 4H), 1.97-1.99 (m, 2H), 2.61 (m, 1H), 2.77 (d, 2H, $J = 7.8$), 3.15 (m, 1H), 3.39 (m, 1H), 3.70-3.74 (m, 2H), 3.92 (s, 3H), 3.94 (m, 1H), 5.21 (br s, 1H), 7.16 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.27 (d, 1H, $J = 1.6$), 7.47 (d, 1H, $J = 2.4$), 7.49 (d, 1H, $J = 1.6$), 7.77 (d, 1H, $J = 9.0$), 8.11 (br s, 2H); IR (neat, cm^{-1}): 3395-2827 (NH_2 , OH).

Synthesis of ureas and thioureas 12a-d. These compounds were prepared from compound **11a** according to the procedure described for **4** (route 2).

***N*-[2-[3-(Cyclopropylmethyl)-7-methoxy-1-naphthyl]-3-hydroxy-propyl]acetamide (12a).** Recrystallized from acetonitrile as a white solid (83% yield); Mp 154-156 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 328.18; ^1H NMR (DMSO- d_6): δ 0.18-0.22 (m, 2H), 0.45-0.49 (m, 2H), 1.03 (m, 1H), 1.78 (s, 3H), 2.60 (d, 2H, $J = 6.7$), 3.39 (m, 1H), 3.46 (m, 1H), 3.66-3.84 (m, 3H), 3.91 (s, 3H), 4.72 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.33 (d, 1H, $J = 2.0$),

7.50-7.55 (m, 2H), 7.75 (d, 1H, $J = 9.0$), 7.91 (br s, 1H); ^{13}C NMR (DMSO- d_6): δ 5.0 (2C), 12.3, 23.1, 41.6, 42.3, 55.6 (2C), 63.3, 102.8, 118.0, 125.1, 126.4, 129.6, 130.2, 132.3, 136.5, 136.7, 157.3, 170.1; IR (neat, cm^{-1}): 3260 (NH), 2993-2845 (OH), 1634 (C=O); Anal. ($\text{C}_{20}\text{H}_{25}\text{NO}_3$) C, H, N.

***N*-[2-[3-(Cyclopropylmethyl)-7-methoxy-1-naphthyl]-3-hydroxy-propyl]propylamide**

(12b). Recrystallized from toluene as a white solid (64% yield); Mp 104-106 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 342.20; ^1H NMR (DMSO- d_6): δ 0.20-0.24 (m, 2H), 0.44-0.48 (m, 2H), 0.89-0.95 (m, 3H), 1.03 (m, 1H), 2.00-2.05 (m, 2H), 2.60 (d, 2H, $J = 6.4$), 3.40-3.47 (m, 2H), 3.70-3.78 (m, 3H), 3.91 (s, 3H), 4.73 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.33 (d, 1H, $J = 1.6$), 7.50-7.54 (m, 2H), 7.77 (d, 1H, $J = 9.0$), 7.81 (br s, 1H); ^{13}C NMR (DMSO- d_6): δ 5.1 (2C), 10.5, 12.4, 29.1, 41.6 (2C), 42.3, 55.7, 63.4, 102.9, 118.1, 125.2, 126.5, 129.6, 130.2, 132.3, 136.5, 136.7, 157.3, 173.8; IR (neat, cm^{-1}): 3238 (NH), 3077-2881 (OH), 1639 (C=O); Anal. ($\text{C}_{21}\text{H}_{27}\text{NO}_3$) C, H, N.

***N*-[2-[3-(Cyclopropylmethyl)-7-methoxy-1-naphthyl]-3-hydroxy-propyl]cyclopropylamide**

(12c). Recrystallized from toluene as a white solid (62% yield); Mp 142-144 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 354.21; ^1H NMR (DMSO- d_6): δ 0.20-0.24 (m, 2H), 0.45-0.48 (m, 2H), 0.54-0.59 (m, 2H), 0.61-0.65 (m, 2H), 1.03 (m, 1H), 1.48 (m, 1H), 2.60 (d, 2H, $J = 7.0$), 3.45-3.50 (m, 2H), 3.68-3.78 (m, 3H), 3.89 (s, 3H), 4.75 (br s, 1H), 7.13 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.32 (d, 1H, $J = 2.0$), 7.51 (d, 1H, $J = 2.4$), 7.55 (d, 1H, $J = 2.0$), 7.76 (d, 1H, $J = 9.0$), 8.10 (br s, 1H); ^{13}C NMR (DMSO- d_6): δ 5.1 (2C), 6.6 (2C), 12.4, 14.2, 41.6 (2C), 42.6, 55.6, 63.5, 103.0, 118.2, 125.1, 126.5, 129.7, 130.2, 132.3, 136.5, 136.8, 157.5, 173.4; IR (neat, cm^{-1}): 3396 (NH), 3073-2914 (OH), 1647 (C=O); Anal. ($\text{C}_{22}\text{H}_{27}\text{NO}_3$) C, H, N.

***N*-Cyclobutylcarbonyl-[2-(3-cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxy-**

propyl]amide (12d). Recrystallized from acetonitrile as a white solid (42% yield); Mp 94-96 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 368.22; ^1H NMR (DMSO- d_6): δ 0.20-0.25 (m, 2H),

0.45-0.48 (m, 2H), 1.03 (m, 1H), 1.64-2.10 (m, 6H), 2.60 (d, 2H, $J = 6.6$), 2.90 (m, 1H), 3.42-3.45 (m, 2H), 3.68-3.72 (m, 3H), 3.91 (s, 3H), 4.72 (br s, 1H), 7.13 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.32 (d, 1H, $J = 2.0$), 7.52-7.55 (m, 2H), 7.66 (br s, 1H), 7.75 (d, 1H, $J = 9.0$); ^{13}C NMR (DMSO- d_6): δ 5.1 (2C), 12.3, 18.3, 25.1 (2C), 39.2, 41.5 (2C), 42.4, 55.6, 63.4, 102.9, 118.0, 125.1, 126.5, 129.6, 130.2, 132.3, 136.5, 136.7, 157.3, 174.7; IR (neat, cm^{-1}): 3304 (NH), 3074-2821 (OH), 1636 (C=O); Anal. ($\text{C}_{23}\text{H}_{29}\text{NO}_3$) C, H, N.

***N*-[2-[3-(Cyclopropylmethyl)-7-methoxy-1-naphthyl]-3-hydroxy-propyl]fluoroacetamide (12e).** To a solution of **11a** (2.0 g, 6.2 mmol) in a mixture of H_2O -EtOAc (40:60 mL) was added K_2CO_3 (2.6 g, 18.8 mmol). The mixture was stirred at room temperature for 2 h and the two phases were separated. The organic phase was washed with water, dried over MgSO_4 and evaporated under reduced pressure. The obtained oil was then dissolved in 25 mL of 2,2,2-trifluoroethanol and ethyl fluoroacetate (2.4 mL, 24.8 mmol) was added dropwise cautiously. The reaction mixture was stirred and refluxed for 12 h. After cooling, the mixture was poured into water (40 mL), extracted twice with ethyl ether (25 mL) and the organic layers were dried over MgSO_4 and evaporated under reduced pressure. The obtained residue was then solubilized in 20 mL of methanol and 10 mL of a solution of NaOH (2 N) was added. The mixture was heated at 40 °C for 30 min, poured into water and acidified with an aqueous solution of HCl (1 M). The mixture was then extracted with diethyl ether and the organic phase was washed, dried over MgSO_4 and evaporated under reduced pressure to give the desired product after recrystallisation from isopropyl ether. White solid (33% yield); Mp 88-90 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 346.18; ^1H NMR (DMSO- d_6): δ 0.20-0.24 (m, 2H), 0.45-0.48 (m, 2H), 1.00-1.03 (m, 1H), 2.61 (d, 2H, $J = 6.8$), 3.47-3.50 (m, 1H), 3.55-3.57 (m, 1H), 3.75-3.83 (m, 3H), 3.91 (s, 3H), 4.76 (d, 2H, $J = 47.1$), 4.79 (br s, 1H), 7.13 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.37 (d, 1H, $J = 1.6$), 7.55 (d, 1H, $J = 1.6$), 7.57 (d, 1H, $J = 2.4$), 7.76 (d, 1H,

$J = 9.0$), 8.25 (br s, 1H); IR (neat, cm^{-1}): 3248, 3077-2832, 1647; Anal. ($\text{C}_{20}\text{H}_{24}\text{FNO}_3$) C, H, N.

Synthesis of ureas and thioureas 12f-j. To a suspension of compound **11a** (6.2 mmol) in dichloromethane (60 mL) at 0 °C, were added respectively triethylamine (12.4 mmol) and the corresponding isocyanate or isothiocyanate (6.3 mmol). The mixture was left to stir for 2 h and the solid formed was filtered, washed with diethyl ether and recrystallized to lead to the desired product.

1-[2-(3-Cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxy-propyl]-3-ethyl-urea (12f). Recrystallized from toluene as a white solid (72% yield); Mp 116-118 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 357.19; ^1H NMR ($\text{DMSO-}d_6$): δ 0.20-0.25 (m, 2H), 0.45-0.49 (m, 2H), 0.91-0.96 (m, 3H), 1.05 (m, 1H), 2.61 (d, 2H, $J = 6.6$), 2.97-3.00 (m, 2H), 3.38-3.42 (m, 2H), 3.66-3.72 (m, 3H), 3.91 (s, 3H), 4.82 (br s, 1H), 5.85 (br s, 2H), 7.13 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.33 (m, 1H), 7.53 (d, 1H, $J = 2.4$), 7.56 (m, 1H), 7.75 (d, 1H, $J = 9.0$); ^{13}C NMR ($\text{DMSO-}d_6$): δ 5.1 (2C), 12.4, 16.2, 34.6, 42.2 (2C), 43.2, 55.6, 63.6, 102.8, 118.1, 125.0, 126.4, 129.6, 130.1, 132.2, 136.7, 136.8, 157.3, 158.7; IR (neat, cm^{-1}): 3368-3291 (NH), 3074-2821 (OH), 1653 (C=O); Anal. ($\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_3$) C, H, N.

1-[2-(3-Cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxy-propyl]-3-propyl-urea (12g). Recrystallized from toluene-cyclohexane (1:1) as a white solid (30% yield); Mp 92-94 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 371.22; ^1H NMR ($\text{DMSO-}d_6$): δ 0.22-0.25 (m, 2H), 0.45-0.50 (m, 2H), 0.78-0.83 (m, 3H), 1.05 (m, 1H), 1.31-1.34 (m, 2H), 2.62 (d, 2H, $J = 6.6$), 2.91-2.95 (m, 2H), 3.42-3.45 (m, 2H), 3.66-3.69 (m, 3H), 3.91 (s, 3H), 4.82 (br s, 1H), 5.80 (br s, 1H), 5.90 (br s, 1H), 7.13 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.34 (d, 1H, $J = 1.6$), 7.52 (d, 1H, $J = 2.4$), 7.56 (d, 1H, $J = 1.6$), 7.76 (d, 1H, $J = 9.0$); ^{13}C NMR ($\text{DMSO-}d_6$): δ 5.0 (2C), 11.8, 12.4, 23.7, 41.6 (2C), 42.1, 43.1, 55.5, 63.6, 102.8, 118.0, 125.0, 126.3, 129.5, 130.1,

132.3, 136.7, 136.8, 157.3, 158.9; IR (neat, cm^{-1}): 3362-3290 (NH), 3011-2877 (OH), 1654 (C=O); Anal. ($\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_3$) C, H, N.

1-[2-(3-Cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxypropyl]-3-methylthiourea (12h). Recrystallized from toluene as a white solid (42% yield); Mp 96-98 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 359.18; ^1H NMR ($\text{DMSO-}d_6$): δ 0.20-0.24 (m, 2H), 0.45-0.48 (m, 2H), 1.05 (m, 1H), 2.61 (d, 2H, $J = 6.6$), 2.73-2.77 (m, 2H), 3.72-3.80 (m, 5H), 3.85-3.94 (m, 4H), 4.78 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.32-7.38 (m, 3H), 7.54-7.57 (m, 2H), 7.76 (d, 1H, $J = 9.0$); ^{13}C NMR ($\text{DMSO-}d_6$): δ 5.1 (2C), 12.4 (2C), 41.6 (2C), 41.8, 55.8, 63.9, 103.0, 118.2, 125.2, 126.6 (2C), 129.6 (2C), 130.2, 132.3, 136.8, 157.3; IR (neat, cm^{-1}): 3264 (NH), 3060-2831 (OH); Anal. ($\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$) C, H, N.

1-[2-(3-Cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxypropyl]-3-ethylthiourea (12i). Recrystallized from toluene as a white solid (51% yield); Mp 130-132 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 373.20; ^1H NMR ($\text{DMSO-}d_6$): δ 0.20-0.23 (m, 2H), 0.46-0.49 (m, 2H), 0.98-1.02 (m, 3H), 1.04 (m, 1H), 2.61 (d, 2H, $J = 6.6$), 3.27-3.31 (m, 2H), 3.72-3.80 (m, 4H), 3.86-3.92 (m, 4H), 4.81 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.26 (br s, 1H), 7.36 (m, 1H), 7.41 (br s, 1H), 7.54-7.57 (m, 2H), 7.75 (d, 1H, $J = 9.0$); ^{13}C NMR ($\text{DMSO-}d_6$): δ 5.1 (2C), 12.4, 14.9, 41.8 (2C), 42.3 (2C), 55.7, 63.9, 102.9, 118.2, 125.2, 126.5, 129.6, 130.2, 132.4, 136.6, 136.8, 157.3, 170.1; IR (neat, cm^{-1}): 3347-2994 (NH), 3060-2831 (OH); Anal. ($\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$) C, H, N.

1-[2-(3-Cyclopropylmethyl-7-methoxy-naphthalen-1-yl)-3-hydroxypropyl]-3-propylthiourea (12j). Recrystallized from cyclohexane-toluene (1:1) as a white solid (50% yield); Mp 122-124 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 387.21; ^1H NMR ($\text{DMSO-}d_6$): δ 0.20-0.23 (m, 2H), 0.47-0.50 (m, 2H), 0.78-0.81 (m, 3H), 1.03 (m, 1H), 1.39-1.41 (m, 2H), 2.62 (d, 2H, $J = 6.6$), 3.25-3.30 (m, 2H), 3.72-3.79 (m, 4H), 3.87-3.93 (m, 4H), 4.80 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.25 (br s, 1H), 7.36 (d, 1H, $J = 1.6$), 7.42 (br s, 1H), 7.55-7.57 (m,

2H), 7.76 (d, 1H, $J = 9.0$); ^{13}C NMR (DMSO- d_6): δ 5.0 (2C), 11.8 (2C), 12.4 (2C), 22.4, 41.8 (2C), 55.7, 63.9, 102.9, 118.1, 125.2, 126.5, 129.6, 130.1, 132.4, 136.6, 136.8, 157.3, 170.7; IR (neat, cm^{-1}): 3360-3088 (NH), 2994-2831 (OH); Anal. ($\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$) C, H, N.

General procedure for the synthesis of compounds 13a-13b. These two compounds were prepared from **11b** according to procedure described for **4**.

***N*-[3-Hydroxy-2-(3-cyclobutylmethyl-7-methoxy-naphthalen-1-yl)propyl]acetamide**

(13a). Recrystallized from acetonitrile as a white solid (86% yield); Mp 140-142 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 342.21; ^1H NMR (DMSO- d_6): δ 1.72-1.82 (m, 7H), 1.96-1.99 (m, 2H), 2.60 (m, 1H), 2.76 (d, 2H, $J = 7.7$), 3.36 (m, 1H), 3.45 (m, 1H), 3.68-3.74 (m, 3H), 3.91 (s, 3H), 4.72 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.25 (d, 1H, $J = 1.6$), 7.43 (d, 1H, $J = 1.6$), 7.54 (d, 1H, $J = 2.4$), 7.73 (d, 1H, $J = 9.0$), 7.91 (br s, 1H); ^{13}C NMR (DMSO- d_6): δ 18.4, 23.0, 28.1 (2C), 37.1, 41.5, 42.2, 42.8, 55.8, 63.3, 102.7, 118.0, 125.2, 126.4, 129.6, 130.2, 132.2, 135.7, 136.5, 157.4, 170.0; IR (neat, cm^{-1}): 3267 (NH), 3090-2856 (OH), 1634 (C=O); Anal. ($\text{C}_{21}\text{H}_{27}\text{NO}_3$) C, H, N.

***N*-[3-Hydroxy-2-(3-cyclobutylmethyl-7-methoxy-naphthalen-1-yl)propyl]propylamide**

(13b). Recrystallized from acetonitrile as a white solid (50% yield); Mp 88-90 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 356.22; ^1H NMR (DMSO- d_6): δ 0.90-0.94 (m, 3H), 1.72-1.80 (m, 4H), 1.92-2.04 (m, 4H), 2.59 (m, 1H), 2.75 (d, 2H, $J = 7.7$), 3.36 (m, 1H), 3.47 (m, 1H), 3.68-3.76 (m, 3H), 3.90 (s, 3H), 4.72 (br s, 1H), 7.11 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.23 (d, 1H, $J = 1.6$), 7.42 (d, 1H, $J = 1.6$), 7.52 (d, 1H, $J = 2.4$), 7.73 (d, 1H, $J = 9.0$), 7.80 (br s, 1H); ^{13}C NMR (DMSO- d_6): δ 10.4, 18.4, 23.2, 28.1 (2C), 37.1, 41.5, 42.2, 42.8, 55.7, 63.2, 102.7, 118.1, 125.3, 126.4, 129.5, 130.2, 132.1, 135.7, 136.5, 157.3, 170.0; IR (neat, cm^{-1}): 3304 (NH), 2966-2845 (OH), 1637 (C=O); Anal. ($\text{C}_{22}\text{H}_{29}\text{NO}_3$) C, H, N.

***N*-[3-Hydroxy-2-(3-cyclopropylmethyl-7-methoxy-naphthalen-1-yl)propyl]fluoro-**

acetamide (13c). Prepared from **11b** following procedure described for **12e**; Recrystallized

from isopropyl ether as a white solid (34% yield); Mp 90-92 °C; MS (APCI, pos. 30 V) m/z : $[M+H]^+$, 360.19; 1H NMR (DMSO- d_6): δ 1.73-1.81 (m, 4H), 1.98-2.00 (m, 2H), 2.60 (m, 1H), 2.76 (d, 2H, $J = 7.7$), 3.46 (m, 1H), 3.55 (m, 1H), 3.71-3.80 (m, 3H), 3.90 (s, 3H), 4.79 (d, 2H, $J = 46.9$), 4.89 (br s, 1H), 7.12 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.28 (d, 1H, $J = 1.6$), 7.44 (d, 1H, $J = 1.6$), 7.56 (d, 1H, $J = 2.4$), 7.74 (d, 1H, $J = 9.0$), 8.24 (br s, 1H); IR (neat, cm^{-1}): 3249 (NH), 3077-2832 (OH), 1647 (C=O); Anal. (C₂₁H₂₆FNO₃) C, H, N.

Preparation of compounds 14a-b.

Methyl *N*-[3-acetylamino-2-(3-acetyl-7-methoxy-naphthalen-1-yl)]propionate (14a).

To a solution of **2a** (3.0 g, 10.0 mmol) in dry dichloromethane (50 mL) at 0 °C was added, portionwise cautiously, aluminum chloride (10.0 g, 75.0 mmol) and the mixture was stirred for 5 min. Acetyl chloride (0.8 mL, 11.0 mmol) was then added dropwise. The mixture was allowed to stir at room temperature for 1 h, poured into water (100 mL) and the organic phase was washed with water, dried over MgSO₄ and evaporated under reduced pressure. The white solid formed was recrystallized from acetonitrile (83% yield); Mp 160-162 °C; MS (APCI, pos. 30 V) m/z : $[M+H]^+$, 344.20; 1H NMR (DMSO- d_6): δ 1.77 (s, 3H), 2.64 (s, 3H), 3.48-3.52 (m, 2H), 3.67 (s, 3H), 4.00 (s, 3H), 4.70 (m, 1H), 7.31 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.76 (d, 1H, $J = 1.8$), 7.82 (d, 1H, $J = 2.4$), 8.08 (d, 1H, $J = 9.0$), 8.30 (br s, 1H), 8.58 (d, 1H, $J = 1.8$); IR (neat, cm^{-1}): 3393 (NH), 1737 (C=O), 1665 (C=O), 1649 (C=O).

Methyl *N*-[3-acetylamino-2-(3-ethylcarbonyl-7-methoxy-naphthalen-1-yl)]propionate (14b).

This compound was prepared from **2a** following procedure described for **14a**; Recrystallized from acetonitrile as a white solid (56% yield); Mp 174-176 °C; MS (APCI, pos. 30 V) m/z : $[M+H]^+$, 358.18; 1H NMR (DMSO- d_6): δ 1.10-1.15 (m, 3H), 1.81 (s, 3H), 3.11-3.14 (m, 2H), 3.50-3.55 (m, 2H), 3.69 (s, 3H), 4.00 (s, 3H), 4.72 (m, 1H), 7.31 (dd, 1H, J

= 9.0, $J = 2.4$), 7.79 (d, 1H, $J = 2.0$), 7.81 (d, 1H, $J = 2.4$), 8.08 (d, 1H, $J = 9.0$), 8.31 (br s, 1H), 8.59 (d, 1H, $J = 2.0$); IR (neat, cm^{-1}): 3365 (NH), 1734 (C=O), 1663 (C=O), 1649 (C=O).

Methyl *N*-[3-acetylamino-2-(3-ethyl-7-methoxy-naphthalen-1-yl)]propionate (15a).

To a solution of **14a** (2.0 g, 5.8 mmol) in 20 mL of trifluoroacetic acid (TFA) was added dropwise triethylsilane (2.4 mL, 15.0 mmol) and the mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure and the white solid obtained was recrystallized from cyclohexane (94% yield); Mp 68-70 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 330.18; ^1H NMR (DMSO- d_6): δ 1.20-1.26 (m, 3H), 1.81 (s, 3H), 2.68-2.73 (m, 2H), 3.50-3.54 (m, 2H), 3.66 (s, 3H), 3.94 (s, 3H), 4.65 (m, 1H), 7.13 (d, 1H, $J = 2.0$), 7.16 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.58 (d, 1H, $J = 2.0$), 7.70 (d, 1H, $J = 2.4$), 7.79 (d, 1H, $J = 9.0$), 8.26 (br s, 1H); IR (neat, cm^{-1}): 3390 (NH), 1743 (C=O), 1630 (C=O).

Methyl *N*-[3-acetylamino-2-(3-propyl-7-methoxy-naphthalen-1-yl)]propionate (15b).

Prepared from **14b** according to the procedure described for compound **15a**; Recrystallized from cyclohexane as a white solid (98% yield); Mp 76-80 °C; MS (APCI, pos. 30 V) m/z : $[\text{M}+\text{H}]^+$, 344.20; ^1H NMR (DMSO- d_6): δ 0.89-0.96 (m, 3H), 1.60-1.65 (m, 2H), 1.81 (s, 3H), 2.63-2.68 (m, 2H), 3.50-3.56 (m, 2H), 3.66 (s, 3H), 3.93 (s, 3H), 4.65 (m, 1H), 7.10 (d, 1H, $J = 2.0$), 7.16 (dd, 1H, $J = 9.0$, $J = 2.4$), 7.56 (d, 1H, $J = 2.0$), 7.70 (d, 1H, $J = 2.4$), 7.78 (d, 1H, $J = 9.0$), 8.24 (br s, 1H); IR (neat, cm^{-1}): 3393 (NH), 1742 (C=O), 1632 (C=O).

***N*-[3-Hydroxy-2-(3-ethyl-7-methoxy-naphthalen-1-yl)propyl]acetamide (16a).** Compound

15a (2.0 g, 6.1 mmol) was dissolved in dry THF (200 mL), stirred and cooled at 0 °C. Aluminum lithium hydride (0.5 g, 12.1 mmol) was then added portionwise cautiously and the mixture was allowed to stir at room temperature for 6 h. 2 mL of water were added followed by the addition of 2 mL of a NaOH solution (1N). The mixture was washed with water and

the organic phase was dried over MgSO₄ and evaporated under reduced pressure to give the desired product as a white solid; Recrystallized from toluene (44% yield); Mp 120-122 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 302.16; ¹H NMR (DMSO-*d*₆): δ 1.22-1.26 (m, 3H), 1.76 (s, 3H), 2.70-2.73 (m, 2H), 3.39-3.42 (m, 2H), 3.73-3.76 (m, 3H), 3.91 (s, 3H), 4.71 (br s, 1H), 7.13 (dd, 1H, *J* = 9.0, *J* = 2.4), 7.31 (d, 1H, *J* = 2.0), 7.48 (d, 1H, *J* = 2.0), 7.54 (d, 1H, *J* = 2.4), 7.74 (d, 1H, *J* = 9.0), 7.91 (br s, 1H); ¹³C NMR (DMSO-*d*₆): δ 15.9, 23.1, 28.8, 41.6, 42.3, 55.7, 63.2, 102.8, 118.1, 124.5, 126.0, 129.6, 130.2, 132.3, 136.7, 138.7, 157.3, 170.1; IR (neat, cm⁻¹): 3260 (NH), 2959-2852 (OH), 1634 (C=O); Anal. (C₁₈H₂₃NO₃) C, H, N.

***N*-[3-Hydroxy-2-(3-propyl-7-methoxy-naphthalen-1-yl)propyl]acetamide (16b).** This compound was prepared from **15b** following procedure described for **16a**; Recrystallized from acetonitrile as a white solid (42% yield); Mp 142-144 °C; MS (APCI, pos. 30 V) *m/z*: [M+H]⁺, 316.19; ¹H NMR (DMSO-*d*₆): δ 0.89-0.93 (m, 3H), 1.62-1.66 (m, 2H), 1.75 (s, 3H), 2.61-2.63 (m, 2H), 3.33 (m, 1H), 3.45 (m, 1H), 3.72-3.74 (m, 3H), 3.90 (s, 3H), 4.71 (br s, 1H), 7.11 (dd, 1H, *J* = 9.0, *J* = 2.4), 7.28 (d, 1H, *J* = 2.0), 7.46 (d, 1H, *J* = 2.0), 7.54 (d, 1H, *J* = 2.4), 7.73 (d, 1H, *J* = 9.0), 7.90 (br s, 1H); ¹³C NMR (DMSO-*d*₆): δ 10.5, 16.0, 23.3, 28.9, 41.9, 42.5, 55.6, 63.1, 102.6, 118.2, 124.0, 125.9, 129.2, 130.0, 132.3, 136.7, 138.3, 157.3, 170.0; IR (neat, cm⁻¹): 3258 (NH), 2959-2849 (OH), 1633 (C=O); Anal. (C₁₉H₂₅NO₃) C, H, N.

Pharmacology: *Reagents and chemicals.* 2-[¹²⁵I]Iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma–Aldrich (Saint Quentin, France) and used without further purification.

Assays for MT₁ and MT₂ receptor subtypes. 2-[¹²⁵I]Iodomelatonin competition binding assay conditions were essentially as previously described [31]. Briefly, binding was initiated by addition of membrane preparations from transfected CHO cells stably expressing the human melatonin MT₁ or MT₂ diluted in binding buffer (50 mM Tris–HCl buffer, pH 7.4, containing 5 mM MgCl₂) to 2-[¹²⁵I]iodomelatonin (20 pM for MT₁ and MT₂ receptors expressed in CHO

cells) and the tested drug. Non-specific binding was defined in the presence of 1 μ M of melatonin. After 120 min incubation at 37 °C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. Filters were washed three times with 1 mL of ice-cold 50 mM Tris–HCl buffer (pH 7.4).

Data from the dose–response curves (seven concentrations in duplicate) were analysed using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield IC₅₀ (inhibitory concentration 50). Affinities are expressed as pKi ($pKi = -\text{Log}_{10} (Ki)$) with $Ki = IC_{50}/1 + ([L]/KD)$, where [L] is the concentration of radioligand used in the assay and KD, the dissociation constant of the radioligand characterizing the membrane preparation.

[³⁵S]GTP γ S binding assay was performed according to published methodology [31]. Briefly, membranes from transfected CHO cells expressing MT₁ and MT₂ receptor subtypes and compounds were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 μ M GDP, 3 mM MgCl₂, and 20 μ g/mL saponin). Incubation was started by the addition of 0.2 nM [³⁵S]GTP γ S to membranes (20 μ g/mL) and drugs, and further followed for 1 h at room temperature. Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice-cold buffer.

Usual levels of [³⁵S]GTP γ S binding (expressed in dpm) were for CHO-MT₂ membranes: 2000 for basal activity, 8000 in the presence of melatonin 1 μ M and 180 in the presence of GTP γ S 10 μ M which defined the non-specific binding. Data from the dose–response curves (seven concentrations in duplicate) were analyzed by using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield pEC₅₀ ($pEC_{50} = -\text{Log}_{10} (EC_{50})$) with EC₅₀ the effective concentration 50%) and Emax (maximal effect) for agonists.

Assays for 5-HT_{2C} receptor subtypes. Serotonin 5-HT_{2C} competition binding assay was determined according to the protocol previously reported in the literature [32]. Membranes from CHO cell lines, stably expressing the human 5-HT_{2C}(VSV) receptors were incubated for

60 min at 37 °C in binding buffer (50 mM Tris–HCl buffer (pH 7.4), containing 10 mM MgCl₂ and 0.1% BSA) containing the radioligand [³H]mesulergine (1 nM). Non-specific binding was defined in the presence of 10 μM mianserine. Reaction was terminated by rapid filtration through GF/B filters presoaked in 0.1% (v/v) polyethylenimine. Filters were washed three times with 1 mL of ice-cold 50 mM Tris–HCl buffer (pH 7.4). Residual radioactivity on filters was measured using a TopCount scintillation counter (PerkinElmer Life Sciences) after addition of Microscint 20. Isotherms were analyzed using non-linear regression to yield IC₅₀. Affinities are expressed as K_i.

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