

Article

Novel Conformationally Constrained Analogues of Agomelatine as New Melatonergic Ligands

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Abstract: Novel conformationally restricted analogues of agomelatine were synthesized and pharmacologically evaluated at MT₁ and MT₂ melatonergic receptors. Replacement of the *N*-acetyl side chain of agomelatine by oxathiadiazole-2-oxide (compound **3**), oxadiazole-5(4*H*)-one (compound **4**), tetrazole (compound **5**), oxazolidinone (compound **7a**), pyrrolidinone (compound **7b**), imidazolidinedione (compound **12**), thiazole (compounds **13** and **14**) and isoxazole moieties (compound **15**) led to a decrease of the melatonergic binding affinities, particularly at MT₁. Compounds **7a** and **7b** exhibiting nanomolar affinity towards the MT₂ receptors subtypes have shown the most interesting pharmacological results of this series with the appearance of a weak MT₂-selectivity.

Keywords: agomelatine; agonist; conformationally restriction; melatonin

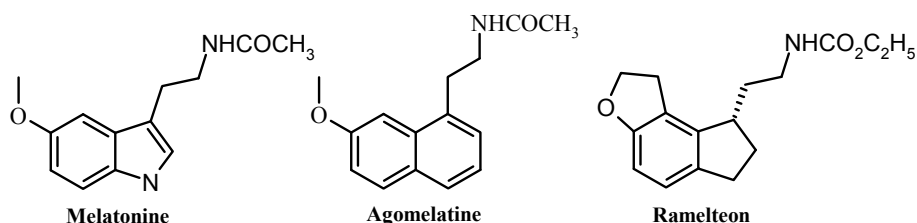
1. Introduction

Melatonin or *N*-acetyl-5-methoxytryptamine (Figure 1), is a neurohormone that is synthesized and secreted from the pineal gland during the period of darkness following a circadian rhythm [1]. Since the demonstration of its role in many physiological processes such as the regulation of immune functions [2], retinal physiology [3], circadian and seasonal rhythms [4] research efforts to identify new melatonergic

ligands grow up continuously. However, much more efforts must be done to clarify the various functions exerted by melatonin and its mechanisms of action.

This neurohormone exerts its multiple pharmacological actions through two G-protein-coupled receptors MT_1 and MT_2 which were cloned in the mid-1990s [2–5]. A third melatonin binding site, MT_3 , having lower affinity than MT_1 and MT_2 has been characterized as the hamster homologue of quinone reductase 2 (QR2 EC 1.6.99.2) [6]. Exploring the exact physiological role of each of these binding sites requires selective MT_1 , MT_2 and MT_3 ligands. Melatonergic MT_1 receptors are expressed in several areas of the brain in particular in the suprachiasmatic nuclei (SCN) and the pars tuberalis. The MT_2 receptors are localized in the SCN and retina. The low affinity binding site, MT_3 is closely related to the detoxifying enzyme quinone reductase 2 and its exact biological relevance in melatonin's effects is still uncertain [7]. Nonetheless, MT_3 has shown to be involved in acute inflammatory responses in the rat [8] and in the regulation of intraocular pressure in the rabbit [9].

Figure 1. Chemical structures of melatonin, agomelatine and ramelteon.



In fact and in order to clarify MT_1 , MT_2 and MT_3 biological functions, over the last years several ligands were synthesized [10–19]. Only ramelteon (Rozerem[®]) [20] and agomelatine (Valdoxan[®]) [21], two MT_1 and MT_2 receptor agonists, are respectively marketed for the treatment of insomnia and major depressive disorders. Agomelatine is the first antidepressant which does not block the reuptake of monoamines. Therefore it might represent the prototype of a new class of antidepressant drugs. The development of new derivatives is of importance in order to increase efficacy and reduce side effects. Agomelatine, which is also a 5-HT_{2C} selective antagonist was revealed to be also potent in resynchronization of circadian rhythms [22,23].

The importance of melatonin as a promising therapeutic target has led to the investigation of the pharmacophoric requirements for its receptors' binding and activation in order to develop selective ligands. Early SAR studies showed that both methoxy group and the *N*-acetyl amino side chain of melatonin are crucial for high receptor affinity and that the relative spatial distance between these groups is also an important factor [24]. In addition, 3D-QSAR analysis of melatonergic ligands revealed that MT_1 and MT_2 binding affinity could be enhanced by replacement and/or conformationally restriction of the amide substituent [25]. This approach could help probing the existing pharmacophore for potent MT_1 and MT_2 selective ligands, and open new therapeutic perspectives by targeting a specific receptor.

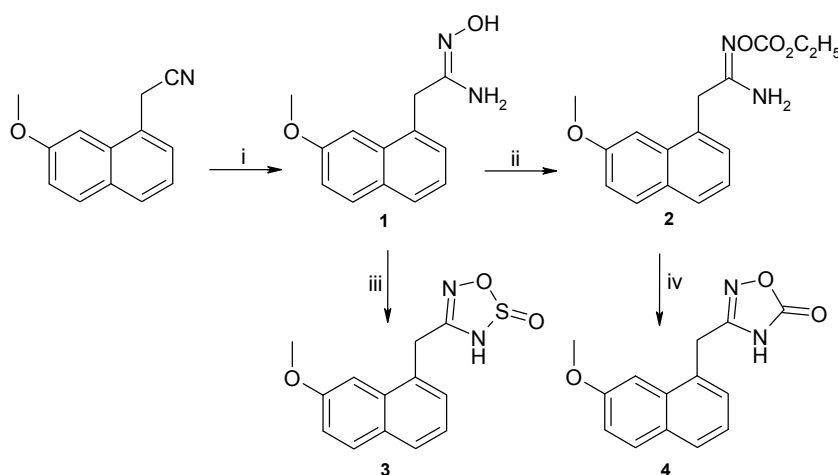
In our continuing efforts to develop new melatonin ligands using the agomelatine as a lead, we previously reported the design and synthesis of melatonergic MT_1 [26,27], MT_2 [28–31] and MT_3 -selective ligands [32–34]. We also were the pioneers in preparing non-selective MT_1 and MT_2 ligands with 5-HT_{2C} activity [17]. In this paper we describe the synthesis and pharmacological evaluation of a novel small series of naphthalenic constrained compounds issued from the incorporation of the amide side chain into heterocycles.

2. Results and Discussion

2.1. Chemistry

The target compounds **3** and **4** were prepared from 2-(7-methoxynaphth-1-yl)acetonitrile [35]. Compound **3** was obtained via a two steps reaction sequence: (1) treatment with hydroxylamine hydrochloride and sodium methoxide in DMSO to afford the amidoxime **1** in accordance with a literature procedure [36]; (2) cyclization with thionyl chloride according to Scheme 1. Compound **2**, which was obtained from amidoxime **1** by reaction with ethyl chloroformate, was cyclized by treatment with potassium carbonate to provide oxadiazolone **4** [37].

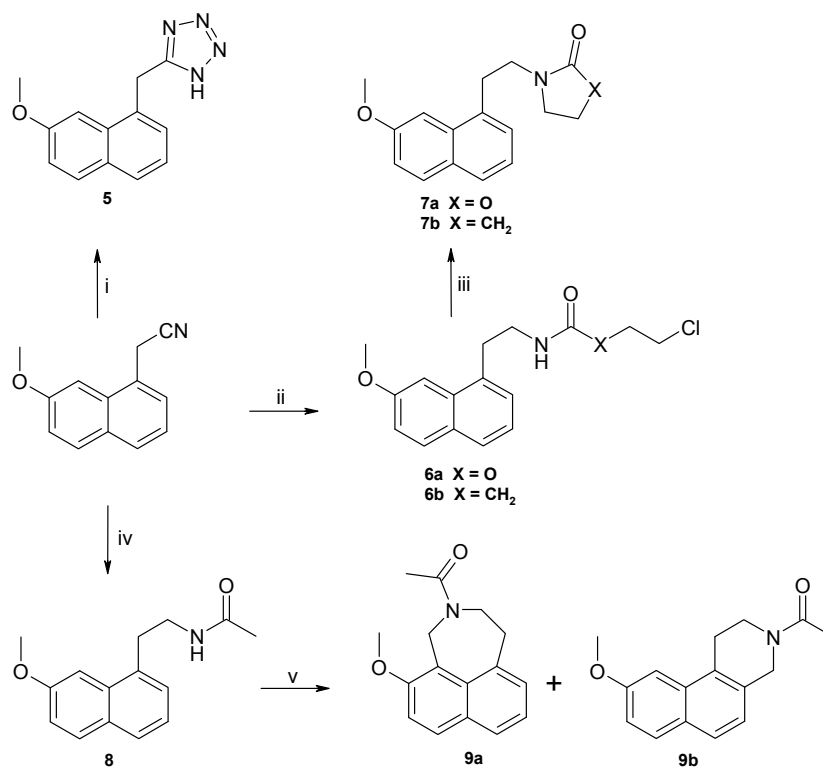
Scheme 1. Synthesis of compounds **3** and **4**.



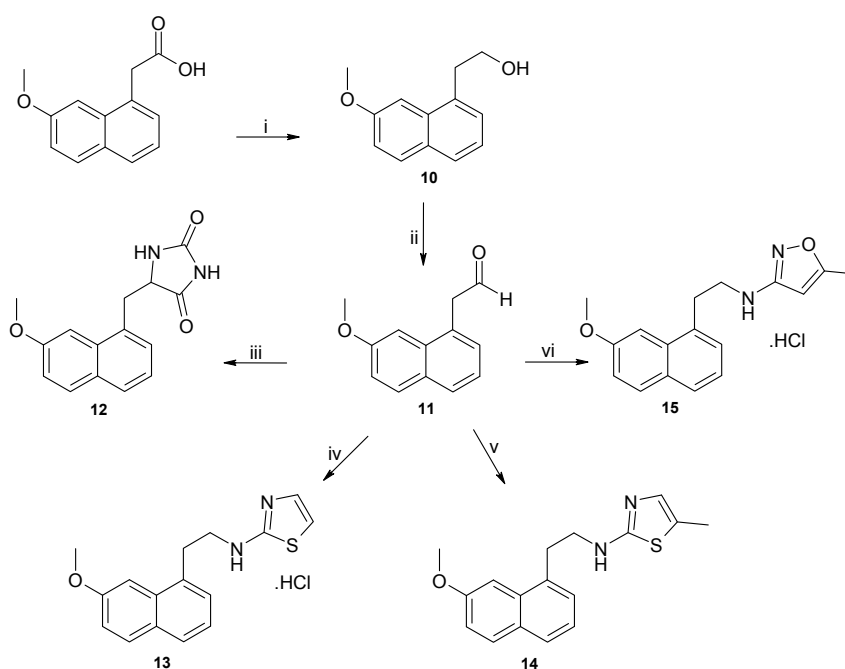
Reagents and conditions: (i) NH₂OH.HCl, NaOMe, MeOH/DMSO, 80 °C; (ii) ClCO₂Et, NEt₃, THF, reflux; (iii) SOCl₂, pyridine, CH₂Cl₂, 0 °C; (iv) K₂CO₃, DMF, 60 °C.

Scheme 2 illustrates the synthetic route to naphthalenic compounds **5–9**. Treatment of 2-(7-methoxynaphth-1-yl)acetonitrile with sodium azide in the presence of tributyltin chloride in DMF gave the desired tetrazole **5** [38]. *N*-acetylated derivatives **6a,b** were derived from 2-(7-methoxynaphth-1-yl)acetonitrile by reduction of the nitrile group and reaction with the appropriate acyl chloride. Carbamate **6a** was then cyclized by heating in an alkaline solution (NaOH) to afford the desired oxazolidinone **7a** [39]. Compounds **6b** and **7b** were synthesized as previously described by us [40]. The agomelatine **8** was converted to cyclic **9a** and **9b** by heating in a large excess of DMSO [41].

Finally, synthesis of compounds **12–15** was carried out as illustrated in Scheme 3. 2-(7-methoxynaphth-1-yl)acetaldehyde (**11**) was obtained from (7-methoxynaphth-1-yl)acetic acid [21] via esterification followed by reduction and Dess Martin oxidation [42]. Compound **11** was then converted to the desired imidazolidine-dione **12** by treatment with potassium cyanide and ammonium carbonate. Compounds **13–15** were prepared under the same conditions by condensation of **11** with the appropriate heterocyclic amine, followed by reduction of the imine generated *in situ* by use of sodium cyanoborohydride in the presence of zinc iodide.

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

Reagents and conditions: (i) Bu_3SnCl , NaN_3 , DMF, $130\text{ }^\circ\text{C}$; (ii) a) H_2 , Raney nickel, EtOH, NH_3 (gas), 50 bars, $60\text{ }^\circ\text{C}$; b) $\text{ClCO}_2(\text{CH}_2)_2\text{Cl}$ or $\text{ClCO}(\text{CH}_2)_3\text{Cl}$, NEt_3 , THF, rt; (iii) 20% NaOH, THF, reflux; (iv) H_2 , Raney nickel, $(\text{CH}_3\text{CO})_2\text{O}$, 50 bars, $60\text{ }^\circ\text{C}$, 4 h; (v) DMSO, reflux.

Scheme 3. Synthesis of compounds **12–15**.

Reagents and conditions: (i) SOCl_2 , MeOH, $0\text{ }^\circ\text{C}$ then LiAlH_4 , Et_2O , rt; (ii) Dess-Martin Periodinane, CH_2Cl_2 , rt; (iii) KCN, $(\text{NH}_4)_2\text{CO}_3$, EtOH/ H_2O , reflux; (iv) 2-amino-1,3-thiazole, $\text{NaBH}_3\text{CN}/\text{ZnI}_2$, MeOH, rt then $\text{HCl}(\text{gas})/\text{Et}_2\text{O}$; (v) 2-amino-5-methyl-1,3-thiazole, $\text{NaBH}_3\text{CN}/\text{ZnI}_2$, MeOH, rt; (vi) 3-amino-5-methyl-1,2-isoxazole, $\text{NaBH}_3\text{CN}/\text{ZnI}_2$, MeOH, rt then $\text{HCl}(\text{gas})/\text{Et}_2\text{O}$.

2.2. Pharmacology

2.2.1. Reagents and Chemicals

2-[¹²⁵I]Iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA, USA). Other drugs and chemicals were purchased from Sigma–Aldrich (Saint Quentin, France).

2.2.2. Assays for MT₁ and MT₂ Receptor Subtypes

2-[¹²⁵I]Iodomelatonin binding assay conditions were essentially as previously described [43]. 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 μM 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, USA) to yield IC₅₀ (inhibitory concentration 50). Results are expressed as pK_i (pK_i = −Log₁₀ (K_i)) with K_i = IC₅₀/1 + ([L]/K_D), where [L] is the concentration of radioligand used in the assay and K_D, the dissociation constant of the radioligand characterizing the membrane preparation.

2.3. Discussion

Conformationally restricted ligands for melatonin receptors were synthesized and their binding affinities at human MT₁ and MT₂ receptors were determined. The data summarized in Table 1 emphasized the lack of good affinities for the MT₁ and MT₂ receptors of the prepared compounds. In fact, in comparison with agomelatine the lock of the ethylamido side chain conformation by its incorporation in rigid structures led to the decrease of the binding affinities at both receptors. This decrease of the melatoninergetic binding affinities is more noticeable for the MT₁ than the MT₂ leading to the appearance of a weak MT₂-selectivity. Only compounds **7a** and **7b** showed an interesting pharmacological profile by conserving a good binding affinity (10^{−8} M) at MT₂ receptors subtypes.

Table 1. MT₁ and MT₂ binding affinities of naphthalenic cyclized compounds.

Compound	K _i (nM) MT ₁	K _i (nM) MT ₂	S (MT ₁ /MT ₂)
Melatonin	0.2 ± 0.02	0.3 ± 0.03	0.17
Agomelatine	0.1 ± 0.01	0.12 ± 0.02	0.83
3	>1,000	1300	>0.77
4	80.0 ± 16.0	25.2 ± 10.7	3
5	380 ± 114	190 ± 84	2
7a	113 ± 18	6.0 ± 0.2	19
7b	68.5 ± 18.2	2.1 ± 0.01	33

Table 1. Cont.

Compound	Ki (nM) MT ₁	Ki (nM) MT ₂	S (MT ₁ /MT ₂)
9a	2500 ± 57	469 ± 44	5.4
9b	3000 ± 27	800 ± 59	3.75
12	2170 ± 63	141 ± 31	15.4
13	33.9 ± 8.1	12.5 ± 0.4	3
14	389 ± 121	354 ± 32	1
15	48.4 ± 11.2	20.3 ± 3.9	2

3. Experimental

3.1. General

All common reagents and solvents were obtained from commercial sources (Sigma-Aldrich Alfa Aesar or Acros Organics) and used without further purification. Compounds were purified on a glass column using Merck Silica Gel 60 (230–400 mesh). Their purity and mass spectra were determined on a Surveyor MSQ Thermoelectron spectrometer (+cAPCI corona sid = 30.00, det = 1400.00 Full ms [100.00–1000.00]). Melting points were determined with a büchi 510 capillary apparatus and are uncorrected. ¹H-NMR spectra were recorded on a Bruker AC300P spectrometer using (Me)₄Si as internal standard and with DMSO-*d*₆ or CDCl₃ as solvents; The chemical shifts are reported in ppm (parts per million) δ and constant (*J*) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplet), q (quartet) and m (multiplet). Infrared spectra were obtained on a Perkin-Elmer FT-IR S1000 in KBr pellets. Elemental analyses for final compounds were performed by CNRS Laboratory (Vernaison, France).

2-(7-Methoxynaphth-1-yl)acetamidoxime (1). A mixture of 2-(7-methoxynaphth-1-yl)acetonitrile (5 g, 25.3 mmol) and hydroxylamine hydrochloride (3.52 g, 50.6 mmol) in DMSO (20 mL) was treated with 25% NaOMe solution in methanol (11.5 mL, 50.6 mmol) and heated at 80 °C for 5 h. After cooling, the solvent was evaporated under reduced pressure. The crude was taken with water, the white solid obtained was washed with water and recrystallized from toluene to afford 3.8 g (65% yield) of **1** as a white solid, mp: 151–153 °C. ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 3.71 (s, 2H), 3.88 (s, 3H), 5.38 (s, 2H), 7.17 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 8.96 (s, 1H). IR (cm^{−1}) 1660 (C=N), 3360, 3460 (NH), 3100–3400 (OH). MS (EI): *m/z* = 231 [M+H]⁺.

N-[(Ethoxycarbonyl)oxy]-2-(7-methoxynaphth-1-yl)acetamidoxime (2). Ethyl chloroformate (0.84 mL, 8.8 mmol) was added dropwise to a suspension of **1** (2 g, 8.7 mmol) and triethylamine (2.4 mL, 17.4 mmol) in 25 mL of THF. Stirring was maintained for 3 h at ambient temperature. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure. The crude was purified by column chromatography (SiO₂, acetone/toluene/cyclohexane: 2/3/5) to give 2.3 g (88% yield) of **2** as a pink solid, mp: 104–106 °C. ¹H-NMR (300 MHz, DMSO-*d*₆ at 50 °C) δ : 1.22 (t, *J* = 7.1 Hz, 3H), 3.82 (s, 2H),

3.91 (s, 3H), 4.14 (q, $J = 7.1$ Hz, 2H), 6.13 (s, 2H), 7.16 (dd, $J = 9.1, 2.5$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 2.5$ Hz, 1H), 7.81 (d, $J = 9.1$ Hz, 1H). IR (cm^{-1}) 1680 (C=N), 1730 (C=O), 3340, 3460 (NH). MS (EI): $m/z = 303$ $[\text{M}+\text{H}]^+$.

4-[(7-Methoxynaphth-1-yl)methyl]-3H-1,2,3,5-oxathiadiazole 2-oxide (3). Thionyl chloride (0.5 mL, 6.7 mmol) in methylene chloride (2 mL) was added dropwise to a mixture of **1** (1.4 g, 6.1 mmol) in methylene chloride (20 mL) and pyridine (1 mL, 12.2 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was recrystallized from cyclohexane/toluene and ethyl ether/petroleum ether to afford 791 mg (47% yield) of **4** as a white solid, mp: 121–123 °C (decomp.). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 3.88 (s, 3H), 4.36 (d, $J = 16.3$ Hz, 1H), 4.42 (d, $J = 16.3$ Hz, 1H), 7.21 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.29–7.49 (m, 3H), 7.78–7.94 (m, 2H), 11.40 (s, 1H). IR (cm^{-1}) 1620 (C=N), 3300 (NH). MS (EI): $m/z = 277$ $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 56.51%; H, 4.38%; N, 10.14%. Found: C, 56.55%; H, 4.43%; N, 10.15%.

3-[(7-Methoxynaphth-1-yl)methyl]-1,2,4-oxadiazole-5(4H)-one (4). Potassium carbonate (1.1 g, 8 mmol) was added to a solution of **2** (1.2 g, 4 mmol) in DMF (10 mL). After 5 h of stirring at 60 °C, the reaction mixture was poured into water and extracted twice with ethyl acetate. The aqueous phase was acidified with a 3 M HCl solution and extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from toluene to give 712 mg of **3** (yield 70%) as a white solid, mp: 185–187 °C (decomp.). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 3.89 (s, 3H), 4.33 (m, 2H), 7.23 (dd, $J = 8.6, 2.5$ Hz, 1H), 7.34 (t, $J = 7.40$ Hz, 1H), 7.39 (d, $J = 2.50$ Hz, 1H), 7.44 (d, $J = 7.40$ Hz, 1H), 7.83 (d, $J = 7.40$ Hz, 1H), 7.89 (d, $J = 8.6$ Hz, 1H), 11.40 (s, 1H). IR (cm^{-1}) 1725 (C=N), 3440 (NH). MS (EI): $m/z = 257$ $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3$: C, 65.61%; H, 4.72%; N, 10.93%. Found: C, 65.64%; H, 4.76%; N, 10.90%.

5-(7-Methoxynaphth-1-yl methyl)-1H-tetrazole (5). A mixture of 2-(7-methoxynaphth-1-yl)acetonitrile (2 g, 1.01 mmol), sodium azide (2.62 g, 40.4 mmol) and tributyltin chloride (10.9 mL, 40.4 mmol) in dry DMF (20 mL) was heated to reflux and monitored by TLC until the reaction was complete (~7 h). After being cooled to room temperature, 1 M HCl (50 mL) was added to precipitate the crude product. The white solid product was collected, washed with water and ether, and dried with phosphorous pentoxide under vacuum and recrystallized from cyclohexane affording 1.21 g (50% yield) of tetrazole **5** as a beige solid, mp: 177–179 °C (decomposition). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6 + \text{D}_2\text{O}$) δ : 3.88 (s, 3H), 4.74 (s, 2H), 7.22 (dd, $J = 9.1, J = 2.3$ Hz, 1H), 7.31–7.47 (m, 3H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.90 (d, $J = 9.1$ Hz, 1H), 7.81 (d, $J = 9.1$ Hz, 1H). MS (EI): $m/z = 241$ $[\text{M}+\text{H}]^+$.

N-(2-Chloroethyl)oxycarbonyl)-2-(7-methoxynaphth-1-yl)ethylamine (6a). 2-Chloroethyl chloroformate (0.87 mL, 8.41 mmol) and triethylamine (1.2 mL, 8.41 mmol) were added to a solution of 2-(7-methoxynaphth-1-yl)ethylamine hydrochloride (2 g, 8.41 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 36 h. After filtration, the filtrate was concentrated under vacuum and purified by column chromatography (SiO_2) using cyclohexane/ethyl acetate; 8/2 as eluant to give 1.7 g (65% yield) of carbamate **6a** as a white solid, mp: 73–75 °C. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 3.04–3.34 (m, 4H), 3.80 (t, $J = 5.2$ Hz, 2H), 3.94 (s, 3H), 4.24 (t, $J = 5.2$ Hz, 2H), 7.18 (dd, $J = 9.1,$

2.1 Hz, 1H), 7.22–7.42 (m, 2H), 7.53 (d, $J = 2.1$ Hz, 1H), 7.60 (t, $J = 5.4$ Hz, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.84 (d, $J = 9.1$ Hz, 1H). MS (EI): $m/z = [M+H]^+$.

N-[(2-(7-methoxynaphth-1-yl)]-1,3-oxazolidin-2-one (**7a**). A mixture of carbamate **6a** (1.2 g, 3.9 mmol) and 20% NaOH (3 mL, 15 mmol) in THF (20 mL) were refluxed for 39 h. The residue was evaporated to dryness, water was added, and the mixture was stirred and extracted with ethyl acetate. The combined organic phases were washed with water (50 mL), dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, cyclohexane/ethyl acetate, 6/4) to afford 868 mg (82% yield) of **7a** as a white solid, mp 78–80 °C. ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 3.24 (m, 2H), 3.47 (m, 2H), 3.56 (t, $J = 8.28$ Hz, 2H), 3.92 (s, 3H), 4.22 (t, $J = 8.37$ Hz, 2H), 7.17 (dd, $J = 8.97, 2.40$ Hz, 1H), 7.30 (m, 1H), 7.36 (d, $J = 6.48$ Hz, 1H), 7.46 (d, $J = 2.41$ Hz, 1H); 7.72 (d, $J = 8.00$ Hz, 1H), 7.83 (d, $J = 8.97$ Hz, 1H). MS (EI): $m/z = 272 [M+H]^+$.

3.2. General Protocol for the Preparation of Compounds **9a** and **9b**

A solution of agomelatine (4 g, 16.4 mmol) in DMSO (100 mL) was refluxed for 15 h. The reaction mixture was poured into ice and extracted twice with ether, organic phase was washed with water and brine and then concentrated under reduced pressure. The crude was purified by column chromatography (SiO₂) using ether as eluant.

1-(10-Methoxy-1,2,3,4-tetrahydro-naphtho[1,8-*cd*]azepin-2-yl)ethanone (**9a**). Recrystallized from isopropyl ether to furnish 1.59 g (38% yield) as a white solid, mp: 107–108 °C. ¹H-NMR (300 MHz, 75 °C, DMSO-*d*₆) δ : 1.88 (s, 3H), 3.44 (t, $J = 6.3$ Hz, 2H), 3.81 and 3.87 (t, t, 2H), 3.93 and 3.97 (s, s, 3H), 5.11 and 5.20 (s, s, 2H), 7.21–7.30 (m, 2H), 7.34 and 7.41 (d, d, $J = 9.2$ Hz, 1H), 7.69–7.73 (m, 1H), 7.77 and 7.83 (d, d, $J = 9.2$ Hz, 1H). IR (cm^{−1}) 1625 (C=O). MS (EI) $m/z = 256 [M+H]^+$. Anal. Calcd for C₁₆H₁₇NO₂: C, 75.27%; H, 6.71%; N, 5.49%. Found: C, 75.25%; H, 6.72%; N, 5.48%.

1-(9-Methoxy-1,2,3,4-tetrahydro-benzo[*ff*]isoquinolein-3-yl)ethanone (**9b**). Recrystallized from isopropyl ether, **9b** was obtained with 2% yield as a white solid, mp: 141–143 °C. ¹H-NMR (300 MHz, 60 °C, DMSO-*d*₆) δ : 2.14 (s, 3H), 3.10 (m, 2H), 3.84 (t, $J = 6.0$ Hz, 2H), 3.92 (s, 3H), 4.75 (s, 2H), 7.16 (m, $J = 8.3$ Hz, 1H), 7.17 (dd, $J = 8.8$ Hz, 1H), 7.27 (m, 1H), 7.69 (d, $J = 8.3$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H). IR (cm^{−1}) 1620 (CO). MS (EI): $m/z = 256 [M+H]^+$. Anal. Calcd for C₁₆H₁₇NO₂: C, 75.27%; H, 6.71%; N, 5.49%. Found: C, 75.29%; H, 6.72%; N, 5.45%.

2-(7-Methoxynaphth-1-yl)ethanol (**10**). Thionyl chloride (27 mL, 370 mmol) was added dropwise to a solution of (7-methoxynaphth-1-yl) acetic acid (20 g, 92.5 mmol) in methanol (350 mL) at 0 °C. After stirring for 5 h, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 10% aqueous potassium carbonate solution and water. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure affording the intermediate ester. The residue was dissolved in ether (100 mL) and added dropwise to a suspension of lithium aluminium hydride (12.4 g, 327 mmol) in ether (200 mL) at 0 °C. The stirring was maintained at room temperature for 4 h. Water (50 mL) and 20% NaOH aqueous solution (12 mL) were added and the mixture was stirred and filtered. After evaporation under reduced pressure, the residue was recrystallized

from cyclohexane to furnish 13.7 g (73% yield) of alcohol **10** as a white solid, mp: 79–81 °C. $^1\text{H-NMR}$ (300 MHz, $\text{CDCl}_3+\text{D}_2\text{O}$) δ : 3.30 (t, $J = 6.69$ Hz, 2H), 3.94 (s, 3H), 3.99 (t, $J = 6.75$, 2H), 7.17 (dd, $J = 9.2$, 2.3 Hz, 1H), 7.24–7.38 (m, 3H), 7.68 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 9.2$ Hz, 1H). IR (cm^{-1}) 3000–3330 (OH). MS (EI): $m/z = 203$ $[\text{M}+\text{H}]^+$.

2-(7-Methoxynaphth-1-yl)acetaldehyde (11). To a stirred solution of alcohol **10** (6 g, 29.6 mmol) in anhydrous CH_2Cl_2 (300 mL) under argon atmosphere was added Dess-Martin periodinane (25 g, 59.2 mmol) and stirred at room temperature for 5 h. The reaction mixture was quenched by adding saturated $\text{Na}_2\text{S}_2\text{O}_4$ (60 mL) and saturated NaHCO_3 (8 mL). The heterogeneous mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated NaHCO_3 and water. The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , CH_2Cl_2) to give 5.2 g (87% yield) of **11** as a yellow oil. $^1\text{H-NMR}$ (300 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$) δ : 3.91 (s, 3H), 4.03 (d, $J = 2.3$ Hz, 2H), 7.08–7.87 (m, 6H), 9.73 (t, $J = 2.3$ Hz, 1H). IR (cm^{-1}) 1700 (C=O). MS (EI): $m/z = 201$ $[\text{M}+\text{H}]^+$.

5-[(7-Methoxynaphth-1-yl)methyl]-imidazolidin-2,4-diones (12). Ammonium carbonate (1.67 g, 17.4 mmol) and potassium cyanide (341 mg, 5.24 mmol) were added to a stirred solution of aldehyde **14** (700 mg, 3.49 mmol) in 20 mL (16 mL/4 mL) of ethanol/water, the mixture was refluxed overnight. After cooling, the reaction mixture was poured into cold water. The resulting precipitate was filtrated, washed with water and recrystallized from isopropyl ether affording 400 mg (42% yield) of **15** as a white solid, mp: 236–238 °C (decomp.). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ : 3.26 (m, 2H), 3.92 (s, 3H), 4.44 (m, 1H), 7.06–7.97 (m, 7H), 10.56 (s, 1H). IR (cm^{-1}) 1680, 1750 (C=O), 3270 (NH). MS (EI): $m/z = 271$ $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: C, 66.65%; H, 5.22%; N, 10.36%. Found: C, 65.68%; H, 5.25%, N, 10.38%.

3.3. General Protocol for the Preparation of Compounds 13–15

To a mixture of compound **11** (0.5 g, 2.49 mmol) and the appropriate heterocyclic amine (10 mmol) in methanol (20 mL) and 0.2 mL of DMF, were added a solution of sodium cyanoborohydride (172 mg, 2.73 mmol) and zinc iodide (437 mg, 1.36 mmol) in methanol (5 mL). The reaction was stirred at room temperature for 5 h and concentrated under reduced pressure to dryness, hydrolyzed and extracted with ethyl acetate. The organic layer was dried (MgSO_4), filtered, and concentrated under reduced pressure.

2-[2-(7-Methoxynaphth-1-yl)]-ethylamino]-1,3-thiazole hydrochloride (13). The crude was purified by column chromatography (SiO_2) using cyclohexane/ethyl acetate; 7/3 as eluant, treatment with gaseous HCl in ether provided 280 mg (35% yield) of hydrochloride salt **13** as a white solid, mp: 156–158 °C. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ : 3.38 (t, $J = 7.1$ Hz, 2H), 3.81 (m, 2H), 3.93 (s, 3H), 6.92 (d, $J = 4.3$ Hz, 1H), 7.19 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.25–7.49 (m, 4H), 7.75 (m, 2H), 10.22 (s, 1H). IR (cm^{-1}) 2500–3160 (N^+H). MS (EI): $m/z = 285$ $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{OS}$: C, 59.90%; H, 5.34%; N, 8.73%. Found: C, 59.94%; H, 5.32%, N, 8.75%.

2-[2-(7-Methoxynaphth-1-yl)ethylamino]-5-methyl-1,3-thiazole (14). Recrystallized from cyclohexane to furnish 364 mg (46% yield) of **14** as a white solid, mp: 150–152 °C (decomp.). $^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6 + \text{D}_2\text{O}$) δ : 2.22 (s, 3H), 3.28 (t, $J = 7.5$ Hz, 2H), 3.47 (m, 2H), 3.95 (s, 3H), 6.71 (s, 1H),

7.11–7.89 (m, 6H). IR (cm^{−1}) 3170 (NH). MS (EI): m/z = 299 [M+H]⁺. Anal. Calcd for C₁₇H₁₈N₂OS: C, 68.43%; H, 6.08%; N, 9.39%. Found: C, 68.39%; H, 6.13%, N, 9.36%.

3-[2-(7-Methoxynaphth-1-yl)ethylamino]-5-methyl-1,2-isoxazole hydrochloride (15). Recrystallized from cyclohexane to afford 333 mg (42% yield) of **15** as a white solid, mp 144–146 °C (decomp.). ¹H-NMR (300 MHz, DMSO-*d*₆ + D₂O) δ : 2.24 (s, 3H), 3.18–3.39 (m, 4H), 3.93 (s, 3H), 5.67 (s, 1H), 7.15 (dd, J = 9.1, 2.1 Hz, 1H), 7.21–7.39 (m, 2H), 7.65 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 9.1 Hz, 1H). IR (cm^{−1}) 2200–3000 (N⁺H). MS (EI): m/z = 283 [M+H]⁺. Anal. Calcd for C₁₇H₁₉Cl N₂O₂: C, 64.05%; H, 6.01%; N, 8.79%. Found: C, 64.07%; H, 6.04%, N, 8.76%.

4. Conclusions

In the search for pharmacological tools for the elucidation of MT₁ and MT₂ biological functions, we synthesized and pharmacologically evaluated a new series of constrained naphthalenic compounds. Indeed, replacement of the *N*-acetyl side chain of agomelatine by oxathiadiazole-2-oxide, oxadiazole-5(4*H*)-one, oxazolidinone, 2-oxopyrrolidine, imidazolidin-2,4-dione, thiazole, 5-methyl-1,3-thiazole, or 5-methyl-1,2-isoxazole hydrochloride resulted in a decrease of the melatoninergic binding affinities particularly towards the MT₁ receptors leading to the appearance of a weak MT₂-selectivity. Compound **7b** conserves good affinity for both melatonin receptors subtypes and exhibited a selectivity of about 33-fold for the MT₂ receptor subtype.

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Sample Availability: Samples of the compounds **5**, **13**, **14** and **15** are available from the authors.