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Tetrahydronaphthalenic derivatives as new agonist and antagonist ligands for melatonin receptors

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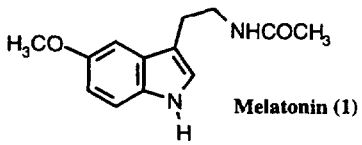
Abstract

Tetrahydronaphthalenic ligands were synthesized and evaluated as melatonin receptor ligands. Biological studies show that the aromaticity of the ring bearing the side chain is not essential for affinity and activity and that replacement of the methoxy group with the bioisostere ethyl which does not offer the possibility of H-bonding, leads to antagonist or forskoline potentiating properties.

1. Introduction



Melatonin (1)

The neurohormone melatonin (*N*-acetyl-5-methoxytryptamin) is principally synthesized by the pineal gland and secreted into the general circulation during the night [1]. It plays a central role in the regulation of circadian and seasonal rhythms in vertebrates.

In humans, melatonin's exact functions remain obscure. Previous works have reported its potential usefulness in biological rhythm disorders such as disturbed sleep–wake cycles, jet lag and seasonal affective disorders [1–5].

In addition to its chronobiologic effects, melatonin could be implicated in various pathologies. It presents a stimulant action on the immunitary response [6–8], which could be used against immunodeficiencies like those seen in viral infections, in stress or during treatment with immunodepressors.

Melatonin also inhibits the development of a number of human cancer cells, particularly in hormonodependant cancers (breast cancer and prostate cancer) and in melanoma [1]. The existence of a synergic relation between melatonin and interleukin 2 could permit regression of non hormonodependant cancers. Moreover, the pineal hormone could increase the effects of a number of anticancerous treatments like surgery, chimiotherapy, and immunotherapy [9,10].

Melatonin has also been described as a powerful antioxydant specifically acting on the most toxic free radical: **OH•** [11]. Thus, it could minimize risks against diseases due to oxydative stress like cardiovascular pathologies, Alzheimer's or Parkinson's disease, or cataract. Furthermore, decrease of melatonin with age could be implicated in aging [11].

However, some problems limit the therapeutic use of melatonin. The first one is its very short biological half-life (20–30 min), due to a rapid catabolism. The second one is the lack of selectivity of melatonin at its target sites. These inconvenients justify the design, synthesis, and pharmacological studies of new agonist and antagonist melatoninergic ligands.

Melatonin's effects seem to be mediated through membrane receptors. A high affinity melatonin receptor

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has been cloned from Xenopus laevis dermal melanophores [12]. It belongs to the G-protein-coupled receptors superfamily with seven α-helix transmembranes and presents a high affinity for melatonin. Recently, three subtypes of G-protein-coupled melatonin receptors have been cloned from mammals and called Mel_{1a}, Mel_{1b} and Mel_{1c} [13]. In the same time, another type of melatonin binding site, 'ML_2' [14], with lower affinity for melatonin, has also been described.

Two chemical groups have been reported to be important for the affinity and the activity of melatonin. It seems clear that the biological activity of melatonin is correlated with the amidic group [15]. On the other hand, the methoxy group is an important factor for the activity and the affinity of melatonin receptor ligands, probably functioning as a hydrogen bond acceptor with serine (Ser 115) residue of the Mel_1 receptor [16].

We have previously shown that replacement of the indole ring with naphthalene, benzothiophen, or benzofuran, according to the aromatic rings bioisostery, does not modify the pharmacological properties [17,18].

Pursuing our research in this area, we have envisaged to complete the structure–activity relationships by replacing the indole heterocycle with a tetrahydronaphthalene. Although these two nucleus are not isosteres, 2-acetamido-8-methoxy-1,2,3,4-tetrahydronaphthalene has been described as a good ligand for melatonin receptor [19]. We therefore wanted to verify if the aromatic nature of the ring bearing the side chain is important.

Moreover, we were interested by the H-bond probably involved between the methoxy group and the binding site. We replaced the oxygen of the methoxy substituent with a methylene, an isosteric group which does not offer the possibility of H-bonding, to study if this H-bond is indispensable for agonist activity and if its suppression could give antagonist compounds.

Finally, variations of the acyl group on the side chain of melatonin have shown that acetyl is not the optimum group and that replacement with propanoyl, butanoyl, or cyclopropylcarbonyl induces an increase in binding affinity [17]. On the other hand, replacement by a cyclobutylcarbonyl leads to antagonist compound [18]: so we have also studied the modulation of this acyl group.

2. Chemistry

Tetrahydronaphthalenic ligands were synthesized from appropriate 1-oxo-7-substituted-1,2,3,4-tetrahydronaphthalenes.

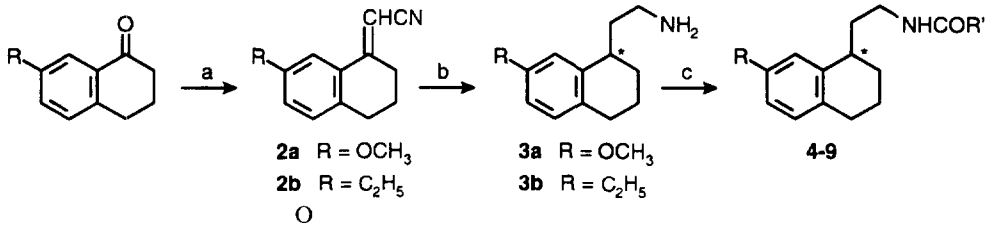
1-Oxo-7-methoxy-1,2,3,4-tetrahydronaphthalene is commercialy available. We have synthesized the 7-ethyl derivative according to the procedure described by Bachman [20]. These two ketones, treated with sodium hydride and diethyl cyanomethylenphosphonate [21], give the corresponding unsaturated nitriles (**2a** and **2b**). One advantage of this synthesis, versus the Reformatsky method which uses zinc and halogenated derivative [22], is that the position of the double bond is certain. Here, the NMR studies showed that the double bond is exocyclic. Moreover, for compound **2a**, proton correlation (COSY) data showed the formation of only the E isomer, although in the case of **2b**, we observed the two isomers E (85%) and Z (15%); these two isomers were not separated. Whereas compound **2a** could be purified by recrystallization, the 1-cyanomethylen-7-ethyl-1,2,3,4-tetrahydronaphthalene (**2b**) is an oil that was hydrolysed in an acidic mixture to the solid primary amide (**10**) which was characterized by elemental analysis. In this case, the double bond migration can be explained by the acid treatment of the reaction [23].

The nitriles are then reduced with hydrogen and Raney Nickel to give the racemic 2-aminoethyl derivatives (**3a**, **3b**). The racemic amidic compounds (**4–9**) are finally obtained by action of the appropriate acylchloride in the presence of potassium carbonate or by use of the acylanhydrid in pyridin [18].

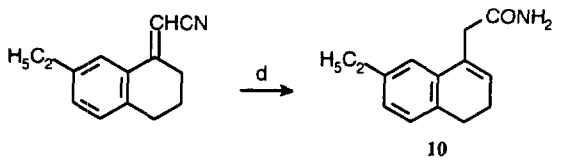
3. Results and discussion

The binding studies were realized with ovine pars tuberalis membranes. The affinity of compounds was determined by competition studies with 2[^{125}I]-iodomelatonin, a specific radioligand for melatoninergic binding sites [24] and the results, shown in Table 1, are expressed in terms of molar IC_{50} values.

Studies concerning the biological activity of compounds are in relation with the inhibitor effect of melatonin on



Scheme 1. (a) NaH, $(C_2H_5O)_2$ P–CH_2CN. (b) H_2/Ni–Ra. (c) K_2CO_3, R'COCl or pyridin, $(R'CO)_2O$



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Scheme 2. (d) HCl/CH_3COOH

the cyclic AMP production induced by forskolin [25]. The compound is agonist if it is able to decrease or to suppress the forskolin induced cAMP production. It is antagonist if it has no activity alone, but is able to suppress melatonin activity. Some ligands induce an increase of cAMP, they are defined as forskolin potentialisators. This last denomination is rather indefinite because we do not know if the ligand acts as an inverse agonist or if it binds with another type of melatonin receptor, coupled with a Gs-protein.

We report here the results concerning the affinity and the activity of the racemate compounds in relation to the melatoninergic receptors.

The racemate of the tetrahydronaphthalenic analogue (compound **4**) of melatonin presents an affinity and an agonist activity similar to melatonin. This result shows that the aromaticity of the ring bearing the side chain is not an essential feature. The indolic nucleus of melatonin just seems to play a tensor role and can be replaced with nonaromatic nucleus if the two pharmacophores are placed, in space, on appropriate positions.

Replacement of the oxygen atom of the methoxy group with the bioisosteric methylene leads to 2-(7-ethyl-1,2,3,4-tetrahydronapht-1-yl)ethylacetamide (**5**), which presents a lower affinity ($2.6\ 10^{-8}$ **M**) than the methoxy derivative. Other ethyl ligands present the mean affinity of 10^{-8} **M**. This decrease of affinity for the 7-ethyl compounds, compared to their methoxy analogues, confirms that the methoxy group plays a role in the recognition of the receptor by the ligand.

None of the 7-ethyl ligands present agonist activity: compounds **5–7** are forskolin potentialisators and compounds **8** and **9** antagonists. While there are a number examples of agonists which do not have methoxy group [19,26,27], in the present case we can assume that the H-bond between the methoxy group and the receptor is essential for the agonist activity. Replacement of the methoxy with an ethyl group may lead to ligands with antagonist or forskoline potentiating properties, according to the amide substitution.

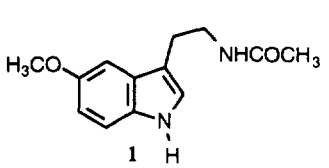
4. Experimental

Melting points were determined on a Buchi 510 capillary and are uncorrected. IR spectra were obtained on a Perkin–Elmer 297 spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were recorded on a WP 80-54 or a AC 300 Brucker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to $(CH_3)_4Si$. Coupling constant are reported in hertz. Elemental analyses for new compounds were performed by CNRS Laboratories (Vernaison, France). The results were within $\pm 0.4\%$ of the theoretical values.

*4.1 General procedure for the synthesis of nitrile derivatives (**2a** and **2b**)*

The synthesis of 1-cyanomethylen-7-methoxy-1,2,3,4-tetrahydronaphthalene (**2a**) is described as example. To a suspension of 2 g (0.05 mol) of NaH (60% in mineral oil) in 30 ml anhydrous tetrahydrofuran, under nitrogen

Table 1



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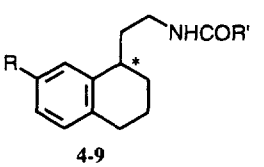

4-9

Compound	R	R'	IC_{50}(M)	Activity
1			$7.6\ 10^{-11}$	Agonist
4	OCH_3	CH_3	$2.6\ 10^{-10}$	Agonist
5	C_2H_5	CH_3	$2.6\ 10^{-8}$	Forskolin potentialisator
6	C_2H_5	C_3H_7	$3.6\ 10^{-8}$	Forskolin potentialisator
7	C_2H_5		$7.8\ 10^{-8}$	Forskolin potentialisator
8	C_2H_5		$3.1\ 10^{-6}$	Antagonist
9	C_2H_5	CF_3	$8.5\ 10^{-8}$	Antagonist

athmosphere, was added dropwise 8.9 g (0.05 mol) of diethylcyanomethylenphosphonate. The mixture was stirred for 1 h (until H_2 evolution was complete). Then, a solution of 5 g (0.028 mol) of 1-oxo-7-methoxy-1,2,3,4-tetrahydronaphthalene in 10 ml of anhydrous tetrahydrofuran was added dropwise. After stirring 24 h at room temperature, the mixture was poured into cold water and extracted with ethyl acetate. The combined extracts were washed with water, dried (magnesium sulfate) and evaporated under vacuum. The residual product was purified either by recrystallization (**2a**) or column chromatography (**2b**).

*4.1.1 1-Cyanomethylen-7-methoxy-1,2,3,4-tetrahydronaphthalene (**2a**)*

Yield 30% from cyclohexane; mp 58–59°C; IR 2190, 1550, 1040 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.70 (m, 2H), 2.65 (m, 4H), 3.78 (s, 3H), 6.31 (s, 1H), 6.97 (dd, 1H, 8.46 and 2.37 Hz), 7.16 (d, 1H, 8.46 Hz), 7.32 (d, 1H, 2.37 Hz). Anal. $C_{13}H_{13}NO$ (C, H, N).

*4.1.2 1-Cyanomethylen-7-ethyl-1,2,3,4-tetrahydronaphthalene (**2b**)*

Yield 60% from column chromatography (ethyl acetate:dichloromethane, 1:4); colourless oil; IR 2200, 1585 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) E isomer δ 1.22 (t, 3H, 7.70 Hz), 1.94 (m, 2H), 2.66 (q, 2H, 7.70 Hz), 2.87 (m, 4H), 5.73 (s, 1H), 7.08 (d, 1H, 7.76 Hz), 7.16 (m, 1H), 7.36 (m, 1H). Z isomer δ 1.22 (t, 3H, 7.70 Hz), 1.94 (m, 2H), 2.66 (q, 2H, 7.70 Hz), 2.87 (m, 4H), 5.23 (s, 1H), 7.08 (d, 1H, 7.76 Hz), 7.16 (m, 1H), 8.14 (m, 1H).

*4.2 (7-Ethyl-3,4-dihydronaphth-1-yl)acetamide (**10**)*

A solution of 0.5 g (0.002 mol) of **2b** in acetic acid (5 ml) and concentrated HCl (14 ml) was heated under reflux for 24 h. The reaction mixture was cooled and then extracted with ethyl ether. The combined extracts were washed with water, dried (magnesium sulfate) and evaporated under vacuum. The residual solid was recrystallized. Yield 20% from cyclohexane; mp 123–125°C; IR 3370, 3180, 1650, 1570 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.21 (t, 3H, 7.57 Hz), 2.33 (m, 2H), 2.61 (q, 2H, 7.57 Hz), 2.78 (t, 2H, 8.07 Hz), 3.41 (s, 2H), 5.58 (m, 2H), 6.08 (t, 1H, 4.34 Hz), 7.07 (m, 3H). Anal. $C_{14}H_{17}NO$ (C, H, N).

*4.3 General procedure for the synthesis of amine derivatives (**3a** and **3b**)*

The synthesis of (*R,S*) 2-(7-methoxy-1,2,3,4-tetrahydronaphth-1-yl)ethylamine hydrochloride (**3a**) is described as example. An NH_3-saturated solution of 3 g (0.015 mol) of **2a** in 50 ml ethanol was hydrogenated over Raney Nickel under pressure (50 bars) at 60°C for 6 h. After filtration and evaporation, the residual oil was dissolved in dry ether and treated with gaseous HCl. The solid obtained was then filtrated and recrystallized.

*4.3.1 (R,S) 2-(7-Methoxy-1,2,3,4-tetrahydronaphth-1-yl)ethylamine hydrochloride (**3a**)*

Yield 58% from toluene:cyclohexane (1:10); mp 135–137°C; IR 3050–2750, 1600, 1030 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.80 (m, 7H), 2.65 (m, 2H), 3.00 (m, 2H), 3.75 (s, 3H), 6.70 (dd, 1H, 7.80 and 3.10 Hz), 6.75 (d, 1H, 3.10 Hz), 6.95 (d, 1H, 7.80 Hz), 8.35 (m, 3H). Anal. $C_{13}H_{20}ClNO$ (C, H, N, Cl).

*4.3.2 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethylamine hydrochloride (**3b**)*

Yield 49% from ethyl acetate; mp 116–118°C; IR 3250–2500, 1605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.14 (t, 3H, 7.04 Hz), 1.67 (m, 6H), 2.63 (m, 7H), 6.96 (m, 3H), 8.00 (m, 3H). Anal. $C_{14}H_{22}ClN$ (C, H, N, Cl).

4.4 General procedure for the synthesis of N*-acylated derivatives (**4–8**)*

The synthesis of (*R,S*) 2-(7-methoxy-1,2,3,4-tetrahydronaphth-1-yl)ethylacetamide (**4**) is described as example. 0.5 g (0.002 mol) of **3a** was added to a solution of 0.83 g (0.006 mol) of potassium carbonate in 5 ml of water. Twenty milliliters of dichloromethane were added and the mixture cooled in an ice bath. Then, 0.18 g (0.0022 mol) of acetylchloride were added dropwise, under vigorous stirring. After 15 min, the organic layer was separated, washed with water, dried (magnesium sulfate), and evaporated under reduced pressure to give a residue that was purified either by column chromatography (**4** and **5**) or recrystallization (**6–8**).

*4.4.1 (R,S) 2-(7-Methoxy-1,2,3,4-tetrahydronaphth-1-yl)ethylacetamide (**4**)*

Yield 80% from column chromatography (ethyl acetate:dichloromethane, 1:1); colourless oil; IR 3270, 1630, 1590, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (m, 6H), 1.95 (s, 3H), 2.77 (m, 3H), 3.35 (m, 2H), 3.80 (s, 3H), 5.66 (m, 1H), 6.67 (m, 2H) 6.97 (d, 1H, 7.90 Hz). Anal. $C_{15}H_{21}NO_2$ (C, H, N).

*4.4.2 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethylacetamide (**5**)*

Yield 62% from column chromatography (ethyl acetate:dichloromethane, 1:1); colourless oil; IR 3260, 1630, 1540 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.21 (t, 3H, 7.60 Hz), 1.80 (m, 6H), 1.96 (s, 3H), 2.58 (q, 2H, 7.60 Hz), 2.72 (m, 2H), 2.81 (m, 1H), 3.37 (m, 2H), 5.63 (m, 1H), 6.96 (m, 3H). Anal. $C_{16}H_{23}NO$ (C, H, N).

*4.4.3 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethylbutyramide (**6**)*

Yield 75% from *n*-hexane; mp 54–56°C; IR 3280,

1630, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, 7.35 Hz), 1.21 (t, 3H, 7.55 Hz), 1.80 (m, 8H), 2.16 (t, 2H, 7.84 Hz), 2.58 (q, 2H, 7.55 Hz), 2.71 (m, 2H), 2.81 (m, 1H), 3.37 (m, 2H), 5.88 (m, 1H), 6.96 (m, 3H). Anal. $C_{18}H_{27}NO$ (C, H, N).

4.4.4 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethylcyclopropylcarboxamide (7)

Yield 80% from *n*-hexane; mp 95–97°C; IR 3260, 1630, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 4H), 1.21 (t, 3H, 7.59 Hz), 1.34 (m, 1H), 1.86 (m, 6H), 2.56 (q, 2H, 7.59 Hz), 2.71 (m, 2H), 2.80 (m, 1H), 3.39 (m, 2H), 5.91 (m, 1H), 6.95 (m, 3H). Anal. $C_{18}H_{25}NO$ (C, H, N).

4.4.5 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethylcyclobutylcarboxamide (8)

Yield 82% from *n*-hexane; mp 97–98°C; IR 3250, 1620, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, 7.58 Hz), 1.72 (m, 2H), 1.86 (m, 6H), 2.21 (m, 4H), 2.58 (q, 2H, 7.58 Hz), 2.72 (m, 2H), 2.81 (m, 1H), 2.98 (m, 1H), 3.38 (m, 2H), 5.39 (m, 1H), 6.97 (m, 3H). Anal. $C_{19}H_{27}NO$ (C, H, N).

4.5 (R,S) 2-(7-Ethyl-1,2,3,4-tetrahydronaphth-1-yl)ethyltrifluoroacetamide (9)

A suspension of 2 g of **3b** (0.008 mol) in 10 ml of pyridine was cooled in an ice bath. Trifluoroacetic anhydride (2 g, 0.009 mol) was then added dropwise. After stirring for 30 min at room temperature, the solution was poured into ice water. The resulting precipitate was filtered, washed with water and recrystallized. Yield 60% from *n*-hexane; mp 66–69°C; IR 3280, 1690, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, 7.59 Hz), 1.85 (m, 6H), 2.58 (q, 2H, 7.59 Hz), 2.73 (m, 2H), 2.84 (m, 1H), 3.74 (m, 2H), 6.52 (m, 1H), 6.97 (m, 3H). Anal. $C_{16}H_{20}F_3NO$ (C, H, N).

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