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Research paper

# Melatonergic ligands: Design, synthesis and pharmacological evaluation of novel series of naphthofuranic derivatives

Elodie Landagaray [a, b, 1], Mohamed Ettaoussi [a, b, *, 1, 2], Romain Duroux [a, b, c], Jean A. Boutin [d], Daniel-Henri Caignard [e], Philippe Delagrange [e], Patricia Melnyk [a, b, c], Pascal Berthelot [a, b, c], Saïd Yous [a, b, c, **]

[a] Université de Lille, F-59000, Lille, France
[b] UDSL, UFR Pharmacie, F-59000, Lille, France
[c] INSERM, UMR-S1172, F-59000, Lille, France
[d] Biotechnologies, Pharmacologie Moléculaire et Cellulaire, Institut de Recherches Servier, 78290, Croissy-sur-Seine, France
[e] Unité de Recherche Chimie Neurosciences, Institut de Recherches Servier, 78290, Croissy-sur-Seine, France

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ABSTRACT

Following our research for new melatonergic ligands, herein we report the design, synthesis and biological evaluation of new series of naphthofuranic derivatives as $MT_1$ and $MT_2$ ligands. Binding affinity results of the prepared compounds revealed good binding affinities at both melatonin receptor subtypes. Particularly, compound **6a** behaved as an $MT_1$ partial agonist and $MT_2$ full agonist and exhibited an excellent binding affinity at $MT_2$ (Ki = 0.09 nM). In addition, lateral chain displacement from position 1 to 2 of the furan core had no effect on the binding affinity at both $MT_1$ and $MT_2$, while elongation of this side chain, led to decreased melatonergic binding affinities.



## 1. Introduction

The neurohormone melatonin (Fig. 1) was discovered and characterized as *N*-acetyl-5-methoxytryptamine more than fifty years ago by Aaron Lerner [1]. Its biosynthetic route was then established starting from the L-tryptophan acid following a circadian rhythm. Melatonin secretion in humans is mainly performed by the pineal gland [2], but also by other regions of the CNS and other tissues and cells such as the retina [3], skin, bone marrow, lymphocytes [4], and gastrointestinal tract [5]. Interestingly, melatonin plays a major role in various physiological processes including, modulation of hormones secretion [6], regulation of sleep-wake cycle and cardiovascular functions [7,8], pain perception [9], immune system and core body temperature control [10]. Furthermore, melatonin was shown to be involved in several pathological processes such as sleep disturbances and insomnia [11], cancer and inflammation [12], neurodegenerative diseases, diabetes, depression and anxiety [13–15]. Although, its endogenous role and mechanism of action have not yet been fully elucidated.

The therapeutic potential of melatonin and most of its physiological effects are mainly mediated *via* activation of two of its receptors named $MT_1$ and $MT_2$ and belonging to the superfamily of G-protein coupled receptors (GPCRs). Cloning of these two receptors revealed that they are coupled to the $G_{\alpha i}$ proteins [16], exhibit a sub-nanomolar binding affinity for melatonin [17], and were localized in different compartments of the human body [18]. In order to provide a better understanding of the melatonergic system, during the last decades much of the research was focused on the discovery of new analogues of melatonin. While the characterization of its receptor-mediated functions requires potent and selective ligands for $MT_1$ and $MT_2$, nowadays and despite the large

* Corresponding author. Université Lille Nord de France, F-59000, Lille, France.
** Corresponding author. Université Lille Nord de France, F-59000, Lille, France.
*E-mail addresses:* m.ettaoussi@yahoo.fr (M. Ettaoussi), said.yous@univ-lille2.fr (S. Yous).
[1] Both investigators equally contributed to this work.
[2] Current address: McGill University, Department of Psychiatry, Montreal QC-Canada.

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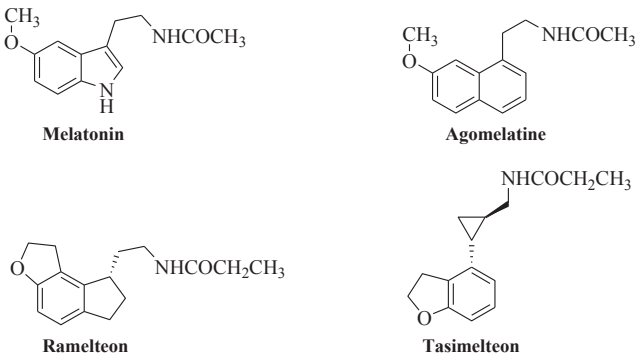


**Fig. 1.** Structures of melatonin and some of its analogues.

number of high affinity non-selective ligands [19], pronounced receptor subtype selective ligands especially for $MT_1$ still remain a real challenge. Accordingly, after more than half a century of intense research only few melatonergic compounds are marketed or under clinical trials. Hence, circadin, ramelteon, agomelatine and tasimelteon (Fig. 1) constitute the only melatonin analogues that are commercialized up to now [20]. For decades, our lab was involved in a large research program of melatonergic ligands that focused on the pharmacomodulation of melatonin. Therefore, the indole scaffold was replaced with different bioisosteres such as benzofuran, benzothiophene, isoquinoline, phthalazine, and naphthalene among others, and different positions of the aromatic nucleus, the lateral acetamide chain and the methoxy group were modulated leading to compounds with different pharmacological profiles [21,22].

Substitution of the indole of melatonin with naphthalene and benzofuran nucleus was of major interest. Firstly, agomelatine the naphthalenic analogue of melatonin has shown a unique profile, owning a sub-nanomolar binding affinity at both melatonergic $MT_1$ and $MT_2$ receptors and a sub-micromolar binding affinity at the serotonergic 5-$HT_{2C}$ receptor subtype. Secondly, the strict benzofuranic analogue of melatonin, **S21767** (Chart 1) was a potent ligand for $MT_1$ and $MT_2$ and was metabolically more stable than melatonin [23]. Therefore, in order to prepare new melatonergic ligands with the agomelatine pharmacological profile and the benzofuran metabolic stability, we investigate the effect of the fusion of these two scaffolds on both melatonergic affinity and activity. Herein, we report a new series of naphthofuranic derivatives as new $MT_1$ and $MT_2$ ligands. The new synthesized naphthofurans were then submitted to a series of additional modulations applied to the lateral chain and the acetamide function (Chart 1). We describe hereafter

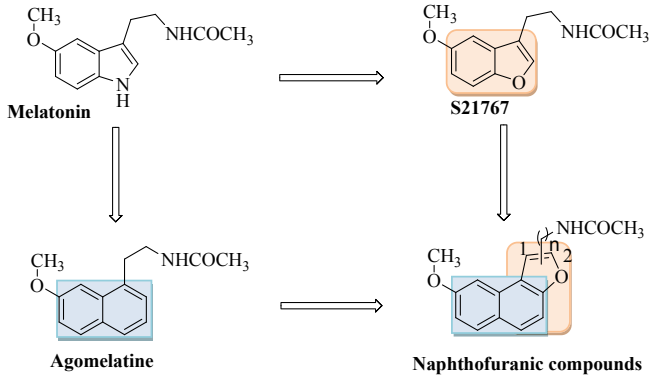


**Chart. 1.**

the syntheses, characterization and biological results of the prepared compounds.

## 2. Results and discussion

### 2.1. Chemistry

The synthetic strategy applied for the preparation of key amines **3** and **6** is shown in Scheme 1. First, acid **1** was prepared from 7-methoxy-beta-naphthol in two steps, by condensation with ethyl 4-chloro-3-oxobutanoate in sulphuric acid [24] followed by the transformation of the resulted chromenone into derivative **1** by treatment with sodium hydroxide [25a]. Second, through two main routes were prepared the key amines **3** and **6**. In route 1, acid **1** was transformed into azide **2** *via* treatment with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (EDCI) and sodium azide. Submission of compound **2** to Curtius rearrangement [25b] has led to the corresponding isocyanate; this non isolated intermediate was subsequently hydrolysed under acid conditions to provide the desired amine **3**. In route 2, acid **1** was first converted into amide **4** through treatment with oxalyl chloride and aqueous ammonia and dehydrated by treatment with trifluoroacetic anhydride (TFAA) to lead to nitrile **5**. Chemical reduction of compound **5** using lithium aluminium hydride and aluminium chloride gave desired amine **6** in a good yield.

In Scheme 2 is outlined the synthetic sequence used for the preparation of the other two key amines **10** and **15**. Formylation of 2,7-dimethoxynaphthalene under Vilsmeier-Haack conditions [26] followed by selective demethylation of the 2-methoxy group *via* treatment with aluminium chloride produced compound **7**. *O*-alkylation of this later compound with the appropriate alkyl bromide in the presence of potassium carbonate led to derivatives **8** and **11**. Submission of **8** and **11** to a base-catalyzed cyclisation reaction has led to naphthofuranic derivatives **9** and **12**. Reduction of the ester **12** by treatment with lithium aluminium hydride provided the alcohol **13**, whom activation by thionyl chloride in the presence of pyridine followed by nucleophilic substitution with sodium cyanide gave nitrile **14** in a good yield. Chemical reduction of nitriles **9** and **14**, by a mixture of lithium aluminium hydride and aluminium chloride as was previously described gave the desired amines **10** and **15**.

Finally, synthesis of the desired final amides, ureas, and thioureas **3a-d**, **6a-c**, **10a-i** and **15a-c** was carried out as illustrated in Scheme 3. Hence, *N*-acylated compounds **3a-c**, **6a-b**, **10a-b** and **15a-b** were obtained from the corresponding amines by reaction with the appropriate acid chlorides according to a variant of the Schotten-Baumann procedure [27]. Fluorinated derivatives **3d** and **10c** were prepared by reaction of the corresponding free amine with ethyl fluoroacetate in 2,2,2-trifluoroethanol. Urea **10d** and thiourea **10g** were obtained from **10** by treatment with potassium cyanate and potassium thiocyanate respectively as illustrated in Scheme 3. Otherwise, the reaction of amine **10** with *N*-methylphenylcarbamate, prepared as it was previously described in the literature [28], produced methylurea **10e**, while alkylureas (**6c**, **10f**, **15c**) and alkythioureas (**10h**, **10i**) were synthesized by treatment of the corresponding amines (**6c**, **10f** and **15c**) with alkyl isocyanate or alkylisothiocyanate.

## 3. Pharmacology

In this paper, we describe the design and synthesis of a new series of naphthofuranic derivatives as melatonin $MT_1$ and $MT_2$ ligands. The new synthesized derivatives are composed of two position isomers differently substituted at position 1 or 2 of the naphthofuran nucleus. To determine their binding affinities and