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Chapter

Synthetic Melatonin Receptor Agonists and Antagonists

Andrew Tsotinis and Ioannis P. Papanastasiou

Abstract

The functions of the pineal hormone melatonin are of intense and continuous interest. Synthetic melatonin receptor analogues, as agonists and antagonists, have been explored, and the molecule can be viewed as consisting of an indole nucleus, acting mainly as a spacer, and the C5-OMe and the C3-ethylamido side chains, acting as pharmacophoric components. The present chapter focuses on the synthetic routes towards these melatonin derivatives, first the aromatic nucleus, then the functionalities that have been introduced to the nucleus, and finally those analogues with restrained conformations and those that are optically active. The importance of the various parameters involved in the agonist and antagonist profile of the compounds is indicated, as is the difference in the action of the chiral melatoninergics.

Keywords: melatonin, indole and bioisosteric derivatives, constrained polycyclic analogues, chiral melatonin analogues

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine **1**) is a hormone ubiquitously distributed in a variety of organisms, such as bacteria, unicellular algae, fungi, plants, vertebrates, and mammalians [1]. Melatonin is mainly known to regulate circadian rhythms by synchronization to environmental cues but participates also in diverse important physiological processes, such as regulation of the visual functions, glucose metabolism, and immune functions (**Figure 1**) [2]. The functions of melatonin are modulated through its binding to G protein-coupled receptors (GPCRs), which activate signaling pathways, as a cascade effect [3]. Up to date, two different types of melatonin receptors have been described in mammals: type 1A (MT1) and type 1B (MT2). Both receptors are located in many regions in the central nervous system and in peripheral tissues as well [4]. X-ray free electron laser (XFEL) studies have recently revealed that MT1 binding site is extremely compact, and ligands interact with MT1 mainly by strong aromatic stacking with Phe179 and auxiliary hydrogen bonds with Asn162 and Gln181 [5]. Comparison of the structures of MT2 and MT1 indicated that, despite conservation of the orthosteric ligand binding site residues, there are significant conformational variations between both melatonin receptor subtypes, which justify the selectivity between the two subtypes [6]. Melatonin was proven to bind to one more co-substrate binding site (MT3), which is a quinone reductase-2 [7]. Melatonin receptors had been cloned in 1990s [8–10] but characterized and described in the 1980s by using the radiolabeled 2-[^{125}I]-iodomelatonin and ^{3}H-melatonin ligands [11, 12]. Herein, we are reviewing the synthetic routes of

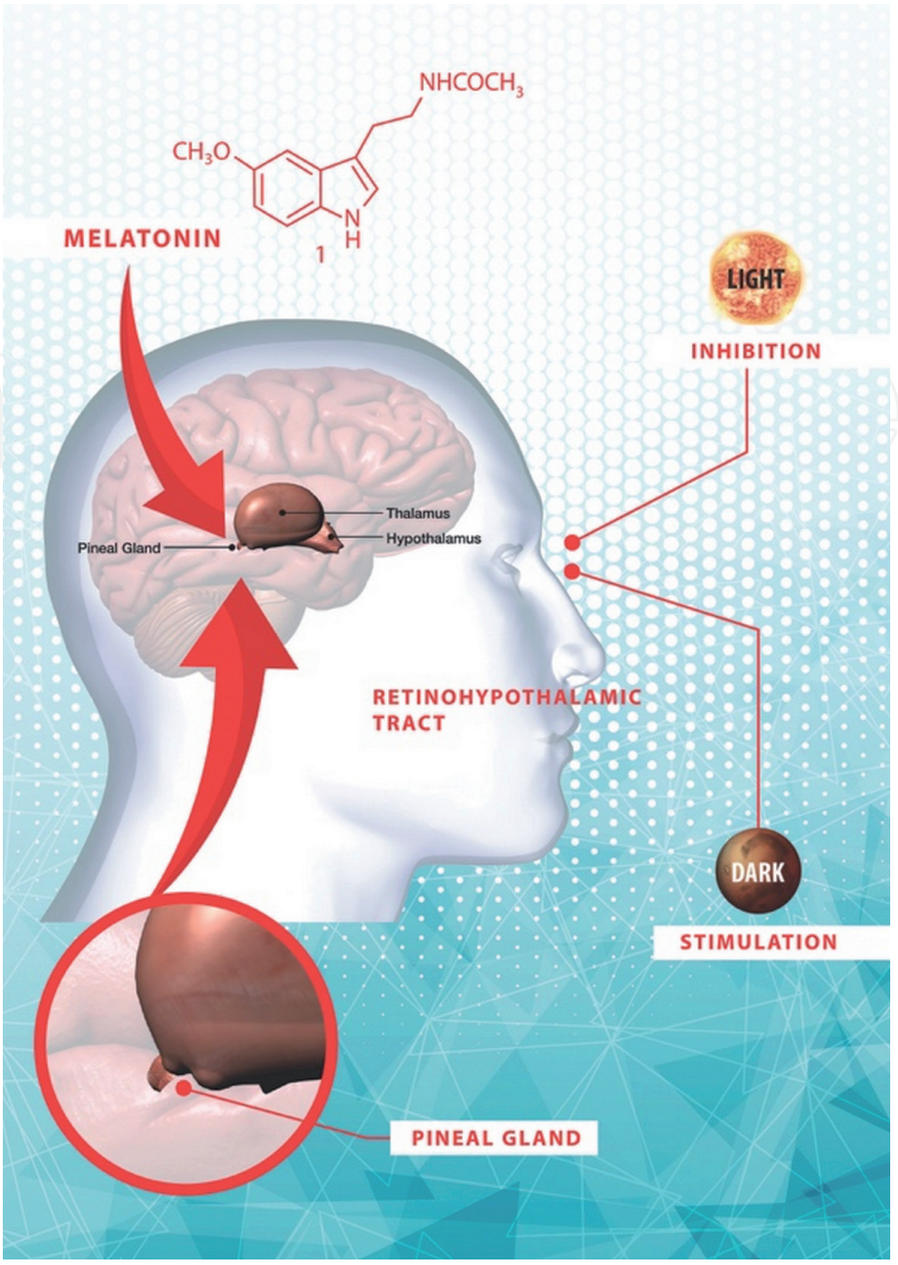


Figure 1.
Regulation of melatonin production.

the main indole and bioisosteric aromatic nucleus derivatives: first, the conformationally restricted; the active chiral compounds second; and the derivatives with substituted 3-side chains third.

2. Indole and bioisosteric derivatives

A guide of general principles has been applied throughout SARs for both melatonin receptors. The C5-OMe group of the indole ring is optimal, while the same substituent at positions 4, 6, or 7 leads to a drastic loss of affinity. However, congeners with a halogen at the 5-position do retain high affinity [13]. The relative position of the methoxy group and the *N*-acetylaminoethyl side chain seems to be the most important structural feature that increases the melatonin receptor binding affinity [14–16]. The syntheses of these derivatives are based on classic chemical procedures [17–19]. The indole ring could also be considered as a spacer [20, 21] with the pyrrole portion not involved in the receptor binding pocket, because it can be replaced

by diverse aromatic scaffolds, such as naphthalene, benzofuran, benzothiophene, or benzocycloalkane rings [14, 22, 23]. Various congeners with substitutions in the positions 2 and 6 of melatonin have been synthesized. Substituents, like methyl, phenyl, or halogen at position 2 of melatonin, can increase receptor binding affinity by *ca* tenfold [24–27]. The presence of an optimal *N*-acyl group with a 2-halogen substitution exhibits very potent affinity [28].

Interestingly, substituents on the 2-position seem to direct the *N*-acetylaminoethyl side chain into the optimal conformation for interaction with the receptor and increase the ligand affinity [29, 30]. 6-Substituted analogues have been prepared [31] with the aim of retarding metabolism, because melatonin is degraded rapidly in vivo, mainly in the liver, by 6-hydroxylation followed by conjugation and excretion in the urine. A halogen substituent at the 6-position reduces binding affinity nonsignificantly, while the binding affinity of 6-hydroxymelatonin is decreased by 5 to 10 times and 6-methoxymelatonin by more than 100 times [32].

One of the synthetic routes for the production of 5-methoxyindole (**4**) is via the Leimgruber-Batcho reaction [33], modified by Repke and Ferguson [34] (**Figure 2**). A successful side chain functionalization was reported by Ates-Alagoz et al. [35] using the Vilsmeier-Haack formylation reaction of 5-methoxyindole (**4**). On the other hand, Righi et al. [36] applied the direct C3 reductive alkylation of *N*-benzyl-5-methoxyindole (**8**), as described in **Figure 2**.

In an attempt to map the receptor requirements, a series of phenylalkyl amides **9**–**11** were prepared and proven to exhibit the minimal structure required for the ligand recognition by melatonin receptors [16, 37, 38] (**Figure 3**).

Some C3-modified melatonin analogues have exhibited interesting melatoninergic activities. It has been shown that small modifications in the acyl chain are able to change the binding affinity for melatonin receptors. A typical modification to increase the activity is the replacement of the acetyl by an *N*-butanoyl chain. Depreux et al. reported a 100-fold higher affinity of 5-methoxy-*N*-butanoyltryptamine than melatonin [14]. Tsotinis et al. reported that upon the appropriate functionalization at the end of the C2 side chain, the azido compounds **16** were produced, which serve as photoactivity labels, while the respective isothiocyanate compounds **17** serve as electrophilic probes (**Figure 4**), in order to produce adducts covalently linked to key amino acid residues of the melatonin receptor subtypes [39].

Luzindole, N-acetyl-2-benzyltryptamine (**21**), is a selective melatonin receptor antagonist with approximately 11- to 25-fold higher affinity for the MT2 than the

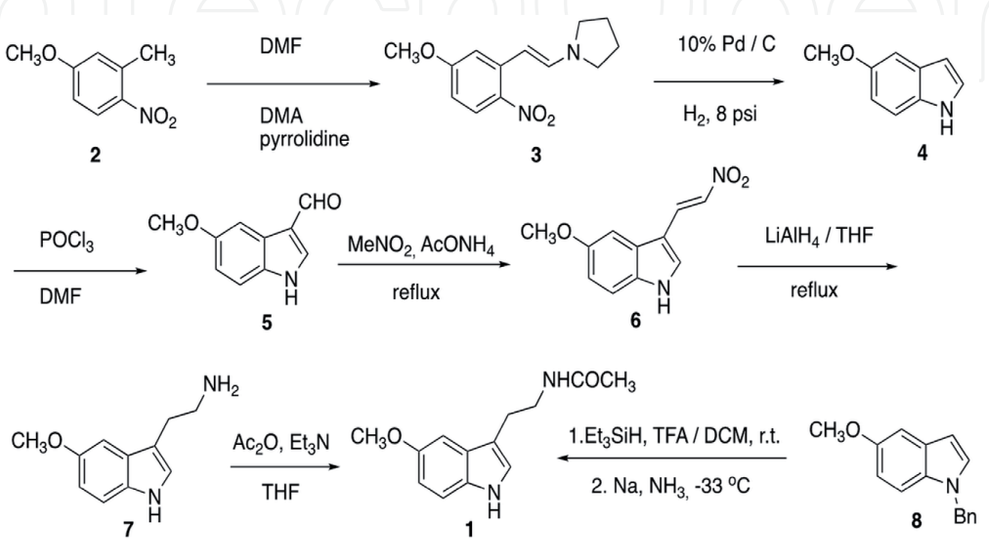


Figure 2.
Highlighted synthetic routes of melatonin ***1****.*

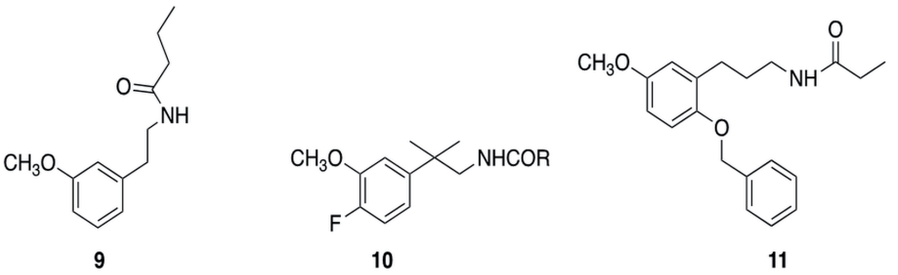


Figure 3.
Phenylalkyl amides.

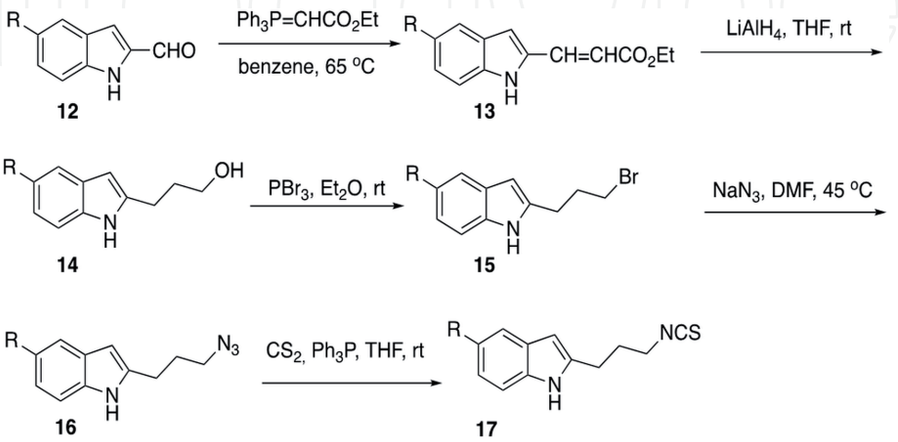


Figure 4.
C2-functionalized melatonin analogues.

MT1 receptor [4]. The synthesis of luzindole, achieved through a Pictet-Spengler reaction and formation of the intermediate β-carboline **19**, was first patented by Dubocovich et al. [40]. In 2008, Tsotinis et al. reported a new method of luzindole synthesis, through the C-3 indole nitroolefin **22**, leading to a much higher overall yield [41] (**Figure 5**).

The benzo[*b*]furan nucleus can replace the indole skeleton and retain its reactivity. 5-Methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (**25**) was prepared from 4-methoxyphenol (**23**) by acylation with chloracetonitrile followed by cyclization [42] (**Figure 6**).

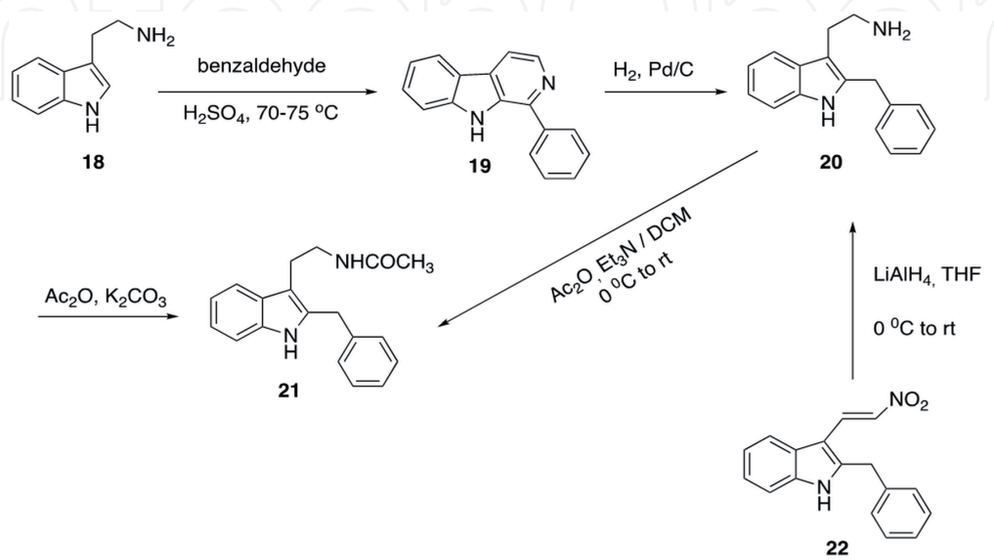


Figure 5.
Luzindole.

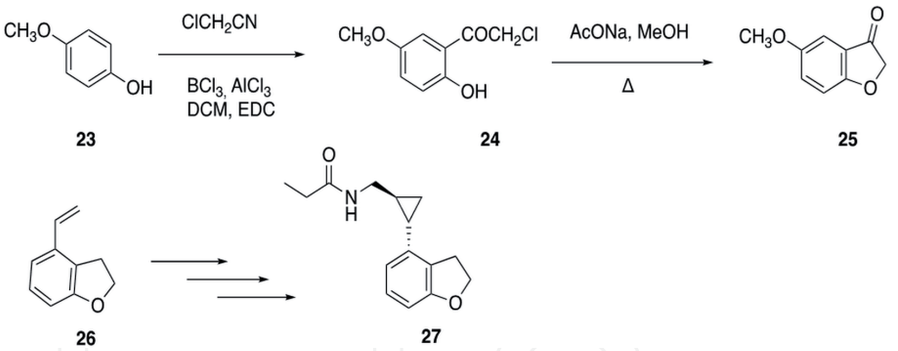


Figure 6.
Tasimelteon.

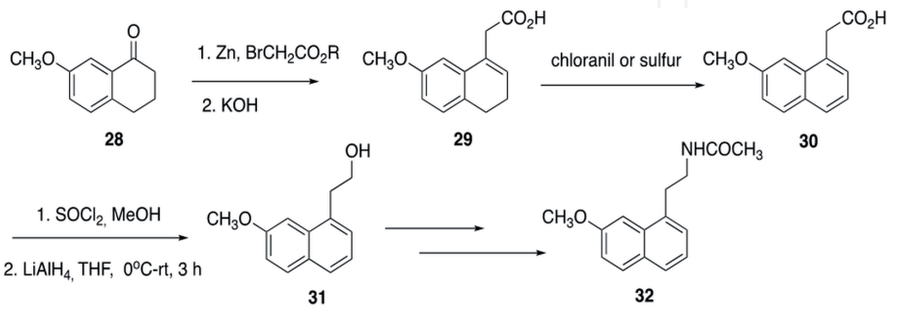


Figure 7.
Agomelatine.

Tasimelteon, *N*-[[(1*R*,2*R*)-2-(2,3-dihydro-1-benzofuran-4-yl)cyclopropyl] methyl] propenamide (**27**), is a melatonin agonist, which bears the benzo[*b*]furan skeleton and was approved by the FDA, in January 2014, for the treatment of non-24 h sleep–wake disorder [43]. The starting material for the synthesis of tasimelteon is the 4-vinyl-2, 3-dihydrobenzofuran (**26**).

The naphthalene scaffold can also be considered as a melatonin-acting biomolecule with high affinity and potency [44, 45]. The preparation of the key intermediate in this synthesis, 2-(7-methoxy-1-naphthyl)ethanol (**31**), is depicted in **Figure 7**. Agomelatine, *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (**32**), was recently approved for medical use in Europe and Australia [46].

3. Constrained polycyclic derivatives

Tricyclic and even larger constrained derivatives have been investigated for their melatoninergic potency. The synthesis of 6,7,8,9-tetrahydropyridino[1,2-*a*]indole (**36**) [47] is illustrated in **Figure 8**.

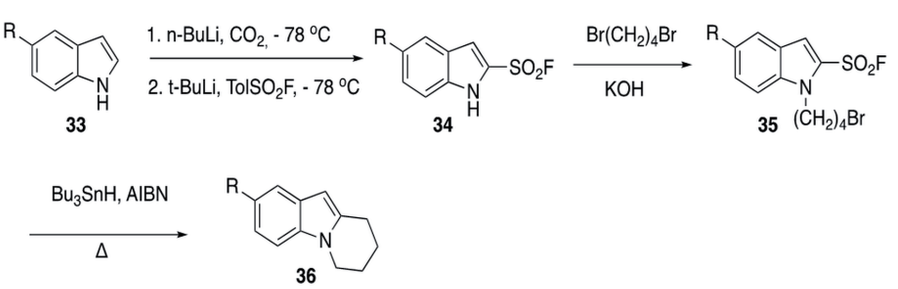


Figure 8.
6,7,8,9-Tetrahydropyridino[1,2-a]indole.

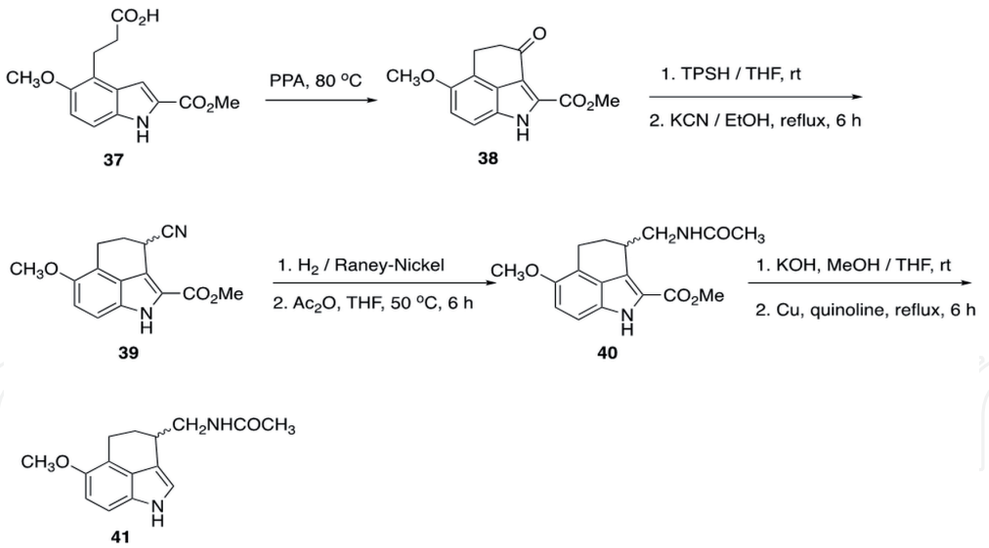


Figure 9.
1,3,4,5-Tetrahydro[cd]indole.

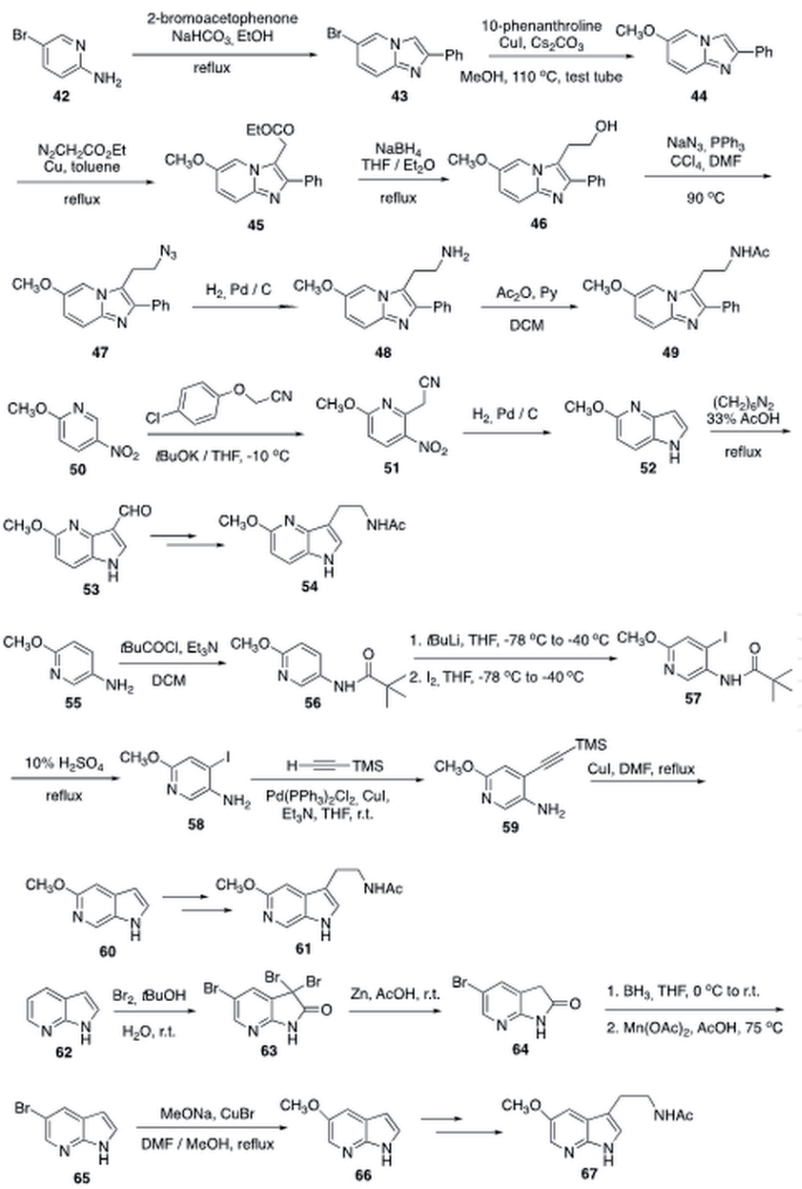


Figure 10.
Azaindoles.

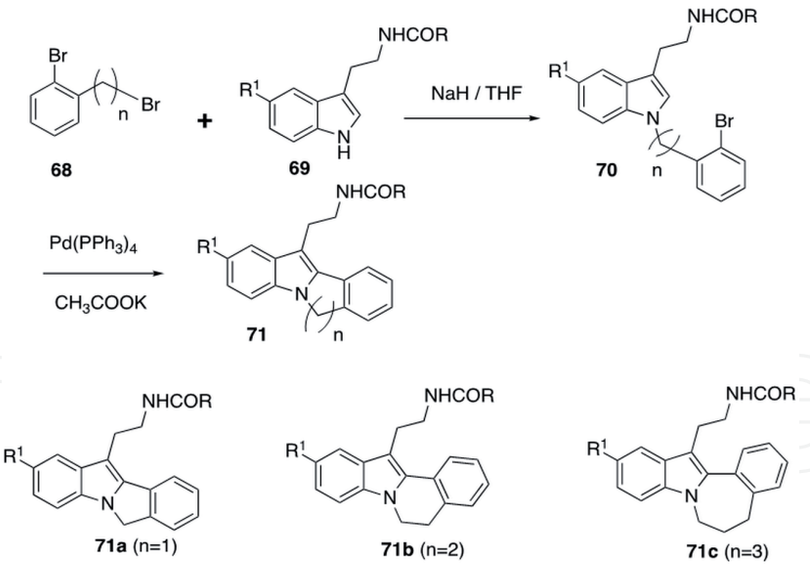


Figure 11.
Isoindolo[2,1-a]indoles and benzo[c]azepeno[2,1-a]indoles.

The 3-substituted 1,3,4,5-tetrahydro[*cd*]indoles exhibit higher melatonin receptor affinity than their more constrained congeners [30]. The key intermediate ketone **38** was obtained upon cyclization of the carboxylic acid **37** with polyphosphoric acid. As shown in **Figure 9**, the ketone **38** was converted to the corresponding cyanide **39**, in two steps. The latter gave then the respective acetamide **40**, and the final tricyclic adduct **41** was prepared by ester hydrolysis followed by decarboxylation of the corresponding acid in boiling quinoline in the presence of copper powder.

Azaindoles have also been proven to exhibit melatoninergic potency. Some melatonin analogues based on 3*a*-aza-, 4-aza-, 6-aza-, and 7-azaindole cores are described in **Figure 10**.

In the synthetic route to the 3*a*-azamelatonin analogue **49**, El Kazzouli et al. [48] reported the treatment of 2-amino-5-bromopyridine (**42**) with 2-bromoacetone and the use of ethyl 2-azidoacetate for the formation of the key intermediate ester **45**. In the synthesis of 3-substituted-4-azaindole **49**, Mazeas et al. [49] have used 2-methoxy-5-nitropyridine (**50**), as starting material, and standard chemistry procedures. The 4-azaindole analogue **50** was proven to be a stronger agonist than melatonin at both melatonin receptors [50]. The preparation of 6-azamelatonin derivative **61** involves the Sonogashira reaction, as reported in the literature [49]. Finally, the 7-azamelatonin congener **67** presents promising melatoninergic potential [49].

The isoindolo[2,1-*a*]indoles and benzo[*c*]azepeno[2,1-*a*]indoles were prepared by Tsotinis et al. [51]. The appropriate *N*-acetyl tryptamine was coupled with the respective dibromide **68**, and the derived *N*-alkyl indole **70** was then cyclized in the presence of $Pd(PPh_3)_4$ to afford the desired products **71 (Figure 11)**.

The pharmacological evaluation has shown that 6*H*-isoindolo[2,1-*a*]indoles (**71a**) are agonists, while the 5,6-dihydroindolo[2,1-*a*]isoquinolines (**71b**) are partial agonists/antagonists, and the 6,7-dihydro-5*H*-benzo[*c*]azepino[2,1-*a*]indoles (**71c**) are antagonists. Thus, the size of the linker between the phenyl ring and the pyrrole nitrogen atom serves as a switch pharmacological probe, spanning from agonist to antagonist melatoninergic action.

4. Chiral melatonin analogues

Some derivatives with constrained conformation also present chirality. Ramelteon is the most emblematic representative example of this class of

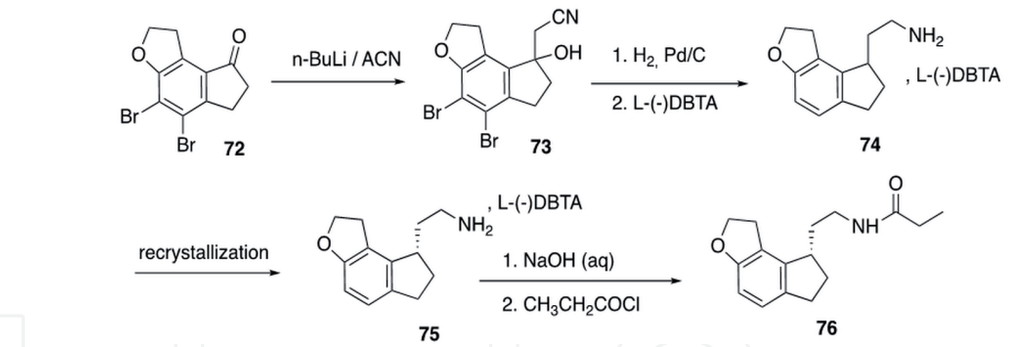


Figure 12.
Ramelteon.

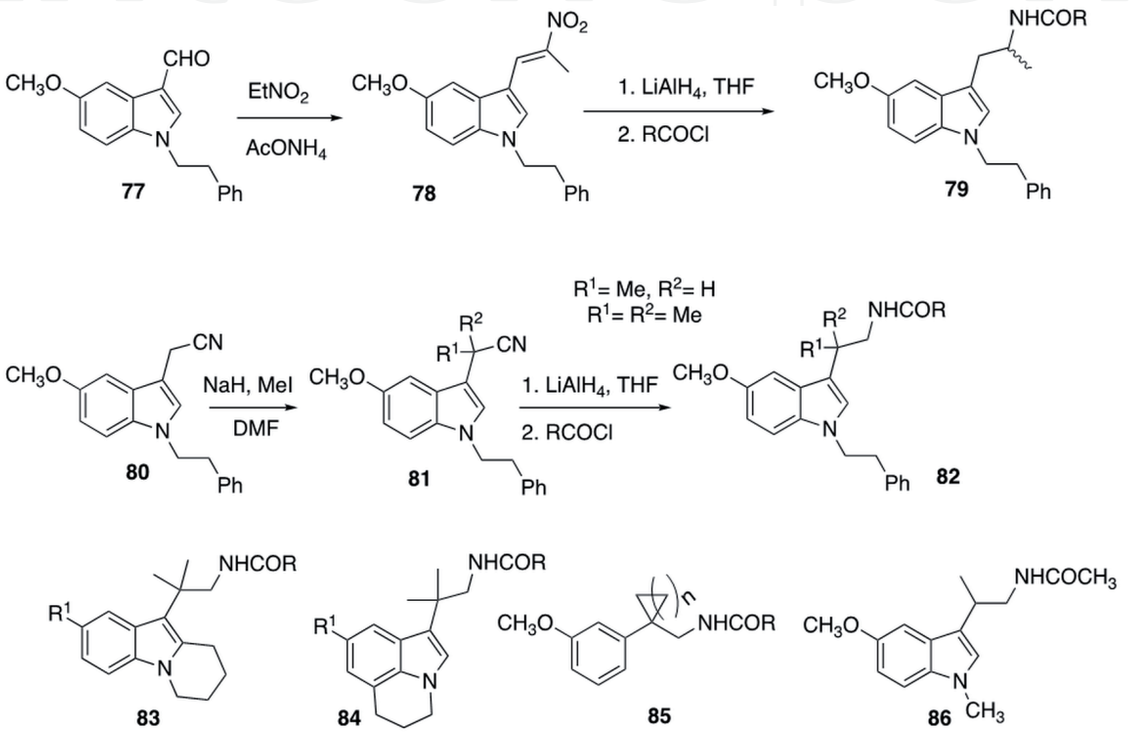


Figure 13.
Examples of chiral melatoninergic analogues and side chain conformationally constrained tricyclic derivatives 83 and 84.

compounds. Ramelteon, *N*-{2-[(8*S*)-1,6,7,8-tetrahydro-2H-indeno[5,4-*b*]furan-8-yl]ethyl}propanamide (**76**) [52], is a melatonin analogue approved by the FDA as a sedative-hypnotic. The following synthetic route [53], illustrated in **Figure 12**, uses dibenzoyl-*L*-tartaric acid as an acid to form the salt at the end of hydrogenation and as the resolution agent as well.

Most of these chiral derivatives are prepared as racemates and, then, in some cases, resolved. The racemate mixture of enantiomers provides an initial estimation of the biology of these compounds, although asymmetric syntheses may then be required if one of the enantiomers exhibits a selective result. Substituents on the 3-side chain, particularly at the β-position, present a preference for the active conformation. This hypothesis has been investigated by assessing the melatoninergic potency of various compounds which bear in their side chain small to large substituents. An example of α- and β-methyl side chain functionalized molecules with enhanced activity is the *N*1-phenethyl-substituted indole derivatives **79** and **82** [54]. The characteristic steps of the synthesis of these probes are illustrated in **Figure 13**. Similar results, in terms of activities and related conformation, have been obtained for the analogues **83**, **84**, and **85** [55–57].

The *β*-methyl, *N*-methyl-substituted melatonin derivative **86** was prepared and resolved by chiral HPLC [58]. The (+) enantiomer has a tenfold higher potency in pigment aggregation in the *Xenopus laevis* protocol, while the (−) enantiomer has a 28-fold selectivity for the MT2 receptor.

5. Conclusions

A selection of key melatoninergic derivatives was reported herein. We pointed out the synthetic routes towards these melatonin analogues, first of the aromatic nucleus, then of the functionalities that have been introduced to the nucleus, and finally of those analogues with restrained conformations and those that are optically active. Much more needs to be explored about the variant functions of melatonin and through which receptor type they exert their action. The range of small molecules having agonist or antagonist effects on the melatonin receptors is large, and new scaffolds keep appearing as drug candidates in different treatments. This work is hoped to assist those seeking to explore the melatonin and melatoninergic field.

Conflict of interest

The authors declare no conflict of interest.

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