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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 mammals [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 ^3H -melatonin ligands [11, 12]. Herein, we are reviewing the synthetic routes of

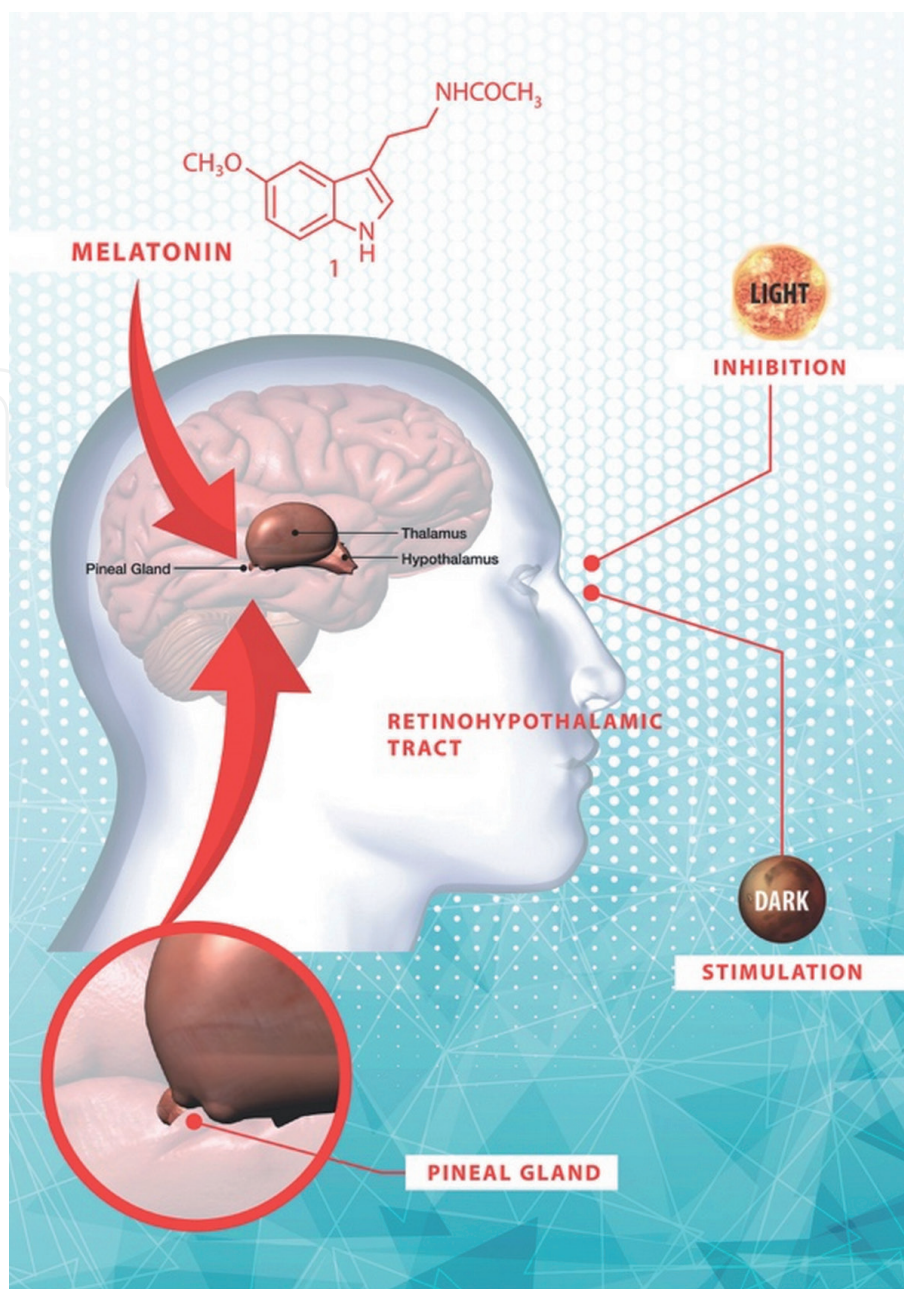


Figure 1.
Regulation of melatonin production.

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 melatonin-ergic 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

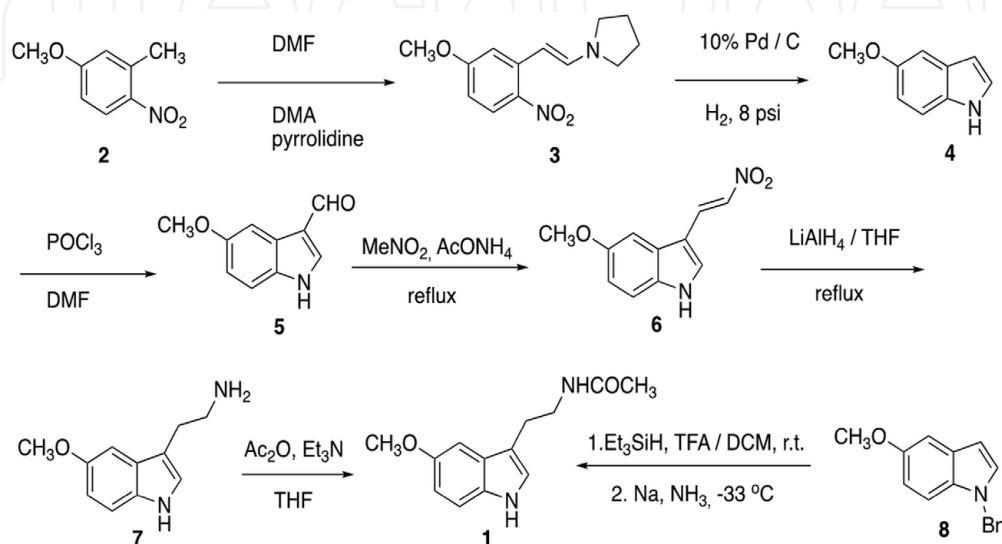


Figure 2.
 Highlighted synthetic routes of melatonin **1**.

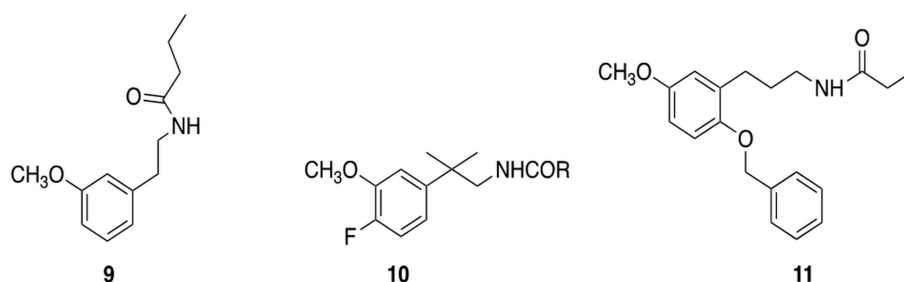


Figure 3.
Phenylalkyl amides.

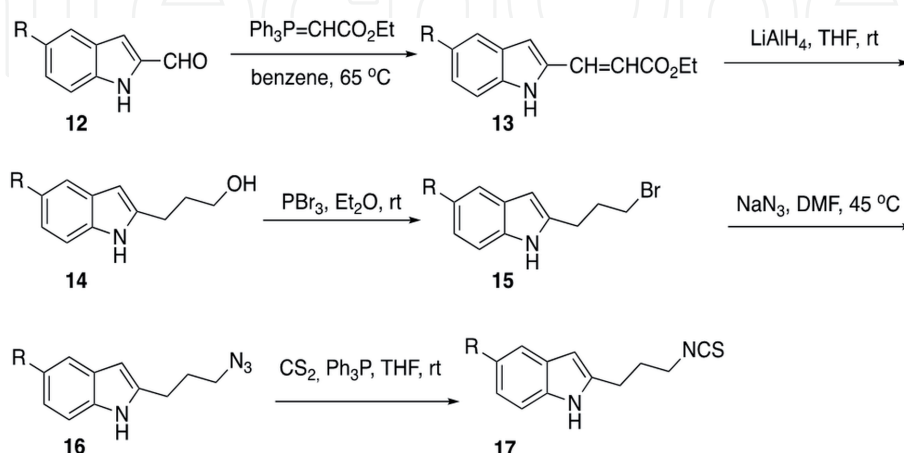


Figure 4.
C2-functionalized melatonin analogues.

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 chloroacetonitrile followed by cyclization [42] (**Figure 6**).

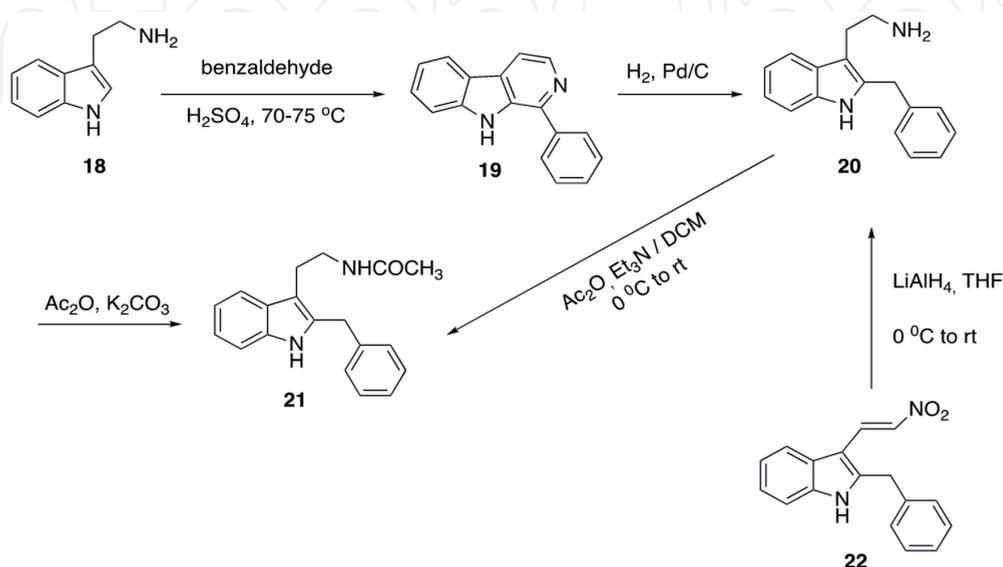


Figure 5.
Luzindole.

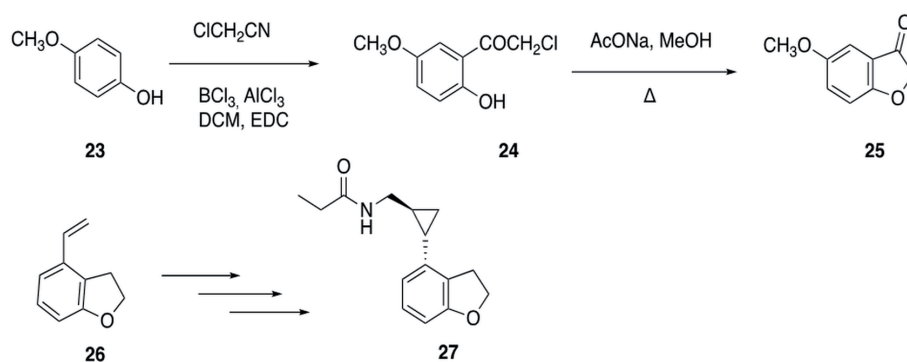


Figure 6.
Tasimelteon.

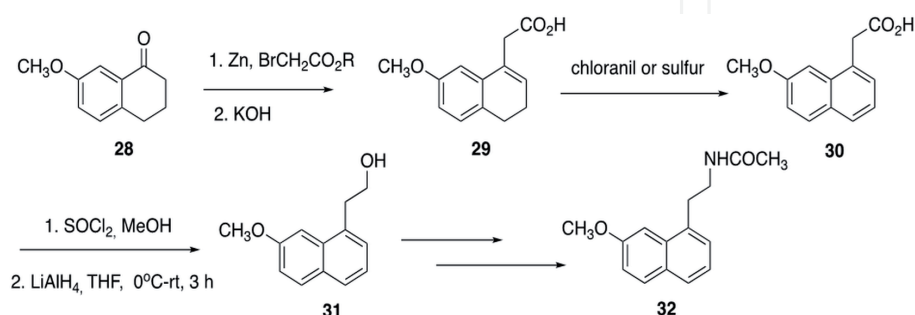


Figure 7.
Agomelatine.

Tasimelteon, *N*-[[*(1R,2R)*-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 melatonergic potency. The synthesis of 6,7,8,9-tetrahydropyridino[1,2-*a*]indole (**36**) [47] is illustrated in **Figure 8**.

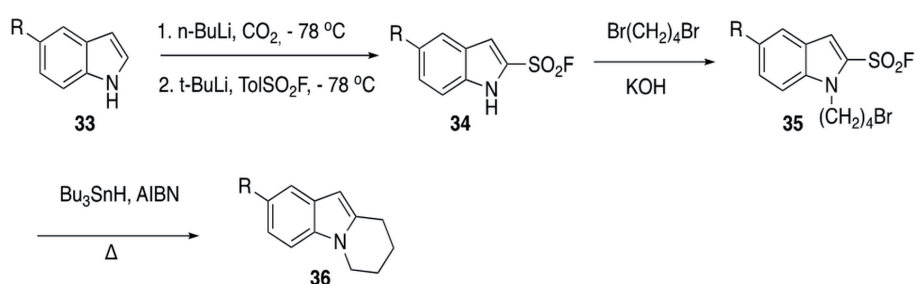


Figure 8.
6,7,8,9-Tetrahydropyridino[1,2-*a*]indole.

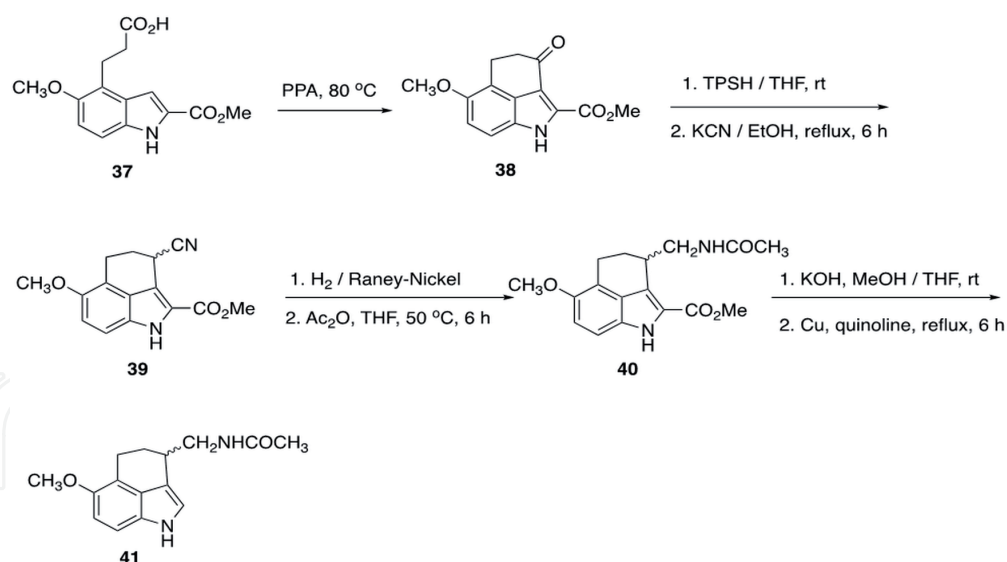


Figure 9.
1,3,4,5-Tetrahydro[cd]indole.

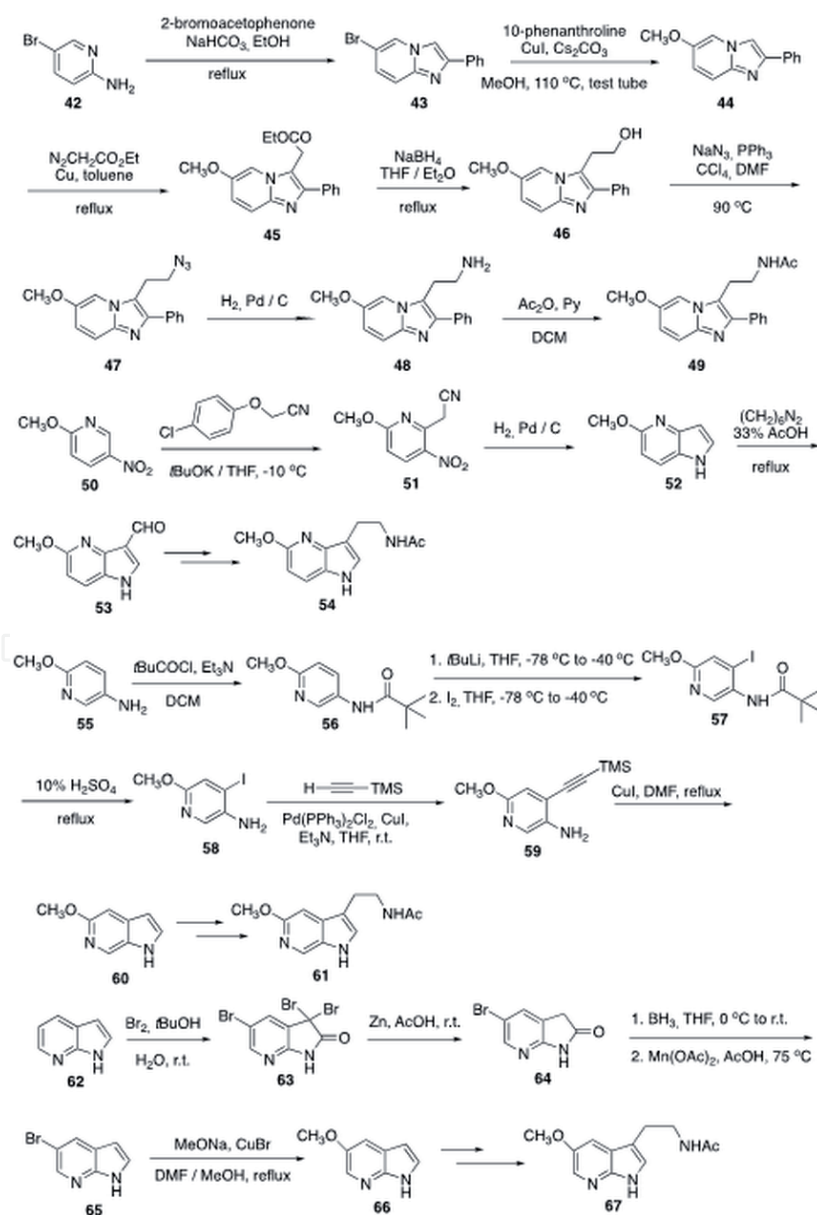


Figure 10.
Azaindoles.

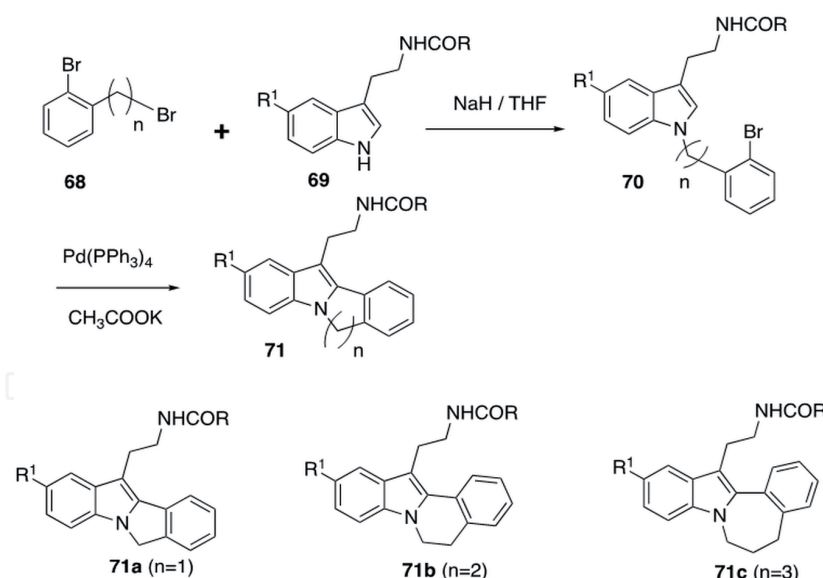


Figure 11.
 Isoindolo[2,1-*a*]indoles and benzo[*c*]azepeno[2,1-*a*]indoles.

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 melatoninergetic 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 melatoninergetic 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(PPh₃)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 melatoninergetic action.

4. Chiral melatonin analogues

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

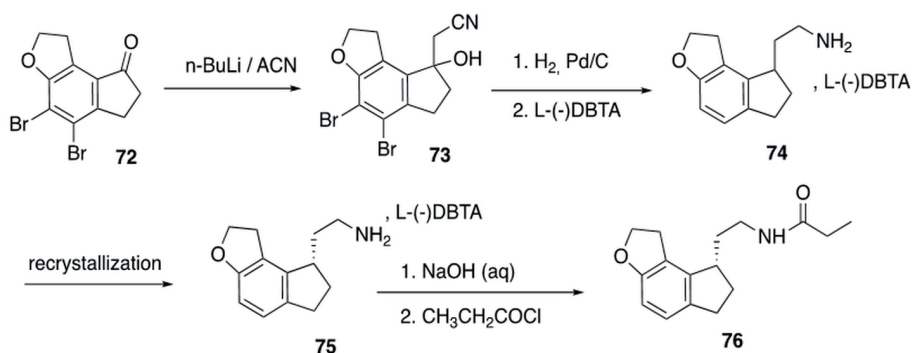


Figure 12.
Ramelteon.

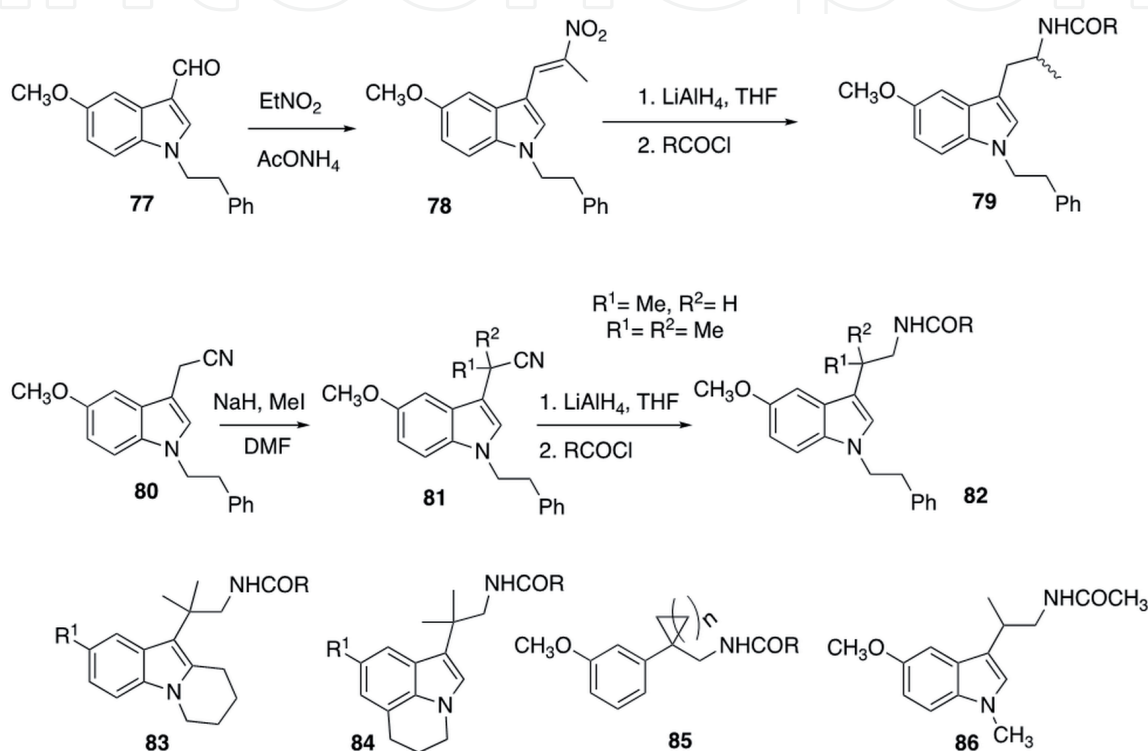


Figure 13.
Examples of chiral melatonergic analogues and side chain conformationally constrained tricyclic derivatives 83 and 84.

compounds. Ramelteon, *N*-{2-[(8*S*)-1,6,7,8-tetrahydro-2*H*-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 melatonergic 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 melatonergic 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 melatonergic field.

Conflict of interest


The authors declare no conflict of interest.

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References

- [1] Zlotos DP, Jockers R, Cecon E, Rivara S, Witt-Enderby PA. MT 1 and MT 2 melatonin receptors: Ligands, models, oligomers, and therapeutic potential. *Journal of Medicinal Chemistry*. 2014;**57**(8):3161-3185. Available from: <https://pubs.acs.org/doi/10.1021/jm401343c>
- [2] Oishi A, Cecon E, Jockers R. Melatonin receptor signaling: Impact of receptor oligomerization on receptor function. In: *International Review of Cell and Molecular Biology*. Cambridge, MA, United States: Elsevier; 2018. pp. 59-77. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1937644818300121>
- [3] Gobbi G, Comai S. Sleep well. Untangling the role of melatonin MT1 and MT2 receptors in sleep. *Journal of Pineal Research*. 2019;**66**(3):e12544. Available from: <http://doi.wiley.com/10.1111/jpi.12544>
- [4] Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J. International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacological Reviews*. 2010;**62**(3):343-380. Available from: <http://pharmrev.aspetjournals.org/lookup/doi/10.1124/pr.110.002832>
- [5] Stauch B, Johansson LC, McCorvy JD, Patel N, Han GW, Huang X-P, et al. Structural basis of ligand recognition at the human MT1 melatonin receptor. *Nature*. 2019;**569**(7755):284-288. Available from: <http://www.nature.com/articles/s41586-019-1141-3>
- [6] Johansson LC, Stauch B, McCorvy JD, Han GW, Patel N, Huang X-P, et al. XFEL structures of the human MT2 melatonin receptor reveal the basis of subtype selectivity. *Nature*. 2019;**569**(7755):289-292. Available from: <http://www.nature.com/articles/s41586-019-1144-0>
- [7] Tan D-X, Manchester LC, Terron MP, Flores LJ, Tamura H, Reiter RJ. Melatonin as a naturally occurring co-substrate of quinone reductase-2, the putative MT 3 melatonin membrane receptor: Hypothesis and significance. *Journal of Pineal Research*. 2007;**43**(4):317-320. Available from: <http://doi.wiley.com/10.1111/j.1600-079X.2007.00513.x>
- [8] Ebisawa T, Karne S, Lerner MR, Reppert SM. Expression cloning of a high-affinity melatonin receptor from *Xenopus* dermal melanophores. *Proceedings of the National Academy of Sciences*. 1994;**91**(13):6133-6137. Available from: <http://www.pnas.org/cgi/doi/10.1073/pnas.91.13.6133>
- [9] Reppert SM, Godson C, Mahle CD, Weaver DR, Slaugenhaupt SA, Gusella JF. Molecular characterization of a second melatonin receptor expressed in human retina and brain: The Mel1b melatonin receptor. *Proceedings of the National Academy of Sciences*. 1995;**92**(19):8734-8738. Available from: <http://www.pnas.org/cgi/doi/10.1073/pnas.92.19.8734>
- [10] Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron*. 1994;**13**(5):1177-1185. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0896627394900558>
- [11] Vakkuri O, Leppäluoto J, Vuolteenaho O. Development and validation of a melatonin radioimmunoassay using radioiodinated melatonin as tracer. *Acta Endocrinologica*. 1984;**106**(2):152-157. Available from: https://ejebioscientifica.com/view/journals/eje/106/2/acta_106_2_002.xml

- [12] Vaněček J, Pavlík A, Illnerová H. Hypothalamic melatonin receptor sites revealed by autoradiography. *Brain Research*. 1987;**435**(1-2):359-362. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0006899387916258>
- [13] Mor M, Rivara S, Silva C, Bordi F, Plazzi PV, Spadoni G, et al. Melatonin receptor ligands: Synthesis of New melatonin derivatives and comprehensive comparative molecular field analysis (CoMFA) study. *Journal of Medicinal Chemistry*. 1998;**41**(20):3831-3844. Available from: <https://pubs.acs.org/doi/10.1021/jm9810093>
- [14] Depreux P, Lesieur D, Mansour HA, Morgan P, Howell HE, Renard P, et al. Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands. *Journal of Medicinal Chemistry*. 1994;**37**(20):3231-3239. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00046a006>
- [15] Langlois M, Bremont B, Shen S, Poncet A, Andrieux J, Sicsic S, et al. Design and synthesis of new naphthalenic derivatives as ligands for 2-^[125I] iodomelatonin binding sites. *Journal of Medicinal Chemistry*. 1995;**38**(12):2050-2060. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00012a004>
- [16] Garratt PJ, Travard S, Vonhoff S, Tsotinis A, Sugden D. Mapping the melatonin receptor. 4. Comparison of the binding affinities of a series of substituted Phenylalkyl amides. *Journal of Medicinal Chemistry*. 1996;**39**(9):1797-1805. Available from: <http://pubs.acs.org/doi/abs/10.1021/jm9508189>
- [17] Plieninger H. The chemistry of indoles. *Organic chemistry, a series of monographs*, Vol. 18. Von R. J. Sundberg. Academic Press, New York–London 1970. 1. Aufl., X, 489 S., s229/—.
- Angewandte Chemie. 1971;**83**(9): 338-338. Available from: <http://doi.wiley.com/10.1002/ange.19710830918>
- [18] Gribble GW. Recent developments in indole ring synthesis—Methodology and applications. *Contemporary Organic Synthesis*. 1994;**1**(3): 145-172. Available from: <http://xlink.rsc.org/?DOI=CO9940100145>
- [19] Gribble GW. Recent developments in indole ring synthesis—Methodology and applications. *Journal of the Chemical Society, Perkin Transactions 1*. 2000;**1**(7):1045-1075. Available from: <http://xlink.rsc.org/?DOI=a909834h>
- [20] Frohn MA, Seaborn CJ, Johnson DW, Phillipou G, Seamark RF, Matthews CD. Structure - activity relationship of melatonin analogues. *Life Sciences*. 1980;**27**(22): 2043-2046. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0024320580904828>
- [21] Heward CB, Hadley ME. Structure-activity relationships of melatonin and related indoleamines. *Life Sciences*. 1975;**17**(7):1167-1177. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0024320575903409>
- [22] Leclerc V, Fourmaintraux E, Depreux P, Lesieur D, Morgan P, Howell HE, et al. Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands. *Bioorganic & Medicinal Chemistry*. 1998;**6**(10):1875-1887. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0968089698001473>
- [23] Fukatsu K, Uchikawa O, Kawada M, Yamano T, Yamashita M, Kato K, et al. Synthesis of a novel series of benzocycloalkene derivatives as melatonin receptor agonists. *Journal of Medicinal Chemistry*. 2002;**45**(19):4212-4221. Available from: <https://pubs.acs.org/doi/10.1021/jm020114g>

- [24] Spadoni G, Mor M, Tarzia G. Structure-affinity relationships of indole-based melatonin analogs. *Neurosignals*. 1999;**8**(1-2):15-23. Available from: <https://www.karger.com/Article/FullText/14564>
- [25] Garratt PJ, Jones R, Rowe SJ, Sugden D. Mapping the melatonin receptor. 1. The 5-methoxyl group of melatonin is not an essential requirement for biological activity. *Bioorganic & Medicinal Chemistry Letters*. 1994;**4**(13):1555-1558. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960894X01805655>
- [26] Garratt PJ, Vonhoff S, Rowe SJ, Sugden D. Mapping the melatonin receptor. 2. Synthesis and biological activity of indole derived melatonin analogues with restricted conformations of the C-3 amidoethane side chain. *Bioorganic & Medicinal Chemistry Letters*. 1994;**4**(13):1559-1564. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960894X01805667>
- [27] Garratt PJ, Jones R, Tocher DA, Sugden D. Mapping the melatonin receptor. 3. Design and synthesis of melatonin agonists and antagonists derived from 2-Phenyltryptamines. *Journal of Medicinal Chemistry*. 1995;**38**(7):1132-1139. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00007a010>
- [28] Sugden D, Rowe SJ. 2-Iodo-*N*-butanoyl-5-methoxytryptamine: A potent melatonin receptor agonist. *Pharmacology Communications*. 1994;**4**:267-276
- [29] Mathé-Allainmat M, Gaudy F, Sicsic S, Dangy-Caye A-L, Shen S, Brémont B, et al. Synthesis of 2-amido-2,3-dihydro-1*H*-phenalene derivatives as New Conformationally restricted ligands for melatonin receptors. *Journal of Medicinal Chemistry*. 1996;**39**(16):3089-3095. Available from: <https://pubs.acs.org/doi/10.1021/jm960219h>
- [30] Spadoni G, Balsamini C, Diamantini G, Di Giacomo B, Tarzia G, Mor M, et al. Conformationally restrained melatonin analogues: Synthesis, binding affinity for the melatonin receptor, evaluation of the biological activity, and molecular Modeling study. *Journal of Medicinal Chemistry*. 1997;**40**(13): 1990-2002. Available from: <https://pubs.acs.org/doi/10.1021/jm960651z>
- [31] Flaugh ME, Crowell TA, Clemens JA, Sawyer BD. Synthesis and evaluation of the antioviulatory activity of a variety of melatonin analogs. *Journal of Medicinal Chemistry*. 1979;**22**(1):63-69. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00187a015>
- [32] Sugden D, Chong NWS, DFV L. Structural requirements at the melatonin receptor. *British Journal of Pharmacology*. 1995;**114**(3):618-623. Available from: <http://doi.wiley.com/10.1111/j.1476-5381.1995.tb17184.x>
- [33] Li JJ. Batcho-Leimgruber indole synthesis. In: *Name Reactions*. Cham: Springer International Publishing; 2014. pp. 34-35. Available from: http://link.springer.com/10.1007/978-3-319-03979-4_17
- [34] Repke DB, Ferguson WJ. Psilocin analogs. III. Synthesis of 5-methoxy- and 5-hydroxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles. *Journal of Heterocyclic Chemistry*. 1982;**19**(4): 845-848. Available from: <http://doi.wiley.com/10.1002/jhet.5570190428>
- [35] Ates-Alagoz Z, Buyukbingol Z, Buyukbingol E. Synthesis and antioxidant properties of some indole ethylamine derivatives as melatonin analogs. *Die Pharmazie*. 2005 Sep;**60**(9):643-647
- [36] Righi M, Topi F, Bartolucci S, Bedini A, Piersanti G, Spadoni G. Synthesis of tryptamine derivatives via a direct, one-pot reductive alkylation

of indoles. *The Journal of Organic Chemistry*. 2012;77(14):6351-6357. Available from: <https://pubs.acs.org/doi/10.1021/jo3010028>

[37] Hu Y, Ho MKC, Chan KH, New DC, Wong YH. Synthesis of substituted *N*-[3-(3-methoxyphenyl)propyl] amides as highly potent MT₂-selective melatonin ligands. *Bioorganic & Medicinal Chemistry Letters*. 2010;20(8):2582-2585. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960894X10002842>

[38] Tsotinis A, Kompogennitaki R, Papanastasiou I, Garratt PJ, Bocianowska A, Sugden D. Fluorine substituted methoxyphenylalkyl amides as potent melatonin receptor agonists. *Medicinal Chemistry Communications*. 2019;10(3):460-464. Available from: <https://pubs.rsc.org/en/content/articlelanding/2019/md/c8md00604k>

[39] Tsotinis A, Afroudakis PA, Davidson K, Prashar A, Sugden D. Design, synthesis, and melatonergic activity of New Azido- and isothiocyanato-substituted indoles. *Journal of Medicinal Chemistry*. 2007;50(25):6436-6440. Available from: <https://pubs.acs.org/doi/10.1021/jm7010723>

[40] Dubocovich ML, Rajadhyaksha VJ, Helmy AA. 2-Aryl *N*-acetyltryptamines and Process of Preparing Such. US 528334; 1994

[41] Tsotinis A, Afroudakis P. Melatonin receptor antagonist luzindole: A facile new synthesis. *Letters in Organic Chemistry*. 2008;5(6):507-509. Available from: <http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1570-1786&volume=5&issue=6&spage=507>

[42] Hammond ML, Zambias RA, Chang MN, Jensen NP, McDonald J, Thompson K, et al. Antioxidant-based

inhibitors of leukotriene biosynthesis. The discovery of 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, a potent topical antiinflammatory agent. *Journal of Medicinal Chemistry*. 1990;33(3):908-918. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00165a005>

[43] Hardeland R. Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders. *Current Opinion in Investigational Drugs*. 2009;10(7):691-701

[44] Yous S, Andrieux J, Howell HE, Morgan PJ, Renard P, Pfeiffer B, et al. Novel naphthalenic ligands with high affinity for the melatonin receptor. *Journal of Medicinal Chemistry*. 1992;35(8):1484-1486. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm00086a018>

[45] Li P-K, Chu G-H, Gillen ML, Parekh T, Witt-Enderby PA. The development of a charged melatonin receptor ligand. *Bioorganic & Medicinal Chemistry Letters*. 1997;7(18):2409-2414. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960894X97004447>

[46] Norman TR, Olver JS. Agomelatine for depression: Expanding the horizons? *Expert Opinion on Pharmacotherapy*. 2019;20(6):647-656. Available from: <https://www.tandfonline.com/doi/full/10.1080/14656566.2019.1574747>

[47] Tsotinis A, Panoussopoulou M, Sivananthan S, Sugden D. Synthesis of new tricyclic melatonergic ligands. *Il Farmaco*. 2001;56(9):725-729. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0014827X01011259>

[48] El Kazzouli S, Griffon du Bellay A, Berteina-Raboin S, Delagrangé P, Caignard D-H, Guillaumet G. Design and synthesis of 2-phenylimidazo[1,2-*a*]pyridines as a novel class of melatonin

- receptor ligands. *European Journal of Medicinal Chemistry*. 2011;**46**(9): 4252-4257. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S022352341100506X>
- [49] Viaud-Massuard M-C, Mazéas D, Guillaumet G. Synthesis of new melatonineric ligands including azaindole moiety. *Heterocycles*. 1999;**50**(2):1065. Available from: <http://www.heterocycles.jp/newlibrary/libraries/abst/07243>
- [50] Jeanty M, Suzenet F, Delagrange P, Nosjean O, Boutin JA, Caignard DH, et al. Design and synthesis of 1-(2-alkanamidoethyl)-6-methoxy-7-azaindole derivatives as potent melatonin agonists. *Bioorganic & Medicinal Chemistry Letters*. 2011;**21**(8):2316-2319. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960894X11002812>
- [51] Faust R, Garratt PJ, Jones R, Yeh L-K, Tsotinis A, Panoussopoulou M, et al. Mapping the melatonin receptor. 6. Melatonin agonists and antagonists derived from 6*H*-isoindolo[2,1-*a*]indoles, 5,6-dihydroindolo[2,1-*a*]isoquinolines, and 6,7-dihydro-5*H*-benzo[*c*]azepino[2,1-*a*]indoles. *Journal of Medicinal Chemistry*. 2000;**43**(6):1050-1061
- [52] Uchikawa O, Fukatsu K, Tokunoh R, Kawada M, Matsumoto K, Imai Y, et al. Synthesis of a novel series of tricyclic indan derivatives as melatonin receptor agonists. *Journal of Medicinal Chemistry*. 2002;**45**(19):4222-4239. Available from: <https://pubs.acs.org/doi/10.1021/jm0201159>
- [53] Xiao S, Chen C, Li H, Lin K, Zhou W. A novel and practical synthesis of Ramelteon. *Organic Process Research & Development*. 2015;**19**(2):373-377. Available from: <https://pubs.acs.org/doi/10.1021/op500386g>
- [54] Sugden D, Davies DJ, Garratt PJ, Jones R, Vonhoff S. Radioligand binding affinity and biological activity of the enantiomers of a chiral melatonin analogue. *European Journal of Pharmacology*. 1995;**287**(3): 239-243. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0014299995004890>
- [55] Tsotinis A, Panoussopoulou M, Hough K, Sugden D. Synthesis and biological evaluation of new β,β' -disubstituted 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl ethylamido melatonineric ligands. *European Journal of Pharmaceutical Sciences*. 2003;**18**(5):297-304. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0928098703000204>
- [56] Tsotinis A, Panoussopoulou M, Eleutheriades A, Davidson K, Sugden D. Design, synthesis and melatonineric activity of new unsubstituted and β,β' -difunctionalised 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-6-alkanamides. *European Journal of Medicinal Chemistry*. 2007;**42**(7):1004-1013. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0223523407000372>
- [57] Tsotinis A, Vlachou M, Papahatjis D, Nikas S, Sugden D. An efficient synthesis of simple β,β -Cyclobisalkylated Melatonineric Phenylalkylamides. *Letters in Organic Chemistry*. 2007;**4**(2):92-95. Available from: <http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1570-1786&volume=4&issue=2&spage=92>
- [58] Tsotinis A, Vlachou M, Papahatjis DP, Calogeropoulou T, Nikas SP, Garratt PJ, et al. Mapping the melatonin receptor. 7. Subtype selective ligands based on β -substituted *N*-Acyl-5-methoxytryptamines and β -substituted *N*-Acyl-5-methoxy-1-methyltryptamines. *Journal of Medicinal Chemistry*. 2006;**49**(12):3509-3519. DOI: 10.1021/jm0512544