Melatonergic drugs in development

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Abstract: Melatonin (N-acetyl-5-methoxytryptamine) is widely known as “the darkness hormone”. It is a major chronobiological regulator involved in circadian phasing and sleep-wake cycle in humans. Numerous other functions, including cyto/neuroprotection, immune modulation, and energy metabolism have been ascribed to melatonin. A variety of studies have revealed a role for melatonin and its receptors in different pathophysiological conditions. However, the suitability of melatonin as a drug is limited because of its short half-life, poor oral bioavailability, and ubiquitous action. Due to the therapeutic potential of melatonin in a wide variety of clinical conditions, the development of new agents able to interact selectively with melatonin receptors has become an area of great interest during the last decade. Therefore, the field of melatonergic receptor agonists comprises a great number of structurally different chemical entities, which range from indolic to nonindolic compounds. Melatonergic agonists are suitable for sleep disturbances, neuropsychiatric disorders related to circadian dysphasing, and metabolic diseases associated with insulin resistance. The results of preclinical studies on animal models show that melatonin receptor agonists can be considered promising agents for the treatment of central nervous system-related pathologies. An overview of recent advances in the field of investigational melatonergic drugs will be presented in this review.

Keywords: MT1/MT2 ligands, circadian rhythms, melatonin

Introduction
Melatonin (MLT), N-acetyl-5-methoxytryptamine (Figure 1), a product of tryptophan metabolism, is the main secretory product of the pineal gland.1 Its release follows a marked circadian rhythm, governed by the central circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus, the highest levels occurring during the period of darkness.2 While MLT concentrations found in circulating plasma and cerebrospinal fluid are almost exclusively of pineal origin, MLT seemed to be also produced in other tissues, such as retina,3,4 lymphocytes,5 and gastrointestinal tract,6,7 but the papers claiming this had no convincing sequel. Tryptophan serves as the precursor for the biosynthesis of MLT. It is converted into serotonin via 5-hydroxytryptophan. Serotonin (5-HT) is then acetylated to form N-acetylserotonin by arylalkylamine N-acetyltransferase, which has also been called “the timezyme”, since N-acetylation of serotonin is usually regarded as the rate-limiting step of MLT formation, and determinant of its circadian rhythm.8 N-acetylserotonin is then converted to MLT by hydroxyindole-O-methyltransferase. In the mammalian pineal gland, MLT biosynthesis is synchronized to the light/dark cycle by the SCN, which receives its input from the retinohypothalamic tract. Special photoreceptive retinal ganglion cells, containing...
The effects of MLT on the Plasmodium cell cycle were first described by Hotta et al in a work that demonstrated that the synchronization of parasite development is lost in pinealectomized mice, but restored when MLT is administered. The effects of MLT in Plasmodium falciparum were extensively evaluated in several works, which revealed a complex signaling pathway. MLT seems to have a central role in the control of parasite replication and the establishment of parasitemia. Therefore, targeting and blocking this
hormone pathway can contribute to the discovery of new antimalarial drugs.

**Melatonergic drugs in clinical and preclinical practice**

As MLT exhibits both hypnotic and chronobiotic properties, it has been used for the treatment of age-related insomnia, as well as of other primary and secondary insomnia. A recent consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia, and circadian rhythm sleep disorders, concluded that MLT is the first-choice treatment when a hypnotic is indicated in patients >55 years. MLT has also been used successfully for the treatment of sleep problems related to perturbations of the circadian timekeeping system, like those caused by jetlag, shift work disorder, and delayed sleep phase syndrome. Unfortunately, a substitution therapy is not easily achieved with MLT. The major obstacle for the purposes of treatment is its rapid elimination from the circulation. Its half-life in the blood varies from less than 30 minutes to (maximally) about 45 minutes. Various factors contribute to its relatively poor bioavailability, such as uptake, hepatic first-pass metabolism; also, perhaps, transient loading to the gastrointestinal tract. Therefore, if only a chronobiotic action is desired (ie, induction of phase shifts to readjust the circadian oscillator system), MLT may be fully effective. However, if the restitution of a complete nocturnal peak would be desired, the clinical outcome with the rapidly-metabolized, natural hormone remains relatively poor. The development of either prolonged-release formulations of the natural hormone, or melatonergic drugs of longer half-life, represents two different solutions to this problem. In 2007, a prolonged-release formulation of MLT (Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) was approved in Europe by the European Medicines Agency (EMEA) for the treatment of insomnia in patients aged >55 years. It was licensed on the basis of the combination of improvement of sleep quality and next-day feeling. Although this formulation improves several sleep parameters by statistical measures, its efficacy is below that of conventional hypnotics. However, it has the advantage of being devoid of the typical side effects of benzodiazepines, such as next-day hangover, withdrawal effects, and dependence liability. Another obstacle for the clinical use of MLT is the lack of selectivity for the different biological targets, including MT₁ and MT₂ receptors. These difficulties should be overcome with the development of selective melatonergic ligands, with improved properties. Numerous patents claiming the use of melatonergic agonists, mostly for the treatment of sleep disorders, have been filed in the past decade. Melatonergic drugs now used in therapy (ramelteon and agomelatine), as well as the most advanced melatonergic ligands under clinical evaluation (tasimelteon and TIK-301) (Figure 2), will be described below.

**Ramelteon**

Ramelteon (Rozerem®, TAK-375, Takeda Pharmaceutical Co, Osaka, Japan) (Figure 2) was the first melatonergic agonist approved for human use. In 2005, it was licensed by the US Food and Drug Administration (FDA) for the treatment of insomnia. It is a tricyclic, synthetic analog of MLT with the chemical name of (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)-ethyl]propionamide. In vitro binding studies have shown that ramelteon’s affinity for MT₁ (Kᵢ = 0.014 nM) and MT₂ (Kᵢ = 0.112 nM) receptors is 3 to 16 times greater than for MLT. The selectivity of ramelteon for MT₁ has been found to be greater than for MT₂, thus suggesting that it targets sleep onset more specifically than MLT itself does. Ramelteon does not bind with substantial affinity to quinone reductase 2, and seems to have no influence on calmodulin-dependent actions, as is known of MLT. It has negligible affinities to the majority of serotonin receptors, except for a rather moderate binding to 5-HT₁A (pKᵢ = 5.25), and to gamma-aminobutyric acid, dopamine, norepinephrine, acetylcholine, and opiate receptors. When compared to MLT, ramelteon has a higher lipophilicity. Therefore, it is more easily taken up and retained by tissues. Ramelteon is usually administered by the oral route at a dose of 8 mg, or 4 mg in elderly subjects, and is rapidly absorbed by the gastrointestinal tract, with an absorption rate, under fasting conditions, of about 84%. It is characterized by a half-life of 0.83–1.93 hours, which is indeed longer than that of MLT (20–30 minutes). Ramelteon undergoes extensive liver metabolism via oxidation to hydroxyl and carbonyl groups, and is then conjugated with glucuronide. Cytochrome P450 isoenzyme CYP1A2 is the major hepatic enzyme involved in ramelteon metabolism. The major metabolite is a product of ω-1 hydroxylation in the propionamide side chain. Although the activity of the major metabolite is 30-fold lower than that of ramelteon, its serum levels are 20 to 100-fold higher than those of the parent drug, suggesting that it may significantly improve several sleep parameters by statistical measures, its efficacy is below that of conventional hypnotics. However, it has the advantage of being devoid of the typical side effects of benzodiazepines, such as next-day hangover, withdrawal effects, and dependence liability. Another obstacle for the clinical use of MLT is the lack of selectivity for the different biological targets, including MT₁ and MT₂ receptors. These difficulties should be overcome with the development of selective melatonergic ligands, with improved properties. Numerous patents claiming the use of melatonergic agonists, mostly for the treatment of sleep disorders, have been filed in the past decade. Melatonergic drugs now used in therapy (ramelteon and agomelatine), as well as the most advanced melatonergic ligands under clinical evaluation (tasimelteon and TIK-301) (Figure 2), will be described below.

![Figure 2 Structures of melatonergic ligands in clinical and preclinical practice.](https://www.dovepress.com/doi-press)
contribute to the overall clinical effect of ramelteon. Like MLT, ramelteon exerts its direct sleep-inducing effects via MT$_1$ receptors located in the SCN, while inducing phase shifting mainly via MT$_2$ receptors. In all clinical studies undertaken so far to evaluate the efficacy and safety of ramelteon in various doses ranging from 4–32 mg/day in patients with chronic insomnia, the drug reduced sleep onset latency and increased sleep duration.\cite{64,65} Besides acting as a sedative-hypnotic drug, ramelteon also exhibited chronobiotic properties.\cite{66} Interestingly, impairment of MLT rhythm may play a role in the development of sleep disturbances and delirium in critically ill patients, and it seems that MLT replenishment could decrease the incidence of these phenomena.\cite{67} Evidence of the association between MLT and delirium is limited.\cite{68} Studies of the effects of ramelteon in delirium have been recently reported.\cite{69}

**Agomelatine**

Another approved melatonergic drug is agomelatine (Valdoxan\cite{63}; S20098, Servier Laboratories, Neuilly-sur-Seine, France) (Figure 2), the naphthalene analogue of MLT, which is licensed in Europe by EMEA for the treatment of major depressive episodes in adults. Agomelatine is a potent MT$_1$ and MT$_2$ agonist (with p$K_i$ values of 10.21 and 9.57, respectively), which displays antagonist behavior at 5-HT$_2C$ serotonin receptors (p$K_i$=6.68).\cite{70} It does not show any significant affinities for muscarinic, histaminergic, adrenergic, or dopaminergic receptor subtypes.\cite{71} The blockade of 5-HT$_2C$ receptors has been interpreted to explain the direct antidepressant actions of agomelatine.\cite{72} This action should be distinguished from its indirect melatonergic actions related to adjustments of circadian rhythms, which are effective in subtypes of depression having an etiology of circadian dysfunction. A synergistic interaction of melatonergic and 5-HT$_2C$-signaling mechanisms has been assumed, to explain the direct antidepressant action of this drug.\cite{73} The stimulation of both melatonin receptors and the blockade of 5-HT$_2C$ seem to be essential for the antidepressant effect of agomelatine.\cite{74} It has been hypothesized that, through this dual action, agomelatine may promote and maintain sleep at night, and help to maintain alertness during daytime. Agomelatine given before sleep would have an immediate sleep-promoting melatonergic effect, which would prevail over its potentially hypnotic 5-HT$_2C$-antagonism. In contrast, during the day, the drug antagonism towards 5-HT$_2C$ receptors would predominate over the melatonergic action, thus having an alerting action.\cite{75} Agomelatine has a short half-life (~2 hours) in humans. It is absorbed rapidly by the oral route and is metabolized in the liver by cytochrome P450 isoenzymes CYP1A2, CYP2C9, 3-Hydroxy-, 3-hydroxy-7-methoxy-, and 7-Demethyl-agomelatine (S20098) were identified as the three metabolites of agomelatine.\cite{76,77} Agomelatine has been also shown to display robust anxiolytic properties, which seem to be superior to those of MLT and which may, again, be explained by a concerted action of melatonergic stimulation and 5-HT$_2C$-inhibition.\cite{78}

In a recent study, agomelatine has been used successfully for treating patients with migraine attacks. Agomelatine administered to patients suffering from migraine attacks (in doses of 25 mg/day for a duration of 6 months) decreased both the frequency and duration of migraine attacks; thus, it reduced the intensity of pain in migraine patients. Moreover, it also reduced significantly the severity of depression and normalized sleep disturbances.\cite{79}

**Melatonin ligands under clinical evaluation**

**Melatonin agonists**

The two nonselective MT$_1$/MT$_2$ agonists tasimelteon and TIK-301 are the most advanced melatonergic drug candidates undergoing clinical trials for the treatment of sleep disorders.

Tasimelteon (VEC-162, BMS-214778, MA-1) (Figure 2) is an orally bioavailable melatonergic drug that has been clinically tested, to phase III, by Vanda Pharmaceuticals Inc (Washington, DC, USA), under license from Bristol-Myers Squibb Co (New York, USA).\cite{80,81} It has a slightly lower affinity to MT$_1$ (p$K_i$=9.45) and a moderately higher affinity than MLT to MT$_2$ (p$K_i$=9.80). No substantial interactions with receptors for other neurotransmitters or neuromodulators, or with other melatonin binding sites have been observed or reported. In some pre-clinical and exploratory trials, the compound has been also tested for antidepressive effects, although no antagonist properties at 5-HT$_2C$ receptors are obvious. In humans, time to maximum plasma concentration (T$_{max}$) values varied from 1.9 to 3.0 hours, with considerable interindividual deviations. Tasimelteon is extensively metabolized by CYP1A2 and CYP3A4 enzymes. It is metabolized by oxidation, resulting in the opening of the dihydofuran ring, followed by further oxidation to carboxylic acid. The major phase II metabolic route is glucuronidation. In the phase III study, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset.\cite{82} Recently, in May 2013, Vanda Pharmaceuticals submitted a new drug application to the FDA, for tasimelteon, for the treatment of...
non-24-hour sleep–wake disorder in subjects suffering total blindness. It is the first FDA-approved medication for this orphan indication. Tasimelteon is recommended for use at a dosage of 20 mg/day, taken before bedtime (at the same time every night), without food.

Vanda Pharmaceuticals intends to launch the drug under the brand name Hetlioz™ in the second quarter of 2014. The same company has also evaluated the use of tasimelteon for the treatment of insomnia in phase II and III studies, while it discontinued development of tasimelteon for the treatment of major depressive disorders in January 2013, after top-line results from a phase III study failed to meet the primary endpoint.

TIK-301 (LY 156735; β-methyl-6-chloromelatonin) (Figure 2) is a melatonergic agonist originally developed by Eli Lilly and Co (Indianapolis, IN, USA) that is now sublicensed to Tikvah Therapeutics Inc. (Atlanta, GA, USA). TIK-301 has received an orphan drug designation by FDA for the treatment of sleep disorders in individuals.

It displays a high affinity towards MT₁ and MT₂ receptors; its affinity for MT₁ receptors (pKᵢ=10.09) is similar to that of melatonin, and even higher for MT₂ (pKᵢ=10.38). The preferential binding to MT₂ is a typical feature of 6-chlorinated melatonin derivatives, and is also observed with 6-chloromelatonin. The half-life of TIK-301 has been reported to be in the range of 1 hour. This only moderately extended action is somewhat surprising, because TIK-301 carries a chlorine atom at position 6 of the indolic moiety, which prevents 6-hydroxylation (ie, degradation) via the major catabolic route of MLT. When tested for its soporific properties, the outcome has been relatively moderate, despite some statistically demonstrable effects. TIK-301 has been reported to also combine properties as a melatonergic agonist and serotonergic antagonist, at both receptor subtypes 5-HT₂c and 5-HT₂, opening new perspectives for its possible antidepressant action.

Melatonergic antagonists

MLT receptor antagonists have only been evaluated in pre-clinical studies; for example, luzindole (N-0774; 2-benzyl-N-acetyltryptamine) for its antidepressant-like effect, S22153 in circadian rhythm entrainment experiments, and ML-23 in the treatment of Parkinson’s disease.

Melatonergic ligands in development

Although the functions of MLT in the body are numerous and extensive, its role in entraining circadian rhythms to the light-dark cycle is probably the best known. Probably for this reason, the effort of most laboratories has been focused upon developing melatonergic drugs for the treatment of circadian pathologies (ie, sleep disturbances or seasonal affective disorders). Thus, during the past decade, a great number of structurally different MLT receptor ligands, which range from simple indole derivatives and their bioisosteres to phenylalkyl amides, and constrained melatonergic agents, have been reported in the literature. According to the guidelines of the International Union of Basic and Clinical Pharmacology, a selective ligand should display at least 50–100 times greater binding affinity and/or potency for one receptor subtype, relative to the other. Applying these criteria, compounds with moderate, approximately ten to 50-fold selectivity and agents showing just two to ten-fold preference for one of the melatonin receptor subtypes are considered to be nonselective. Below, the most recent and interesting melatonergic ligands will be briefly reported (Figure 3).

Nonselective MT₁/MT₂ melatonergic ligands

Most of the melatonergic ligands are not able to distinguish between MT₁ and MT₂ receptors, or they show just a preference in binding affinity for one of the subtypes (eg, maximally 50-fold selectivity). Their structures range from bioisosteric MLT analogs, obtained by exchange of the indole nucleus with others (mostly heteroaromatic rings), to ring-opened derivatives and conformationally constrained analogues. Recently, bioisoteric relationships between the indole nucleus and both 4-azaindole and indene nuclei have been demonstrated. Actually, 4-azametatonin (Figure 3-1) has shown identical MT₁ (Kᵢ=0.24 nM) and MT₂ (Kᵢ=0.36 nM) binding affinities to MLT, for receptors expressed in HEK-293 cells, while indene (Figure 3-2) showed indeed five to ten times higher affinities than MLT, in both receptor subtypes, expressed in CHO cells. Moreover, regarding bioisoteric substitutions of the indole nucleus, a series of chiral phenoxylalkyl and phenylthioalkyl amides have been always reported.

This study provided compounds with nanomolar affinity for both MT₁ receptor subtypes, expressed in NIH3T3 cells. The (S)-enantiomers behave as eutomers at both MT₁ and MT₂ receptors. The highest stereoselectivity was observed for the thioanalog shown in Figure 3-3a (Kᵢ distomer/Kᵢ eutomer ratio: 457, for MT₁ receptors). Of particular interest, the (S)-compound shown in Figure 3-3b displayed binding affinity for MT₁ receptors (pKᵢ=9.14), close to that of MLT, behaving as a full agonist in [³⁵S]GTP/S binding assay. Recently, new series of tricyclic analogues, obtained by the insertion of the methoxy group into a ring, have been reported as MLT...
ligands. Some of the newly synthesized compounds showed higher binding affinity at both receptors than MLT itself. Compounds 4a and 4b in Figure 3 were the most interesting derivatives. Functional activity studies showed full agonist activity of these compounds with half maximal effective concentration in the nanomolar range. MLT ligands with the N-acylaminoethyl side chain partly incorporated into a ring have been frequently reported, as in compounds 5a and 5c in Figure 3.

Selective MT₂ melatonergic ligands
Numerous efforts to develop selective MT₁ or MT₂ ligands have been also reported. Selectivity towards MT₂ is much easier to accomplish than for MT₁, and many series of MT₂-selective ligands have been studied. 4-P-PDOT (4-phenyl-2-propionamidotetralin) is a well-known, highly MT₂-selective antagonist, displaying 330 times greater affinity for MT₂ (Kᵢ=1.5 nM) than for MT₁ (Kᵢ=501 nM), in receptors expressed in COS-7 cells. 4-P-PDOT exists in the form of four stereoisomers, a pair of cis and a pair of trans enantiomers. Only recently, all four single stereoisomers of 4-P-PDOT have been separated and pharmacologically evaluated at receptors expressed in NIH3T3 cells, in terms of their binding affinities and intrinsic activities (GTPγS assay). The euomer for (+/-)-cis-4-P-PDOT is the (+)-(2S,4S) enantiomer shown in Figure 3-6,
displaying ~170-fold greater affinity for MT₁ than for MT₂ receptors, and 15% and 45% intrinsic activity at MT₁ and MT₂, relative to MLT. The (~)-2R,4R mirror image shows ~3 times less agonist potency. A few years ago, a series of benzothiophene analogs was evaluated at receptors expressed in CHO cells. Acetamide (Figure 3-7a) and allyl carbamoyl (Figure 3-7b) displayed 65.5- and 220-fold selectivity towards MT₂ receptors, respectively. Both ligands were demonstrated to be MT₂ selective agonists. A high selectivity against MT₁ was obtained by modifying the compound shown in Figure 3-2, to obtain the compound shown in Figure 3-8, which showed a 1,200-fold MT₂ selectivity, when evaluated at MLT receptors expressed in CHO cells.³⁴

Selective MT₁ melatonergic ligands

Development of MT₁-selective ligands is still a challenge, and only a few examples of selective compounds have been reported so far. Preferential binding to MT₁ receptors is, at maximum, ~100 times higher for MT₁ than for MT₂. A ~10-fold selectivity towards MT₁ receptors was found for the compounds shown in Figure 3-9a and 9b. Compound 9b behaves as an MT₁/MT₂ agonist in a cAMP assay, at receptors expressed in CHO cells. Recently, a series of dimeric ligands has been designed. The most interesting compounds were those shown as 10a and 10b (Figure 3). In particular, analogue 11b exhibited the highest MT₁ affinity (3.4 nM) and was 54 times more selective for MT₁ than for MT₂ receptors. Both compounds behave as partial MT₁/MT₂ agonists, as assessed through [³⁵S]GTPγS binding analysis. A structurally-related series of N-(anilinoalkyl)amides, bearing 3-arylalkylxoyl substituents, was also examined. The highest selectivity was found for compound 11 (Figure 3), which was 78-fold more selective towards MT₁ (MT₁: \( K_i = 1.17 \) nM; MT₂: \( K_i = 91.2 \) nM), acting as a partial agonist at both receptor subtypes.

Investigational melatonergic drugs

Melatonin receptor agonists offer promising possibilities for treating neurological and sleep disorders related to circadian dysfunction, and other disorders, such as various subtypes of depression and anxia, and metabolic diseases. This paragraph summarizes progress in the development of melatonergic drugs (Figure 4). However, it should be noted that investigational melatonergic drugs have been mainly characterized with regard to MT₁ and MT₂ receptors, whereas data on interference with other signaling pathways and on other melatonin binding sites are mostly missing or have, at least, not been disclosed. To date, it is difficult to judge whether an absence of effects mediated by binding sites different from the MTL membrane receptors represents a disadvantage, or the advantage of higher drug specificity, relative to MLT. There is increasing evidence that MLT plays an important role in modulating learning and memory processing. For example, MLT facilitates memory performance in the novel object recognition (NOR) task and water-maze task in rats. Neu-P11 is an MT₁/MT₂ receptor agonist and a serotonin 5-HT₁A receptor agonist, recently developed for the treatment of insomnia. Neu-P11 has been shown to promote sleep, improve insulin sensitivity, and exert antidepressant and anxiolytic activities in rodent models. Recent studies have demonstrated that Neu-P11 enhances memory performance in the NOR task in rats, and improves neuronal and cognitive impairments in a rat model of AD (induced by intrahippocampal Aβ(1–42) injection), thus proposing Neu-P11 as a novel agent for the treatment of AD. Recently, a new 1-N substituted melatonin analog, M3C has been proposed for the treatment of anxiety. It has been demonstrated to be effective as an anxiolytic-like agent in pinealectomized rats, at doses lower than any other melatonin analogues previously reported. Data suggest that the anxiolytic properties of M3C may be mediated by MT₁ and MT₂ receptors. Evidence of the oncostatic properties of MLT in hormone-dependent breast cancer is stimulating research for synthetic molecules useful in breast cancer therapy. In the last few years, two nonselective benzofuran MT₁/MT₂ melatonin receptor agonists (S23219-1 and S23478-1) have been tested for their in vitro and in vivo antitumoral activity, and it has been determined that these compounds are more effective than MLT in inhibiting proliferation and promoting apoptosis of MCF-7 cells, as well as in inducing regression of N-nitroso-N-methylurea- (NMU) induced rat mammary tumors. The moderately MT₂-selective partial agonist UCM765 has been reported to promote non-rapid eye movement sleep (NREMS) in rats and mice. This effect is nullified by the pharmacological blockage or genetic deletion of MT₂ receptors. Remarkably, the effects of this ligand on sleep are different from those of nonselective MT₁/MT₂ agonists. For example, the structurally-related MT₁/MT₂ agonist UCM793 slightly decrease sleep onset, without effect.
on NREMS maintenance, similar to ramelteon, indicating that dual MT₁/MT₂ agonistic activity accounts for the effect on sleep onset, whereas selectivity for MT₂ receptors has an additional effect on NREMS maintenance. Because of the selective promotion of NREMS, MT₂ receptors could become an interesting future target for the treatment of sleep disorders. Preliminary data were also reported concerning anxiolytic effects of UCM765 in rats. Recent studies were aimed at understanding how MLT influences the quality of the three vigilance states of sleep in adult Sprague-Dawley male rats. The effects of MLT on 24-hour vigilance states were studied and compared with those produced by UCM793 and a selective MT₁ receptor partial agonist (UCM924). UCM924 has the same binding profile as the MT₁ receptor, but, unlike UCM765, it is more metabolically stable, thus showing a longer half-life. In particular, UCM924 has the free phenyl ring of UCM765 protected by a fluorine, and the methoxy group is bioisosterically replaced with bromine. The authors demonstrated that the three compounds do not increase the quantity of sleep, but differently influence the quality of the three vigilance states. Studies also demonstrated that selective activation of MT₂ receptors increases NREMS duration more than do MLT and nonselective MT₁/MT₂ receptors. Thus, selective MT₁ receptor agonists have high potential to be further developed as novel hypnotic agents. Recently, new melatonin-related compounds were developed to modulate the human malaria parasite cell cycle and block the parasite’s development, acting as antimalarials. These novel indole derivatives showed very significant antimalarial activity, opening good perspectives for the development of new drugs with novel mechanisms of action. Recently, a new MLT agonist (Figure 3-3c), displaying potent antioxidant activity and strong cytoprotective activity against H₂O₂-induced cytotoxicity, has been reported. The same compound has been shown to perform as a Ca²⁺/calmodulin-dependent kinase II (CaMKII) inhibitor. This compound, which presents both of these characteristics, should be a valid candidate for further investigations. In fact, both antioxidant and CaMKII-inhibiting properties might prove beneficial in neurodegenerative disorders. Thus, it should be very useful to obtain an MLT analogue that shows antioxidant capability and, at the same time, inhibits CaMKII, since this is, in turn, an important source of oxidative stress.

**Conclusion**

Recent advances in the field of melatonergic drugs have been reported in this review, focusing on agents in therapy, as well as new MT₁/MT₂ ligands in development. Many of the current melatonergic drugs used in therapy or in clinical development, indicated for the treatment of depression (agomelatine) and sleep disorders (ramelteon, tasimelteon, TIK-301), have dual action; for example, agomelatine for MT₁/MT₂ and 5-HT₂C, TIK-301 for MT₁/MT₂, and 5-HT₂C/5-HT₃. Therefore, drug therapies targeted at multiple receptors seem to be preferable to those selective for one type of receptor. Most researchers have pursued high affinity for a single therapeutic target, combined with high selectivity, believing that this will maximize efficacy, minimize side effects, and give the drug a therapeutic window. However, this view has been challenged in recent years, with the introduction of the concept of polypharmacology. It has been found that activity at multiple therapeutic targets can result in superior efficacy and safety, giving opportunities for the discovery of better drugs.

**Disclosure**

The authors declare that they have no conflicts of interest in this work.

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