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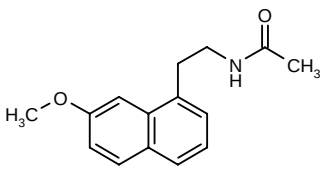
Agomelatine

Prop INN

Antidepressant
Treatment of Bipolar Disorder
Melatonin Agonist/5-HT_{2C} Antagonist

S-20098

N-[2-(7-Methoxy-1-napthyl)ethyl]acetamide



$C_{15}H_{17}NO_2$
Mol wt: 243.3043
CAS: 138112-76-2
EN: 193166

Abstract

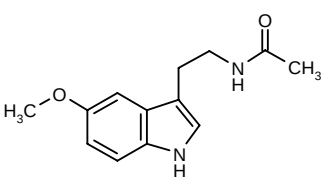
Agomelatine is a metabolically stable analogue of melatonin that is known to act as a selective and specific agonist at melatonin receptor sites in the hypothalamus. Agomelatine has also been shown to act as a competitive antagonist at serotonin receptors, giving it the novel pharmacological profile of a MASSA (Melatonin Agonist and Selective Serotonin Antagonist). Its ability to mimic the action of melatonin means that it is a potential candidate for the treatment of disorders characterized by dysfunction of biological rhythms (*e.g.*, sleep disorders/depression). A recent randomized, controlled trial has shown that agomelatine 25 mg/day is as effective as paroxetine in the treatment of patients with major depressive disorder and bipolar disorder, yet exhibits a more favorable tolerability profile than the traditional antidepressant in this group. Agomelatine, therefore, holds great promise for use as an antidepressant drug with a unique mode of action and is currently undergoing further clinical investigation.

Synthesis

Reformatskii reaction between 7-methoxy-1-tetralone (I) and the organozinc reagent generated from ethyl bromoacetate, followed by dehydration of the intermediate carbinol in the presence of P_2O_5 gives 2-(7-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)acetic acid ethyl ester (II). Aromatization of compound (II) by heating with sulfur at 215 °C results in the corresponding naphthalene derivative (III), which is submited to basic hydrolysis of the ethyl ester group (III) to provide 2-(7-methoxy-1-naphthyl)acetic acid (IV) (1). After activation of (IV) with $SOCl_2$, the crude acid chloride is treated with ammonium hydroxide to produce amide (V), which by direct reduction with $LiAlH_4$ furnishes amine (VI) in low yields (2, 3). An alternative procedure consists of the dehydration of amide (V) with trifluoroacetic anhydride to afford nitrile (VII), which is then reduced to the desired amine (VI) by catalytic hydrogenation (1-4). Finally, agomelatine is obtained by reaction of amine (VI) with acetyl chloride in pyridine (1) or in a biphasic medium (H_2O–$CHCl_3$) under Schotten-Baumann conditions (2-4). Scheme 1.

Introduction

Melatonin [I] is an endogenous neurohormone involved in the regulation of circadian rhythms in both humans and mammals. It is produced exclusively at night by the pineal gland, and acts at melatonin receptors concentrated in the suprachiasmatic nuclei (SCN) of the hypothalamus. The hypothalamus is responsible for the control and execution of circadian rhythm patterns. It receives neural inputs from SCN neurons, whose firing rates are determined by melatonin levels. Melatonin therefore has a chronobiotic function in that it works to alter the timing of physiological and behavioral processes through its action and its hypothalamic binding sites.



[I]

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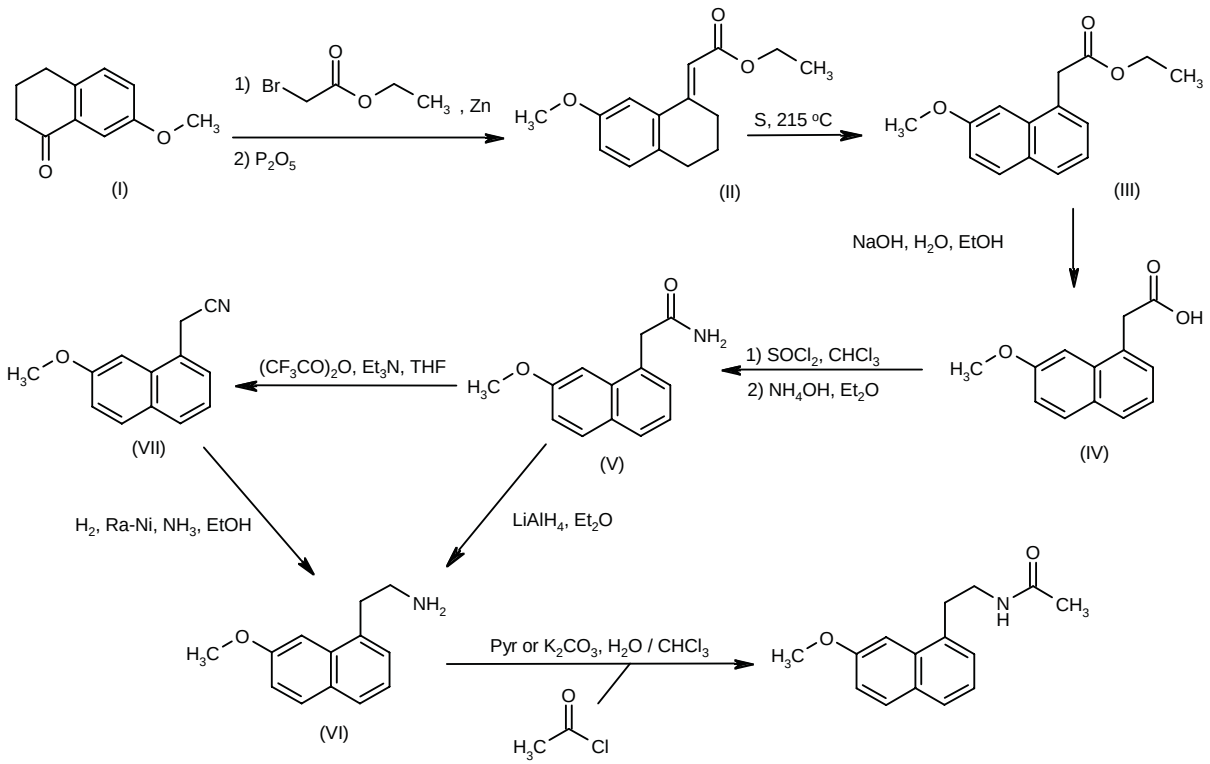
Scheme 1: Synthesis of Agomelatine



Melatonin is known as an internal time-keeper, as it has been shown to reset the biological clock normally regulated externally via the light-dark cycle. This ability to alter circadian rhythm synchronization implies its potential use in the treatment of conditions associated with problems in this area. Use of melatonin in the treatment of disorders characterized by circadian rhythm dysfunction has been limited, however, due to its associated short half-life (consequent to a high catabolism rate) and poor selectivity at melatonin receptor sites in the SCN (3, 5).

A number of melatonin analogues have been strategically designed to overcome the problems associated with melatonin administration. Molecular modeling studies identified the indole ring as the structural site of catabolic inactivation, making it an ideal candidate for isosteric modification. Agomelatine is the naphthalenic bioisostere of melatonin, as it has a naphthalene nucleus substituted for the indole ring, rendering it more metabolically stable when compared with melatonin (4, 6, 7).

Disruption of circadian rhythm patterns has been implicated as an etiological factor in the pathophysiology of depression. This disorganization of internal rhythms is said to be characteristic of mood variation. Therefore, the normalization of such impairments has been heralded as a potential new therapeutic target for the treatment of depression.

Tricyclic antidepressants, while effective in treating mild to severe forms of depression, are associated with an extensive tolerability profile, making them a nonviable option to many patients. The newer selective serotonin reuptake inhibitors (SSRIs) are better tolerated when compared with their tricyclic predecessors, and have recently become the most widely used antidepressant agents. However, problems with specific side effects (particularly affecting sexual function) have compromised treatment compliance in some patients. There is also evidence to suggest that while SSRIs are effective in mild to moderate forms of depression, they may not be as effective in patients exhibiting very severe forms of the disease. Therefore, research efforts are still being directed towards finding new antidepressant agents that are effective in all forms of depression and that are associated with a reduced side effect profile. Agomelatine has been proposed as one such candidate for antidepressant therapy.

Pharmacological Actions

Agomelatine is a potent and specific agonist at melatonin receptor sites in the hypothalamus. Cloning studies identified two distinct groups of melatonin receptors in the SCN, namely high-affinity ML_1 and low-affinity ML_2 receptors. High-affinity ML_1 receptors have been further

Table I: In vitro pharmacological profile of agomelatine compared to other selected melatonin receptor agonists (from Prous Science Integrity®).

	Melatonin receptor affinity pK_i		Agonistic activity - cAMP assay pIC_{50}	
Compound	MT_1	MT_2	MT_1	MT_2
Agomelatine	10.4	10.5	9.38	10.3
GR-196429	9.85	9.79	7.98	9.06
Melatonin	10.1	9.72	9.53	9.74

Receptor affinities (pK_i) evaluated on human cloned melatonin MT_1 and MT_2 receptors by displacement of [^{3}H]-melatonin. Agonism potency (pIC_{50}) evaluated by the inhibition of forskolin-induced cAMP production in cells transfected with human melatonin MT_1 or MT_2 receptors (original data from refs. 9, 44).

classified into mt_1 and MT_2 subtypes, which are responsible for melatonin's circadian rhythm function and retinal function effects, respectively. Both mt1 and MT_2 receptor subtypes belong to the family of G-protein-coupled receptors mediated by their inhibitory action on adenylate cyclase. SCN neurons themselves exhibit a circadian rhythm in their discharge activity *in vitro*, which is attuned to the light-dark cycle representative of circadian rhythm function. Agomelatine has been shown to bind specifically and selectively to mt_1 and MT_2 sites in a number of *in vitro* and *in vivo* animal studies (8, 9) (Table I).

Melatonin acts to downregulate mt_1 receptor density following selective binding to these receptors in the SCN. Research has shown this effect of receptor downregulation in the pars tuberalis of the rat. A similar decrease in mt_1 receptor density was observed following agomelatine administration, providing further support for its action as a full agonist at this receptor subtype (10).

Melatonin also acts to decrease firing of hypothalamic SCN cells. The effects of agomelatine administration on the firing rates of light-sensitive SCN cells have been assessed. *In vivo* analysis showed that intraperitoneal injection of agomelatine in male Syrian hamsters produced a dose-dependent decrease in SCN firing similar to that following melatonin administration (ED_{50} = 0.91 and 1.15 mg/kg, respectively). Time to suppression was also comparable between groups, although time to recovery was significantly longer in the agomelatine-treated hamsters, implicating a longer duration of action following agomelatine administration. Similarly, *in vitro* analysis showed that ionophoretic application of agomelatine had a comparable action to melatonin in its ability to reduce SCN neuronal firing (11, 12). Chronic treatment does not appear to alter the sensitivity of SCN neurons to agomelatine exposure, with no change being observed following both *in vitro* and *in vivo* analysis (13).

Agomelatine's classification as a chronobiotic drug also comes from research showing its ability to mimic the action of melatonin in the synchronization of circadian rhythm patterns. This has most often been shown by way of behavioral studies in rodents, where daily patterns of locomotor activity, running wheel activity and fluctuations in body temperature have been shown to be altered by both melatonin and agomelatine (14, 15).

Agomelatine administration has been shown to alter these measures of circadian rhythm function in three ways. Firstly, agomelatine can entrain free-running rhythms by setting up a circadiaan pattern in animals after external time-keepers are removed (*i.e.*, after exposure to constant darkness). This ability to synchronize rest-activity rhythms in free-running animals is dose-dependent, and requires the integrity of the SCN (*i.e.*, SCN-lesioned rats do not entrain following either agomelatine or melatonin, lending further support here for its action at melatonin receptors). The pineal gland appears not to be involved, however, as pinealectomized rats retain the ability to entrain circadian rhythm function. These observations applied to orally administered as well as peripherally injected rodents (16-19).

Secondly, agomelatine can reset a preexisting circadian rhythm following a phase shift. Behavioral studies show that agomelatine has the ability to reentrain rats following an 8-h phase advance of the light-dark cycle *in vivo*. While these effects are dose-dependent, the action of agomelatine has been shown to have a ceiling effect, with injection of 1 mg/kg obtaining maximal reentrainment in a rodent model. Agomelatine has also been shown to reentrain circadian rhythms in an *in vitro* model, with similar changes to SCN firing rates being reported following an 8-h phase advance (20-23).

Finally, agomelatine can correct age-related changes to environmental stimulus response. Age is associated with a decline in responsiveness to the circadian clock, in particular to the phase shifting effects of activity-inducing stimuli. Long-term treatment with agomelatine has been shown to reduce the time taken for reentrainment following a phase advance in the light-dark cycle. Agomelatine administration can therefore be used to restore resynchronization ability in animals that have reduced circadian rhythm responsiveness. This effect was once again shown to be dose-dependent, and was reversed after discontinuation of the drug (24, 25).

Agomelatine does not always mimic the action of melatonin, however, in that it has separate effects to those elicited in the hypothalamus that are not achieved with melatonin administration. Further to its classification as a selective melatonin receptor agonist, recent research has identified a separate mode of action of this drug. It seems as though agomelatine's effects are also mediated via its function as a competitive antagonist at the $5\text{-}HT_{2C}$ receptor.

Agomelatine was shown to antagonize the penile erections normally induced by serotonin receptor activation in Wistar rats. Penile erections were induced by administration of mCPP and Ro-60-0175 (selective $5\text{-}HT_{2C}$ receptor agonists), then were diminished dose-dependently following addition of agomelatine. Melatonin administration had no effect in this paradigm. As agomelatine mimics the effects of melatonin at the melatonin receptor site, it was concluded that the effects of

melatonin here were distinct from its melatonin agonist properties, and were instead due to 5-HT_{2C} receptor antagonism (26).

Recent results from receptor binding studies gave further support to this notion of a secondary mode of action for agomelatine. *In vitro* analysis of receptor binding in CHO cells showed that agomelatine acts as an antagonist at the 5-HT_{2C} receptor subtype (pK_i and pK_b = 6.2 and 5.9, respectively). Agomelatine displayed competitive antagonism properties here, displacing 5-HT agonist activation at 5-HT_{2C} receptor sites without producing an independent action. Agomelatine also worked as an antagonist at the 5-HT_{2B} receptor (pK_i and pK_b = 6.5 and 6.6, respectively) as well as exhibiting low-affinity binding at 5-HT_{2A} sites ($pK_i < 6$). Serotonergic binding activity was only observed at doses higher than would normally be given to activate melatonergic receptors (27).

Agomelatine has, therefore, been shown to have a unique pharmacological profile, as it elicits its effects by binding to hypothalamic M_1 and M_2 receptors, as well as by blocking the 5-HT_{2C} receptor. The compound has become known as a Melatonin Agonist and Selective Serotonin Antagonist (MASSA).

There has been some evidence to suggest that the differing mechanisms of action of agomelatine may be dependent on the timing of administration of the drug, with evening dosing being similar to its action at the melatonin receptors, while morning administration is attributable to its serotonergic properties. Furthermore, only the morning activity and not the nighttime activity of agomelatine was able to be blocked with the melatonin receptor antagonist S-22153 (27, 28).

Interest in agomelatine has increased dramatically in recent times due to its prospective use as a novel antidepressant agent. Interest grew following the presentation of results of a number of animal studies demonstrating agomelatine to be an effective antidepressant in a series of well-validated animal models of depression.

The effects of agomelatine were initially studied in olfactory bulbectomized rats compared with control rats (undergoing a sham operation). Results were compared with administration of the typical antidepressant therapy, imipramine. Ambulation scores were statistically similar among animals treated with agomelatine (10 or 50 mg/kg) and imipramine (10 mg/kg); however, control rats showed a significantly higher level of ambulation when compared with vehicle-treated animals. These findings supported the potential use of agomelatine as an antidepressant in humans (29).

The antidepressant efficacy of agomelatine was further tested in a number of experiments. Chronic i.p. administration of agomelatine (10 and 50 mg/kg) was compared with melatonin (10 and 50 mg) and the typical antidepressants imipramine (10 mg/kg) and fluoxetine (10 mg/kg), in a chronic mild stress model of depression. Agomelatine reversed chronic mild stress-induced anhedonia, with a magnitude and time course similar to that of the traditional antidepressant drugs, independent of the time of administration. Agomelatine was shown to be a potent and rapidly-acting antidepressant in this model (28, 30).

Results from the learned-helplessness model of depression also heralded agomelatine as an effective antidepressant. In this study, oral administration of agomelatine (2, 10, 50 and 100 mg/kg) was compared with melatonin (2, 10 and 50 mg/kg) and imipramine (64 mg/kg) in rats subjected to an uncontrollable aversive stimulus. Results were compared with those obtained from helpless control animals, and non-helpless control animals. Agomelatine was shown to be equivalent to imipramine in its ability to reverse the learning deficit caused by exposure to aversive stimuli. Once-daily administration was superior to twice-daily administration of agomelatine, with the most significant antidepressant effects being noted with the 10 mg/kg dose (31).

Finally, the antidepressant efficacy of agomelatine was tested using the forced swim test. Here investigators showed that acute and repeated-dose treatment with agomelatine (2, 10 and 50 mg/kg) had an antidepressant effect in Wistar rats and Swiss mice, as demonstrated by a significantly reduced duration of mobility at all doses tested. Results following agomelatine were comparable to those attributable to imipramine and fluoxetine administration, whereas treatment with melatonin showed no effect (32, 33). It should be noted, however, that results from a separate group published 4 years previous to the aforementioned trials showed null results with agomelatine administration in a forced swim test. Investigators claimed that agomelatine had no antidepressant effect in this setting (34).

Rats and rhesus monkeys did not self-administer agomelatine in a preclinical evaluation of its effects at the GABA receptor. These results were important in that they suggested that while agomelatine might exhibit antidepressant effects, it was not associated with self-administration in animals, which has been shown to be similar to the propensity for recreational abuse in humans. The authors concluded that, although agomelatine shares some properties of CNS depressant agents, the potential for intoxication and abuse is limited, making it an even more ideal candidate for use as an antidepressant (35, 36).

Clinical Studies

Results from preclinical trials prompted investigators to carry out a pilot dose-finding study in patients with major depressive disorder. A double-blind randomized study was undertaken in order to find a dose applicable for antidepressant use in this population. A total of 28 inpatients were administered agomelatine at doses of 5 or 100 mg/day for 28-56 days. Groups were comparable at baseline. Antidepressive efficacy was shown at both doses, although the 5 mg/day group of patients showed more benefits as compared to the 100 mg/day group. The tolerability profile was comparable between groups, although there were a greater number of severe

Table II: Clinical studies of agomelatine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Major depression	Randomized, double-blind	Agomelatine, 5 mg x 4-8 wk Agomelatine, 10 mg x 4-8 wk	28	Both agomelatine doses significantly benefitted patients, with a slightly better reduction in MADRS scores in the 5 mg group. Both doses were also safe, although adverse events were more common in the higher dose group	37
Bipolar II disorder, depression	Randomized, double-blind, multicenter	Agomelatine, 1 mg po od x 8 wk (n=141) Agomelatine, 5 mg po od x 8 wk (n=147) Agomelatine, 25 mg po od x 8 wk (n=137) Paroxetine, 20 mg po od x 8 wk (n=147) Placebo (n=139)	711	In patients with severe major depression or bipolar II disorder, agomelatine at a dose of 25 mg was safe and more effective than placebo in all individual depression scores, including retardation, anxiety and insomnia	38

adverse events reported by the 100 mg/day patients. It was concluded that agomelatine was an effective antidepressant agent in inpatients with major depressive disorder. Oral administration of 5 mg/day had comparable efficacy and was better tolerated than 100 mg/day, making it a more suitable candidate for a dosing target in future trials (37).

A multinational group of researchers recently reported that agomelatine was as effective as the traditional antidepressant paroxetine in the treatment of depression (38). Investigators from France, Belgium and the U.K. published results from their recently conducted randomized, double-blind, placebo-controlled trial in 711 patients aged 18-65 years with a DSM-IV diagnosis of major depressive disorder (n=698) or bipolar disorder (n=13). Patients were randomized to receive agomelatine 1, 5 or 25 mg/day or paroxetine 20 mg/day in the evening for an 8-week period. All patients underwent a placebo run-in period for 1 week. Patients who responded to this placebo run-in were excluded from further analysis. Antidepressant efficacy was measured on the 17-item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale and the Clinical Global Impression-Severity of Illness scale. The anxiety associated with depression was also measured on the Hamilton Anxiety Scale.

Efficacy analysis showed that agomelatine 25 mg/day was as effective as paroxetine in its ability to improve depression scores. Analysis of individual scores showed that agomelatine 25 mg/day improved all depressive symptoms in relation to placebo-treated patients (p <0.05 for all symptoms). Time to first response was also significantly reduced in agomelatine patients compared with patients receiving paroxetine (2 *vs.* 4 weeks, respectively; p <0.05). There was a dose-dependent effect seen here, although patients treated with agomelatine 1 and 5 mg/day showed no improvement in depression score or response rate when compared with placebo (39).

Tolerability data showed that agomelatine was better tolerated than paroxetine in this population. The adverse event rate was comparable between placebo and agomelatine patients at all doses. However, paroxetine-treated patients experienced a significantly higher rate of adverse events compared with the other groups (66% *vs.* 55% and 51% for placebo and agomelatine 25 mg, respectively). The majority (85%) of all events reported were mild to moderate in severity, with the most commonly experienced side effects being gastrointestinal in nature. Withdrawals due to adverse events were comparable between groups (40).

Secondary analysis of the effect of agomelatine on the anxiety associated with depression showed that the compound also displays an anxiolytic effect in these patients. It is common for patients to experience anxiety symptoms in combination with depressive symptomatology. Agomelatine 25 mg/day significantly reduced Hamilton Anxiety Rating Scale (HARS) scores when compared with placebo. This finding was confirmed by analysis of a subgroup of patients who were never users of anxiolytics prior to study onset. Paroxetine administration had a similar effect (41).

Another secondary analysis of efficacy in patients with severe depression (*i.e.*, patients with HAM-D scores > 25 at baseline) showed that agomelatine 25 mg/day was superior to paroxetine in the treatment of these patients when compared with placebo. These findings imply the potential specific use of agomelatine in difficult-to-treat, or severely depressed patients (42).

Finally, remission rates were shown to significantly increase with agomelatine 25 mg/day (30% of patients) as compared to placebo (15% of patients) and were comparable to rates following paroxetine administration (26% of patients). Investigators concluded that a higher remission rate was indicative of the long-term efficacy of agomelatine in patients with depression (43).

The results of these 2 studies are summarized in Table II.

Conclusions

Agomelatine is a novel antidepressant drug candidate exhibiting a unique pharmacological profile.

Administration of agomelatine 25 mg/day has been shown to be as effective as paroxetine in the treatment of major depressive disorder and bipolar disorder, yet is associated with a more favorable tolerability profile. Agomelatine is especially effective in the treatment of severely depressed patients, an effect that was not observed in patients undergoing paroxetine therapy. Secondary analysis showed that agomelatine is also effective in treating anxiety symptoms associated with depression. Agomelatine, therefore, shows great promise as a new antidepressant agent and is currently in phase III clinical trials for this indication.

Source

Servier Laboratoires (FR).

References

1. Andrieux, J., Houssin R., Yous, S., Guardiola, B., Lesieur, D. (ADIR et Cie.). *Novel derivs. with a naphthalenic structure, their process of preparation and pharmaceutical compsns. containing them.* EP 0447285, FR 2658819, JP 1995048331, US 5318994.

2. Adam, G., Guardiola-Lemaitre, B., Yous, S., Lesieur, D., Morgan, P., Howell, H.-E., Andrieux, J., Caignard, D.-H., Pfeiffer, B., Renard, P. *Novel naphthalenic ligands for the melatonin receptor.* J Pharm Belg 1992, 47: 374-80.

3. Yous, S., Andrieux, J., Howell, H.E., Morgan, P.J., Renard, P., Pfeiffer, B., Lesieur, D., Guardiola-Lemaitre, B. *Novel naphthalenic ligands with high affinity for the melatonin receptor.* J Med Chem 1992, 35: 1484-6.

4. Depreux, P., Lesieur, D., Mansour, H.A. et al. *Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands.* J Med Chem 1994, 37: 3231-9.

5. Caignard, D.H., Lesieur, D., Depreux, P., Renard, P., Guardiola, B., Delagrange, P. *Structure-activity relationships of melatonin analogues.* 13th Int Symp Med Chem (Sept 19-23, Paris) 1994, Abst O43.

6. Lesieur, D., Leclerc, V., Morgan, P., Renard, P., Guardiola, B. *Design and structure activity relationships of naphthalenic ligands of the melatonin receptor.* 14th Int Symp Med Chem (Sept 8-12, Maastricht) 1996, Abst SL-07.6.

7. Lesieur, D., Leclerc, V., Chavatte, P., Marot, C., Renard, P., Guardiola-Lemaitre, B. *Melatonin, a suitable lead compound for rational drug design.* Thérapie 1998, 53: 429-37.

8. Neu, J., Niles, L.P., Brough, P.A., Chen, J.J., Snieckus, V., Firnau, G. *Analog binding to melatonin receptors in chick brain: Effects of GTP and prazosin.* Med Chem Res 2000, 10: 114-21.

9. Browning, C., Beresford, I.J.M., Giles, H. *Differential pharmacological characterisation of human recombinant melatonin mt_1 and MT_2 receptors.* Br J Pharmacol 1998, 124(Suppl.): Abst 34P.

10. Masson-Pévet, M., Recio, J., Guerrero, H.Y., Mocaer, E., Delagrange, P., Guardiola-Lemaitre, B., Pévet, P. *Effects of two melatonin analogues, S-20098 and S-20928, on melatonin receptors in the pars tuberalis of the rat.* J Pineal Res 1998, 25: 172-6.

11. Scott, G., Delagrange, P., Guardiola-Lemaître, B., Mocaër, E., Rusak, B. *Effects of a melatonin agonist and antagonist on hamster suprachiasmatic nucleus (SCN) neurons in vitro.* Soc Neurosci Abst 1996, 22(Part 2): Abst 551.18.

12. Ying, S.-W., Rusak, B., Delagrange, P., Mocaër, E., Renard, P., Guardiola-Lemaître, B. *Melatonin analogues as agonists and antagonists in the circadian system and other brain areas.* Eur J Pharmacol 1996, 296: 33-42.

13. Rusak, B., Ying, S.-W., Mocaër, E. *Chronic treatment with S20098 or melatonin does not alter suprachiasmatic nucleus (SCN) neuron responses to these agonists.* Soc Neurosci Abst 1997, 23(Part 1): Abst 420.8.

14. Van Reeth, O., Olivares, E., Zhang, Y., Zee, P.C., Mocaer, E., Defrance, R., Turek, F.W. *Comparative effects of a melatonin agonist on the circadian system in mice and Syrian hamsters.* Brain Res 1997, 762: 185-94.

15. Kräuchi, K., Cajochen, C., Möri, D., Graw, P., Wirz-Justice, A. *Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature.* Am J Physiol - Regul Integr Comp Physiol 1997, 272: R1178-88.

16. Pitrosky, B., Kirsch, R., Malan, A., Mocaer, E., Pevet, P. *Organization of rat circadian rhythms during daily infusion of melatonin or S20098, a melatonin agonist.* Am J Physiol - Regul Integr Comp Physiol 1999, 277: R812-28.

17. Martinet, L., Guardiola-Lemaitre, B., Mocaer, E. *Entrainment of circadian rhythms by S-20098, a melatonin agonist, is dose and plasma concentration dependent*. Pharmacol Biochem Behav 1996, 54: 713-8.

18. Redman, J.R., Francis, A.J. *Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal.* J Biol Rhythms 1998, 13: 39-51.

19. Redman, J., Francis, A., Smith, A. *Possible sites of action of the melatonin agonist S20098.* Neuropsychopharmacology 1994, 10(3S, Part 2): Abst P-117-79.

20. Van Reeth, O., Olivares, E., Zhang, Y., Turek, F.W., Mocaer, E., Defrance, R. *A melatonin-agonist, S-20098, induces phase shifts in the circadian clock of rodents according to a phase response curve and a dose response curve.* 16th Eur Winter Conf Brain Res (March 16-23, Serre-Chevalier) 1996, Abst.

21. Redman, J.R., Guardiola-Lemaitre, B., Brown, M., Delagrange, P., Armstrong, S.M. *Dose dependent effects of S-20098, a melatonin agonist, on direction of re-entrainment of rat circadian activity rhythms.* Psychopharmacology 1995, 118: 385-90.

22. Van Reeth, O., Olivares, Y., Zhang, F.W., Turek, F.W., Defrance, R., Mocaer, E. *S-20098, a melatonin-agonist, phase shifts the circadian clock of mice and Syrian hamsters according to a phase-response-curve.* Soc Neurosci Abst 1994, 20(Part 2): Abst 588.6.

23. Mason, R., Delagrange, P., Guardiola, B. *Melatonin and S-20098 mediated resetting of rat suprachiasmatic circadian clock neurones in vitro.* Proc Br Pharmacol Soc (Jan 5-7, Cambridge) 1993, Abst C32.

24. Van Reeth, O., Weibel, L., Olivares, E., Maccari, S., Mocaer, E., Turek, F.W. *Melatonin or a melatonin agonist corrects age-related changes in circadian response to environmental stimulus.* Am J Physiol - Regul Integr Comp Physiol 2001, 280: R1582-91.

25. Weibel, L., Turek, F.W., Mocaer, E., Van Reeth, O. *A melatonin agonist facilitates circadian resynchronization in old hamsters after abrupt shifts in the light-dark cycle.* Brain Res 2000, 880: 207-11.

26. Protais, P., Chagraoui, A., Mocaër, E. *S 20098 (agomelatine) antagonizes the penile erections induced by the stimulation of 5-HT$_{2C}$ receptors in Wistar rats.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.1.E.051.

27. Cussac, D., Newman-Tancredi, A., Pasteau, V., Millan, M.J. *Antagonist properties of the melatonin agonist, S20098 (agomelatine) at recombinant, human (h) serotonin 5-HT$_{2C}$ receptors.* 23rd CINP Congr (June 23-27, Montreal) 2002, Abst P.1.E.064.

28. Papp, M., Gruca, P., Mocäer, E. *Evidence for two components in the mechanism of action of S20098 (agomelatine) in a chronic mild stress animal model of depression.* Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.1.058.

29. Cranston, I., Irons, J., Norman, T.R. *An investigation of the potential antidepressant activity of agomelatine in the bilateral olfactory bulbectomised rat.* Australas Soc Psychiatr Res Conf (Dec 4-6, Canberra) 2002, Abst 31.

30. Papp, M., Gruca, P., Mocaër, E. *The antidepressant activity of S 20098 (agomelatine) in the chronic mild stress is related to both its melatonin agonist and 5-HT$_{2C}$ antagonist properties.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.1.E.046.

31. Bertaina-Anglade, V., Mocaër, E., Drieu la Rochelle, C. *Antidepressant-like action of S 20098 (agomelatine) in the learned helplessness test.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.1.E.048.

32. Barden, N., Labbé, M., Vacher, R., Mocaër, E. *Antidepressant action of S-20098 (agomelatine) in a transgenic mouse model.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.1.E.045.

33. Bourin, M., Mocaër, E., Porsolt, R. *Efficacy and behavioural profile of S 20098 in the despair test after acute and repeated administration.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.1.E.047.

34. Cryan, J., McGrath, C., Leonard, B.E., Burrows, G.D., Norman, T.R. *The effects of melatonin and melatonin receptor ligands in the rat forced swim test.* 21st CINP Cogr (July 12-16, Glasgow) 1998, Abst PM01006.

35. Wiley, J.L., Dance, M.E., Balster, R.L. *Preclinical evaluation of the reinforcing and discriminative stimulus effects of agomelatine (S-20098), a melatonin agonist.* Psychopharmacology 1998, 140: 503-9.

36. Tenn, C.C., Niles, L.P. *The antidopaminergic action of S-20098 is mediated by benzodiazepine/GABA$_A$ receptors in the striatum.* Brain Res 1997, 756: 293-6.

37. Lôo, H., Daléry, J., Macher, J.-P., Payen, A. *Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatoninergic agonist and selective 5-HT$_{2C}$ receptor antagonist, in the treatment of major depressive disorders.* Encéphale 2002, 28: 356-62.

38. Lôo, H., Hale, A., D'haenen, H. *Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT$_{2C}$ antagonist, in the treatment of major depressive disorder: A placebo-controlled dose range study.* Int Clin Psychopharmacol 2002, 17: 239-47.

39. Lôo, H., D'haenen, H., Hale, A. *S-20098 in patients with major depressive or bipolar II disorders: Effect on individual depressive symptoms.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.3.E.034.

40. Lôo, H., D'haenen, H., Hale, A. *A double-blind trial of S-20098 in patients with major depressive or bipolar II disorders: Dose-ranging study.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.3.E.033.

41. Lôo, H., D'haenen, H., Hale, A. *A double-blind study of S-20098 in patients with major depressive or bipolar II disorders: Effect on anxiety.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.3.E.031.

42. Lôo, H., D'haenen, H., Hale, A. *S-20098 in patients with major depressive or bipolar II disorders: Efficacy in severely depressed patients.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.3.E.032.

43. Lôo, H., D'haenen, H., Hale, A. *A double-blind study of S-20098 in patients with major depressive or bipolar II disorders: Effect on remission.* Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.3.E.030.

44. Beresford, I.J.M., Browning, C., Starkey, S.J. et al. *GR196429: A nonindolic agonist at high-affinity melatonin receptors.* J Pharmacol Exp Ther 1998, 285: 1239.

Additional References

Ting, N., Thambyraja, A., Sugden, D., Scalbert, E., Delagrange, P., Wilson, V.G. *Pharmacological studies on the inhibitory action of melatonin and putative melatonin analogues on porcine vascular smooth muscle.* Naunyn-Schmied Arch Pharmacol 2000, 361: 327-33.

Roberts, J.E., Hu, D.N., Martinez, L., Chignell, C.F. *Photophysical studies on melatonin and its receptor agonists.* J Pineal Res 2000, 29: 94-9.

Chu, Y.S., Shieh, K.R., Yuan, Z.F., Pan, J.T. *Stimulatory and entraining effect of melatonin on tuberoinfundibular dopaminergic neuron activity and inhibition of prolactin secretion.* J Pineal Res 2000, 28: 219-26.

Simonin, G., Bru, L., Lelievre, E., Jeanniot, J.P., Bromet, N., Walther, B., Boursier-Neyret, C. *Determination of melatonin in biological fluids in the presence of the melatonin agonist S 20098: Comparison of immunological techniques and GC-MS methods.* J Pharm Biomed Anal 1999, 21: 591-601.

Bucher, B., Gauer, F., Pévet, P., Masson-Pévet, M. *Vasoconstrictor effects of various melatonin analogs on the rat tail artery in the presence of phenylephrine.* J Cardiovasc Pharmacol 1999, 33: 316-22.

Van Reeth, O., Olivares, E., Turek, F.W., Granjon, L., Mocaer, E. *Resynchronisation of a diurnal rodent circadian clock accelerated by a melatonin agonist.* NeuroReport 1998, 9: 1901-5.

Cajochen, C., Kräuchi, K., Möri, D., Graw, P., Wirz-Justice, A. *Melatonin and S-20098 increase REM sleep and wake-up propensity without modifying NREM sleep homeostasis.* Am J Physiol - Regul Integr Comp Physiol 1997, 272: R1189-96.

Kirsch, R., Mocaer, E., Pitrosky, B., Pévet, P. *Entrainment of rat circadian rhythms by daily infusions of S20098 and melatonin.* Soc Neurosci Abst 1997, 23(Part 1): Abst 420.9.

Van Reeth, O., Olivares, E., Mocaer, E., Zee, P.C., Turek, F.W., *A melatonin agonist increases the phase-shifting effects of dark pulses in old hamsters.* Soc Neurosci Abst 1997, 23(Part 1): Abst 420.1.

Grassi-Zucconi, G., Semprevivo, M., Mocaer, E., Kristensson, K., Bentivoglio, M. *Melatonin and its new agonist S-20098 restore synchronized sleep fragmented by experimental trypanosome infection in the rat.* Brain Res Bull 1996, 39: 63-8.