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Synthesis of new *N*-(arylcyclopropyl)acetamides and *N*-(arylvinyl)acetamides as conformationally-restricted ligands for melatonin receptors

Laurence Morellato [a], Marie Lefas-Le Gall [a], Michel Langlois [a], Daniel-Henri Caignard [b], Pierre Renard [b], Philippe Delagrange [b], Monique Mathé-Allainmat [c,*]

[a] Université de Paris-Sud, BIOCIS – UMR CNRS 8076, Faculté de Pharmacie, 5 rue J. B. Clément, 92296 Châtenay-Malabry, France
[b] Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France
[c] Université de Nantes, CNRS, UMR 6230, Chimie Et Interdisciplinarité: Synthèse Analyse Modélisation (CEISAM), UFR Sciences et Techniques, 2, rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

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ABSTRACT

N-(Arylcyclopropyl)acetamides and *N*-(arylvinyl)acetamides or methyl ureas have been prepared as constrained analogues of melatonin. The affinity of these new compounds for chicken brain melatonin receptors and recombinant human MT_1 and MT_2 receptors was evaluated using 2-[^{125}I]-iodomelatonin as radioligand. Strict ethylenic or cyclopropyl analogues of the commercialized agonist agomelatine (Valdoxan®) were equipotent to agomelatine in binding bioassays. However, the ethylenic analogue was more effective than the cyclopropyl one in the melanophore aggregation bioassay, but was still less potent than the disubstituted 2,7-dimethoxy-naphtalenic compounds.

Melatonin (*N*-acetyl-5-methoxytryptamine) **1** (Fig. 1) is the vertebrate pineal gland hormone secreted during darkness.[1] It regulates the circadian rhythm[2] in a large number of animals, including man. The hormone can be used to control diseases associated with circadian rhythm disorders[3,4] or sleep disorders.[5] It also has a promising role as an analgesic drug[6] and has shown immunomodulatory and antioxidant properties, protecting organisms against both bacterial[7] and viral[8] infections. In addition, melatonin has been reported to have antiproliferative effects on mammary cell lines[9,10] and its involvement has been suggested in the regulation of vascular tone.[11]

It has been demonstrated that a number of the effects of melatonin are mediated through G protein-coupled receptors[12] and coupling to class A family of G-proteins appears to be the common signaling pathway for those receptors characterized to date. Cloning studies have revealed two recombinant mammalian melatonin receptors, termed MT_1 and MT_2,[13,14] for which the pharmacological properties have been intensively studied during the last two decades.[15] Great interest has developed in the search for new molecules capable of mimicking or antagonizing the responses to melatonin. These novel compounds have been derived from the indole ring or its bioisosteres such as naphthalene.[16] The non-selective naphthalenic strict structural analogue of melatonine, agomelatine **2** (Fig. 1, Valdoxan®), was the first found to control circadian rhythms disorders[17] and is now marketed for the treatment of depression[18] due to its antagonist activity for the 5-HT_{2C} receptor subtype.[19]

The development of high-affinity conformationally-locked compounds appeared to be an interesting and rational approach to obtain a clear insight into the structural parameters involved in the binding to the receptor site, as well as information about the selectivity rules for both receptor subtypes. Several constrained structures were synthesized with the amido side chain introduced into a ring or conjugated with the aromatic ring. These compounds were either tricyclic indole derivatives, such as compound **3** (Fig. 1), or unsaturated analogues of melatonin, such as compound **4** (Fig. 1), with the *trans* restricted conformation.[20] In the naphthalene series, phenalene derivatives, such as compounds **5** and **6** (Fig. 1), were described by us.[21,22] Our studies have demonstrated the superiority of the partially constrained derivative **6** over the totally rigid compound **5** in its binding to the human MT_1 and MT_2 receptors. On the other hand, the 2-amido-phenalene derivative **5** differed in its pharmacological profile because it was shown to be an antagonist in the *Xenopus laevis* melanophore aggregation test.[23] However, no clear structural information was obtained with these derivatives to enable the design of compounds with marked selectivity.

* Corresponding author.
E-mail address: monique.mathe@univ-nantes.fr (M. Mathé-Allainmat).

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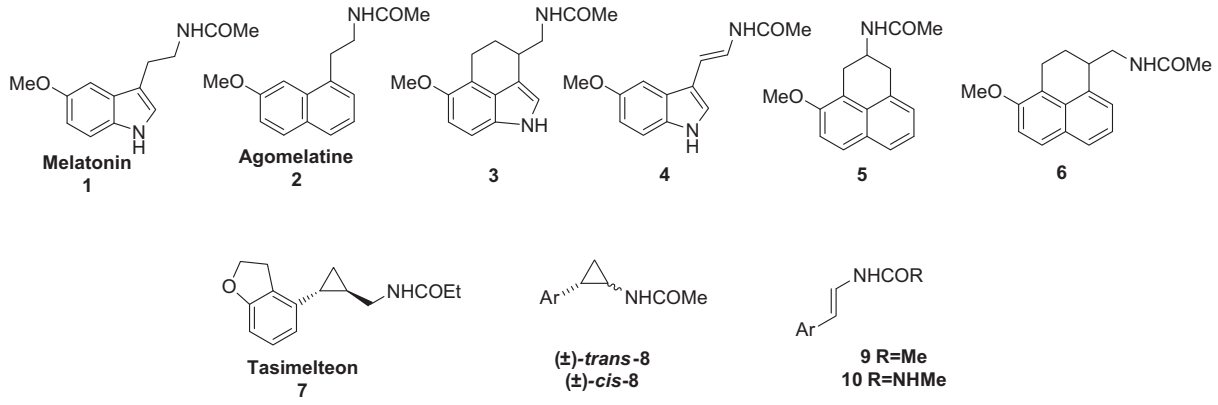
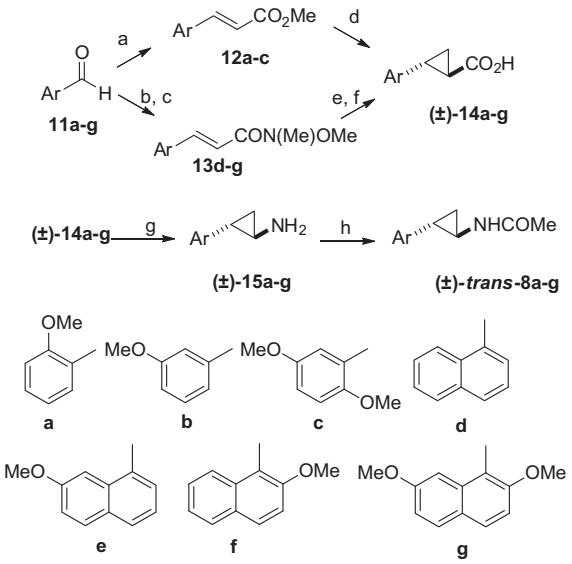


Figure 1. Melatoninergic analogues.



Scheme 1. Reaction conditions: (a) $CH_2(CO_2H)_2$, piperidine, pyridine, MeOH, concn H_2SO_4; (b) NaH, $(EtO)_2POCH_2CO_2Et$, THF, then NaOH, MeOH; (c) CH_2Cl_2, DMF, $(COCl)_2$, NH(Me)OMe·HCl; (d) CH_2N_2, Et_2O, $Pd(OAc)_2$, CH_2Cl_2, 2 N NaOH, MeOH; (e) Me_3SOI, NaH, DMSO; (f) *t*-BuOK, Et_2O, H_2O; (g) EtOCOCl, Et_3N, acetone, NaN_3, H_2O, toluene, 80 °C, 20% HCl, Δ; (h) $(CH_3CO)_2O$, Na_2CO_3, CH_2Cl_2, H_2O.

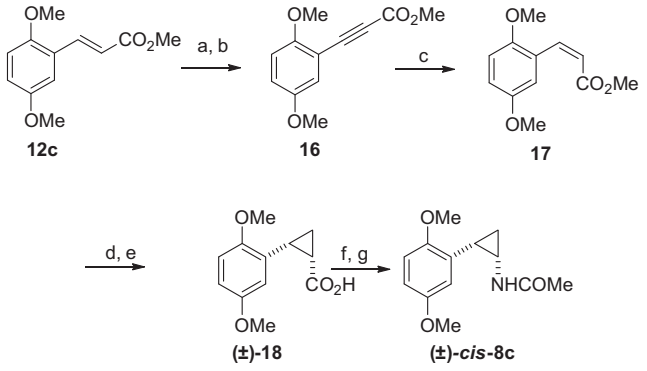
In a further approach to understand the influence of the conformation of the ethylamido side chain on the potency and the pharmacological profile of melatoninergic compounds, we synthesized *N*-(arylcyclopropyl)acetamide derivatives (±)-**8** and *N*-(arylvinyl)acetamide and methyl urea derivatives **9** and **10**, respectively (Fig. 1). It should be noted that Bristol-Myers Squibb patented semi-constrained *trans* cyclopropyl compounds such as tasimelteon **7**,[24a] a non-selective hMT_1 and hMT_2 agonist and published a few years later the benzoxazole analogues.[24b] Today, compound **7** has entered phase III clinical trial for the treatment of insomnia.[25]

Substituted aromatic scaffold were selected amongst our previously published melatoninergic compounds with marked potency in the naphthalene and phenyl series.[26,27] For a better comparison with melatonin **1** and agomelatine **2**, only the acetamido analogues will be presented here.

The arylcyclopropane derivatives (±)-*trans*-**8** were synthesized according to the synthetic pathways represented in Scheme 1.

The aromatic aldehydes **11** were transformed into the ethylenic compounds **12** or **13**, through a classical Knoevenagel reaction with malonic acid or a Wadsworth–Emmons condensation with triethylphosphonoacetate followed by Weinreb amide formation from the corresponding acid. Two different methods were applied to introduce the cyclopropane ring. With *trans* cinnamic esters (Scheme 1, compounds **12a–c**), the addition of diazomethane (prepared by the basic decomposition of Diazald®) gave the corresponding *trans* phenylcyclopropane esters.[28] These were directly hydrolyzed into the *trans* phenylcyclopropane carboxylic acids **14a–c**. With naphthalene analogues, this method failed because of some reactivity of the aromatic ring with diazomethane. Consequently, the arylcyclopropane carboxylic acids (±)-**14d–g** were prepared by the addition of a sulfur ylide, generated from trimethylsulfoxonium iodide[29] in the presence of sodium hydride, on the unsaturated *N*-methyl-*O*-methylamides **13d–g** followed by a smooth hydrolysis with *t*-BuOK and H_2O in diethyl ether.[30] The carboxylic acids (±)-**14** were transformed into the corresponding acylazides *via* mixed anhydride formation followed by nucleophilic substitution with sodium azide. Curtius rearrangement afforded the expected amines (±)-**15a–g** after acidic hydrolysis of the isocyanates. These amines, obtained as either the free base or the hydrochloride salt, were acylated with acetic anhydride into *N*-acetamido derivatives (±)-*trans*-**8a–g**.

The influence of the *trans* or *cis* stereochemistry of the cyclopropane derivatives on the affinity for melatonin receptors could be determined by the preparation and evaluation of the (±)-*cis*-**8c** compound. The synthesis of (±)-*cis*-**8c** (Scheme 2) began by the addition of bromine to cinnamate **12c** followed by elimination in basic medium to furnish the propynoate **16.**[31] Ester **16** was than hydrogenated in the presence of Lindlar catalyst to yield *cis*-cinnamate **17** in 38% yield.



Scheme 2. Reaction conditions: (a) Br_2, CH_2Cl_2; (b) KOH, EtOH; (c) H_2, $Pd(CaCO_3)$, PbO, EtOH, rt; (d) CH_2N_2, Et_2O, $Pd(OAc)_2$, CH_2Cl_2; (e) 2 N NaOH, MeOH; (f) EtOCOCl, Et_3N, acetone, NaN_3, H_2O, toluene, 80 °C, 20% HCl; (g) CH_3COCl, Et_3N, CH_2Cl_2.