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Research Article

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A concise synthesis of 2-(1,2,3,4-tetrahydro-6-methoxynaphthalen-4-yl) ethanamine, a key intermediate in the elaboration compound library of agomelatine analogs

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ABSTRACT

Agomelatine, a melatonin-like antidepressant drug based on a naphthalene scaffold, has received considerable attention these last twenty years. This drug molecule undergoes important liver first pass effect and suffers therefore of a short plasma half-life. In an effort to circumvent this drawback, we designed an approch based on the use of a tetraline scaffold to replace the original naphthalene template. Using a concise synthetic method involving a three-step approach and starting a commercially available tetralone precursor,we successfully designed a tetraline scaffold, a pivotal template which could be further elaborated into a compound library of agomelatine analogs. Further work is now under progress along this line.

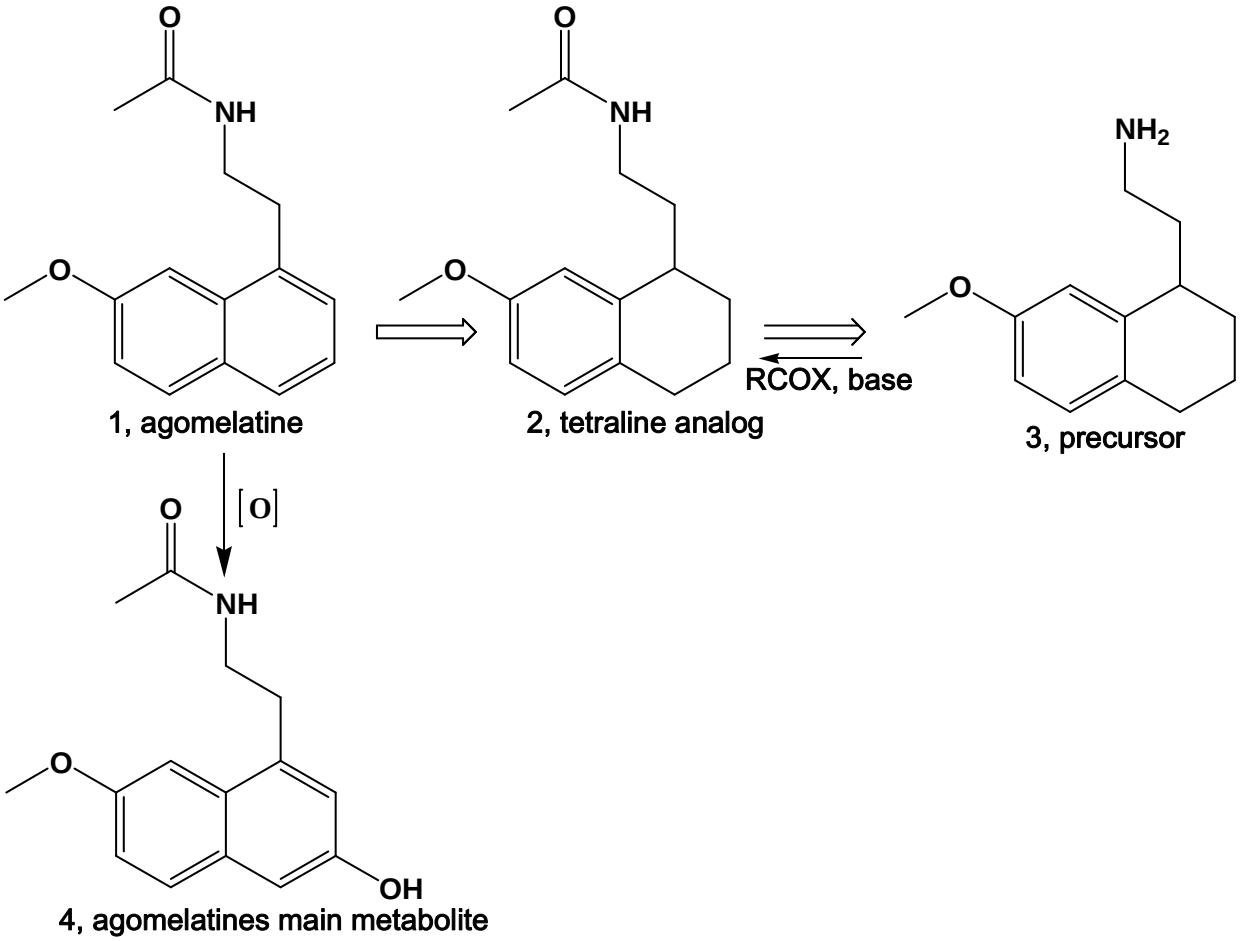
Keywords: agomelatine, melatonin, melatonergic agonist, thioamide, tetrahydronaphthalenic, bioisostere, microwave activation.

INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine),which is the endogenous ligand for melatonin receptors, plays an important role in modulating various physiological activities through acting on the different subtypes MT1, MT2 and the long-time elusive MT3 [1,2]. Due to its inherent short plasma half-life, melatonin is poorly endowed for druggability and consequently over the years since its discovery synthetic surrogates have appeared on the scene[3]. Agomelatine, a prominent one among them, (marketed under the different trade names of Valdoxan, Melitor, and Thymanax) is a melatonergic antidepressant, which was developed in the 1990's by the French pharmaceutical company Servier. It is used for the management of major depressive disorders and was reported to have a reduced level of side-effects compared to various other classical antidepressants. Moreover, Agomelatine may also have positive effects on the quality of the sleep[4]. Agomelatine is a melatonergic agonist atMT1 (Ki=0.10nM±0.01nM) and MT2 receptors (Ki=0.12nM±0.02nM)) as well as, a 5-HT2C antagonist (IC_{50}=270nM; pKi=6.15±0.04). The chemical structure of agomelatine is very similar to that of melatonin : while melatonin contains an indole framework, agomelatine possesses a naphthalene ring system which is a classical bioisostere of indole[5].

More specifically, the melatonin neurohormone exerts multiple pharmacological actions through two G-protein-coupled receptors MT1 and MT2which were already cloned in the mid-1990's. A so-called third melatonin binding site, the elusive MT3, having intrinsec lower affinity than MT1 andMT2 sites has later on been characterized as the hamster homologue of quinone reductase 2 (QR2 EC 1.6.99.2) [6]. Melatoninergic MT1 receptors are expressed in

several areas of the brain and in particular in the suprachiasmatic nuclei in the central nervous system (CNS) and the *pars tuberalis*. The MT2 receptors are present also in the CNS and the retina. Low affinity binding site MT3's exact biological relevance in mediating melatonin's physiological effects remains rather uncertain. Nevertheless, MT3 was shown to be involved in acute inflammatory responses in the rat and in the regulation of intraocular pressure in the rabbit [7].Agomelatine appears to be the first antidepressant marketed drug which does not inhibit monoamines reuptake. Consequently, it can be considered as the prototype of a new class of antidepressant drugs. Development of new analogs of this template remains therefore of paramount importance both for tuning up efficacy and reducing side-effects. Agomelatine, which is also a 5-HT2C selective antagonist was shown also to be a potent agent in resynchronization of the circadian rhythm [8].



Scheme 1. Retro-synthetic approach to the design and synthesis of tetraline analog of agomelatine

The importance of melatonin's receptors as a promising therapeutic target led to investigating pharmacophoric requirementsin order to improve binding affinity and obtain more selective ligands. Early SAR studies showed that both methoxy group and the *N*-acetylamino side chain of melatonin are crucial pharmacophoric components for high receptor affinity and that the relative distance and orientation between these groups must be considered also as an important factor . Moreover, 3D-QSAR analysis of melatoninergic ligands indicated that MT1 and MT2 binding affinities could be enhanced by conformational restriction of the amide side-chain. This approach may open up new therapeutic perspectives by targeting more efficiently and selectively the MT1 receptor. Indeed, agomelatine acts in the treatment of depressive symptomatology by a dual mode of action, *i.e.* both on MTI/MT2 melatoninergic receptors and 5-HT2C, a property utilized by current antidepressant drugs. This original mode of action allows to improve sleep efficiency and resynchronize the disrupted circadian rythms. It is known indeed that disruption of the sleep-wake cycle regulation is one of the main causes of depressive disorders [9-13].

Although agomelatine (**1**) is absorbed rapidly by the oral route, it is heavily metabolized in the liver through cytochrome P450 1A2 and 2C9 isoenzymes. The mean plasma half-life of agomelatine is 2.3 hours, due to major liver first-pass effect and unfortunately the oral bioavailability is <10%[14]. In an effort to correct this problem, based on structure-toxicity relationships and molecular modeling considerations,we designed an agomelatine analog using a tetraline scaffold. To this end, it became necessary to scale up the synthesis of a precursor which coud be then engaged in the construction of an agomelatine-like compound library. This paper reports our efforts along this

line specially with a view to optimizing and validating our route in order to have available an easy synthetic method which be applied to the construction of a compound library. The design of the tetrahydronaphthalenic analog (**2**) of agomelatine is presented in the Scheme 1 along with the structure of the precursor (**3**).

EXPERIMENTAL SECTION

General Procedures

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on a Bruker 400 spectrometer. Compounds were dissolved in DMSO-d_6. Chemical shifts are expressed in the δ scale with TMS as internal standard. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merk, Darmstadt, ref. 5735). All reported compounds were routinely checked in two standard solvents, *i. e.* acetone/toluene/cyclohexane (solvent A, 5:2:3, v/v/v) and chloroform/methanol (solvent B, 90/10, v/v). Reverse-phase thin layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merck), methanol: water (75/25, v/v). All compounds reported were found homogenous under such TLC and HPLC conditions. All reagents were purchased from Aldrich. All solvents were of the ACS reagent grade (Aldrich). Microwave-assisted synthesis experiments were performed using a CEM focused microwave synthesis system unit, model Discover (CEM Corporation Matthews, NC 28106-0200, USA; *cfr* www.cemsynthesis.com) in a 10 ml vessel equipped with a temperature and pressure-resistant septum available from the same commercial provider.

(E)-2-(2,3-dihydro-6-methoxynaphthalen-4(1H)-ylidene)acetonitrile (5). To a slurry of sodium hydride (1.2 g, 50 mmol) in dry THF (20 ml) was added dropwise over 15 min diethyl cyanomethylphosphonate (9 g, 50 mmol). After 1 h digestion, a solution of 6-methoxy-1-tetralone (5.1 g, 30 mmol) in dry THF (20 ml) was added dropwise over 15 min. The red solution was stirred at room temperature for 72 h, after which time THF was evaporated *in vacuo* and the residue was partionned between ether and distilled water. The ether solution was dried over magnesium sulfate, filtered and the filtrate was evaporated *invacuo* to give a powder which was recrystallized from ethanol:water to give a TLC pure material. Yield: 65 %. Mp = 58-60°C. IR and ^{1}H-NMR spectra are in all respects identical to that reported in the literature[15].

Classical synthesis of 5. A solution of 1.2 g of cyanoacetic acid and 1.7 g of 7 methoxy1-tetralone was treated with 1.0 g of p-toluenesulfonic acid hydrate and 1.0 g of piperidine in 20 ml of toluene. The heterogeneous mixture was heated under reflux using a dean-Stark water separator for 4 h until the reaction medium became clear and ~ 85% of the theorical amount of water was collected. The organic layer was then washed with an equivalent volume of 0.5 N NaOH and the toluene was evaporated *in vacuo* to give an oily residue which was recristallized from cyclohexane to give **5** with a 55 % yield. MP= 57- 59 °C. IR and ^{1}H-NMR are identical in all respects to that reported in the literature[15]. This synthesis was also carried out under microwave activation on a 1:10 scale.

(R, S) -2-(1, 2, 3, 4-tetrahydro-6-methoxynaphthalen-4-yl) ethanamine (3). To a stirred solution of (E)-2-(2,3-dihydro-6-methoxynaphthalen-4(1H)-ylidene)acetonitrile (5) (10 g, 50 mmol) in glacial acetic acid (50 ml) was added in one portion thioacetamide (7.5 g, 100 mmol) and then drop wise over 1 h period with concentrated hydrochloric acid (10 ml). After 24 h at room temperature, the reaction medium was evaporated *in vacuo* and the residue was dissolved in 100 ml of absolute ethanol and treated with 10 g of freshly prepared Raney nickel. The suspension was stirred and refluxed for 4 h after which time it was filtered. The filtrate was then treated was 2.5 g of 5 % palladium on charcoal in a Parr bottle and hydrogenated at room temperature using a Parr apparatus under an initial pressure of 45 psi for 2 h. The slurry is then filtrated using Celite and the filtrate is evaporated *in vacuo*. The final oily residue is dissolved in 50 ml of absolute ethanol, treated with concentrated hydrochloric acid, evaporated *in vacuo* and triturated with diethyl ether to give a precipitate which is collected on a Buchner funnel. Yield = 72 %. MP = 135 - 137°C. IR and ^{1}H-NMR spectra are identical to that reported in the literature[15].

7-ethyl-2-tetralone (7). To a solution of 5.0g of 4-ethylphenylbutyric acid (25 mmol) in 30 ml of polyphosphoric acid at 80°C was added portionwize 5g of phosphorus pentoxyde over 15 min period. The reaction medium turned reddish was stirred at 80°C for another 4 h, and was treated with 500 g of ice. After one hour digestion, the usual work up with diethyl ether gave oil which was rapidly filtered over silica gel using CH_2Cl_2 as eluent. This material was used as such in the next step. A sample was treated with 2.4-dinitrophenylhydrazine in diglycine and gave a crystalline 2, 4-dinitrophenylhydrazone derivative with MP 271-273°C in perfect accordance with the literature [16]. It should be noted that this synthesis can be expedited in 6 min using microwave activation at 250 W power.

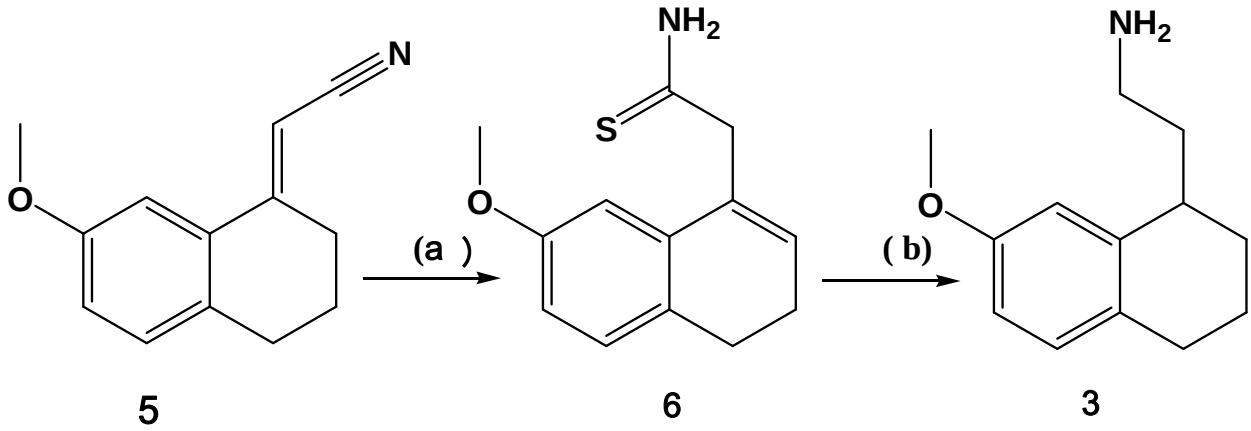
(R, S)-2-(7-ethyl-1.2.3.4-tetrahydro-1-naphthyl) ethylamine (8). Using the same sequence of reactions as for **1,** we obtained a hydrochloride with a 45% yield. MP= 116-118 °C , ^{1}H-NMR (300 MHz, DMSO-d6) 1.14 (t,3H, J=

7.0 Hz) , 1.67 (m,6H, 3 CH_2) , 2.63 (m, 7H, 3 CH_2 and 1CH), 6.81-7.11 (m, 3 H arom. H). This material was identical in all respects to that described previously [17].

RESULTS AND DISCUSSION

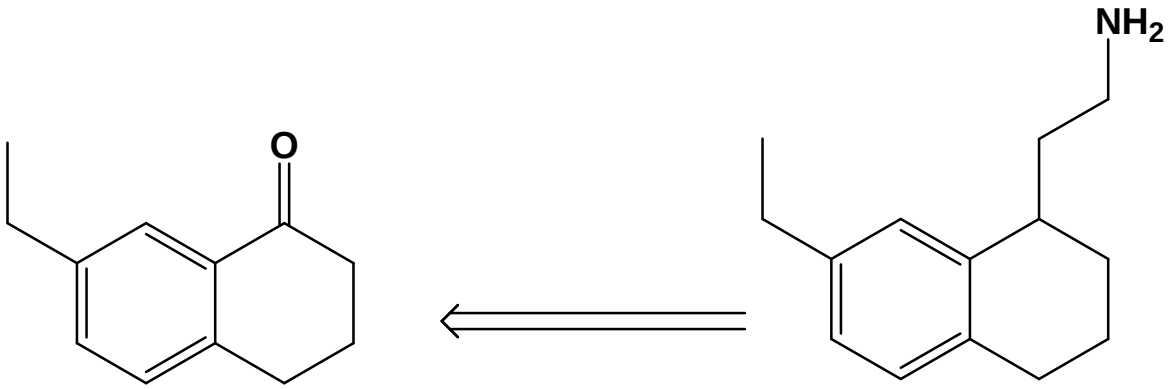
The main metabolic pathway of melatonin leading to **4** involves hydroxylation in 3-position due to activation of this position which is in conjugation with the methoxy substituent [18]. To interrupt the propagation of this electrodonating mesomeric effect, the most obvious strategy is to switch from aromatic sp2 carbons to sp3 carbons by formal reduction of the concerned ring. Examination of the literature reveals that compound **2** has been previously reported and shows an interesting binding affinity profile for MT1 (Ki=0.26 nM) which is very similar to that of the endogenous ligand [15]. This result clearly indicates that the aromaticity of the ring bearing the side chain may not be an essential feature for melatoninergic agonist activity. Melatonine's indole ring appears to play mostly a tensor role and can therefore be replaced by a non-aromatic moiety provided the two pharmacophore side-chains are correctly positioned, one versus the other in space.

Our synthetic route to the title compound is depicted in the Scheme 2. 6-Methoxy-1-tetralone, a compound that is nowadays readily commercially available, when treated with sodium hydride and diethyl cyanomethylenephosphonate, gives the corresponding unsaturated nitrile (**5**). Provided the reaction is performed under controlled temperature and for 3 days, a 65 % yield can be warranted. The main advantage of this route*i. e.*Wadsworth-Emmons reaction*vs.* the Reformatsky reaction which makes use of metal zinc and a halogenated precursor [19], is that the exact location of the double bond can be properly ascertained. Here, the ^{1}H-NMR studies showed as previously reported that the double bond was *exo*-cyclic. Moreover, for compound **5**, ^{1}H-correlation COSY NMR data showed the selective formation of the E isomer exclusively, in accordance with the precedence in the literature (15).



Scheme 2: Synthetic route to (*R, S*)-2-(1,2,3,4-tetrahydro-6-methoxynaphthalen-4-yl)ethanamine. Methods : (a) $CH_3C(=S)NH_2$, CH_3COOH, cc. HCl, 24 h, rt.; (b) Raney nickel, absolute, EtOH, reflux, 4 h; cyclohexene 5% Pd/C, 45 psi, 2h, rt

The synthesis then proceeded *via in situ* thiohydrolysis of **5** using thioacetamide as sulfurization transfer agent under acid catalysis; this process is accompanied with the migration of the double from an*exo-cyclic* position to an*endo-cyclic* localization, a process known to be acid-catalyzed and, proceeding *via* the formation a tertiary carbocation intermediate. Desulfurization was accomplished using freshly prepared Raney nickel in refluxing absolute ethanol and after filtering the excess of Raney nickel and the concomitantly resulting black nickel sulfide(NiS), reduction of the double bond was carried out by catalytic tranfer hydrogenation using cyclohexene and 5% palladium on charcoal in the same solvent. It is noteworthy that intermediate thioamide **6** does not have to be formally isolated and the synthesis can be easily upscaled. Compound **1** had spectral data similar to that of the material obtained by the classical method. The overall yield could be optimized up to 72 %. To further substantiate our synthetic approach, we synthesized the 7-ethyl analog **(8)** using the corresponding tetralone as starting material (**7**) as shown on Scheme 3**.**It should be noted that both **1** and **8** contain a chiral center. The resolution of the enantiomers can be achieved CD-EKC technique[17].



7 **8**

Scheme 3:Retro-synthesis of the ethyl-analog (8) from the tetralone precursor (7)

CONCLUSION

Using a concise synthetic method involving a three-step approach, we successfully designed a tetraline scaffold, an original template which subsequently could be further elaborated into a compound library of agomelatine analogs. Further work is now under progress along this line.

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