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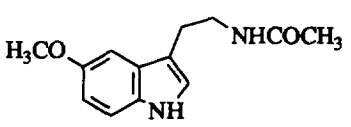
SYNTHESIS AND BIOLOGICAL ACTIVITY OF CONFORMATIONALLY RESTRICTED TRICYCLIC ANALOGS OF THE HORMONE MELATONIN

V. Leclerc[1], P. Depreux[1], D. Lesieur[1*], D.H. Caignard[2], P. Renard [2], P. Delagrange[2], B. Guardiola-Lemaitre[2], P. Morgan[3]

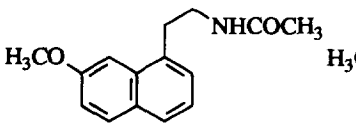
[1]Institut de Chimie Pharmaceutique, 3 rue du Professeur Laguesse, B.P. 83, 59006 Lille France
fax : 19.33.20.96.43.61 ; E-mail : dlesieur @ phare.univ-lille2.fr
[2] ADIR et Cie., 1 rue Carle Hébert, 92415 Courbevoie France.
fax : 19.33.16.1.46.41.60.11
[3] Rowett Research Institute, Aberdeen, Scotland, United Kingdom.

Abstract : A serie of rotationally restricted tricyclic naphthalenic and tetrahydronaphthalenic analogs of the hormone melatonin has been synthesized, the C-7 oxygen being incorporated in a pyran, furan or dioxan heterocyclic ring. The receptor binding profile of these compounds is a function of the directionality of the lone pairs electrons of this C-7 oxygen. In these two studied analogous series the agonist activity seems to be correlated with the existence of a naphthalene nucleus.

Since its discovery in the amphibian melanocytes[1], the hormone melatonin (N-acetyl 5-methoxytryptamine) has become an area of increased activity in recent years. Melatonin is now considered as an important mediator of photoperiod implied in the regulation of seasonal physiological processes[2], and in man, melatonin has a potential usefulness to a number of therapeutic areas such as those related to the desynchronisation of biological rhythms, like disturbed sleep-wake cycles[3,4], seasonal disorders[4] and depression[4]. The application of melatonin in therapeutic, however, is limited because of its inadequate metabolic stability[5] (very short biological half-life) as well as its poor selectivity of action. For these reasons, development of novel analogs provides a strategic approach to overcome these limitations and to define melatonin receptor subtypes pharmacology. Our design of novel melatonin ligands was based on the structure of melatonin where replacement of the indole nucleus by the bioisosteric naphthalene one led to **1**, an equipotent melatonin ligand[6,7]. Our previous studies have also shown that the aromatic character of the cycle bearing the acetylaminoethyl side chain is not necessary since the affinity of the tetrahydronaphthalene derivative **2** is the same as that of the corresponding naphthalenic lead compound[8].



Melatonin



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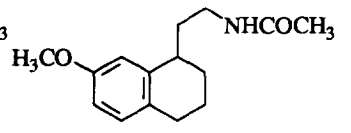

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Several investigations of structure-activity relationships have been reported and the informations available to us suggest that both the N-acetyl and 5-methoxy substituents are necessary for biological activity and binding affinity at the receptor level[9]. From the studies of Garratt et al.[10], it seems clear now that the biological activity of some indolic analogs of melatonin is correlated with the conformation of the C-3 N-acetylaminoethyl side chain and with the distance between this group and the 5-methoxy one. These studies gave a considerable justification to the view that the higher activity of 2-halo or 2-phenyl derivates of melatonin arised from the C-3 side chain being restricted into favourable conformations for interaction with the receptor[11].

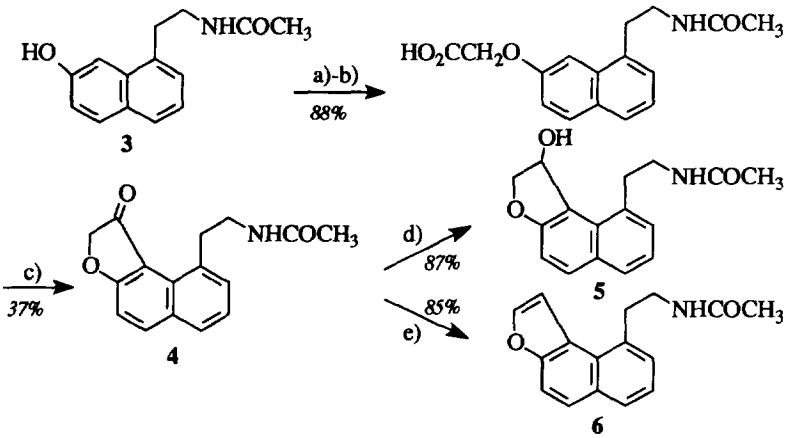
On the other hand, as previously mentioned, the methoxy group is an important factor for the activity and the affinity of melatonin receptor ligands. It has generally been assumed that the 5-OCH_3 group of melatonin functions as a hydrogen bond acceptor with serine (Ser 115) group of the recently cloned "ML1" receptor[12]. In order to progress in the area to the spatial and electronic restrictions imposed by the receptor structure on melatonin analogs and thus to explore the directionality requirements of this hydrogen bond accepting interaction, it appeared to us very desirable to design and synthesize conformationally restricted analogs of melatonin. Most of our efforts have been directed towards the synthesis of conformationally restricted tricyclic analogs of the C-7 methoxy group of the naphthalenic bioisostere of melatonin, lead compound **1**. This research has given rise to the synthesis of naphtho[2,1-b]pyrans and naphtho[2,1-b]furans (**4-9**). 7,8 and 6,7 cyclised tetrahydronaphthalene **10** and **12** derivatives were also considered.

We report here the synthesis and biological activity of these melatonin analogs. Conformational requirements are also discussed on the basis of the structure-activity study.

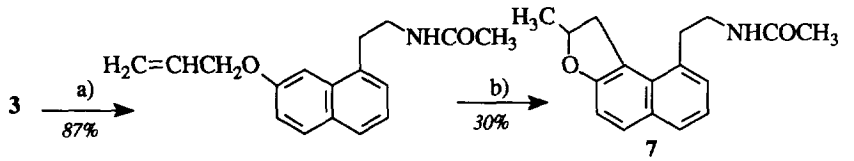
The naphthalenic compounds were synthesized as shown in the following schemes. In most cases the starting material is the previously described[7] 7-hydroxynaphthalene derivative **3**.

The naphtho[2,1-b]furanoketone **4** was obtained using an intramolecular cyclization of an aryloxyacetic acid[13]. $NaBH_4$ reduction of **4** led to **5**[14]. Use of excess of reducing agent in acidic medium permitted access to **6**[15]. Reaction of **3** with allyl bromide gave an allylether that under an acidic lithium perchlorate catalyzed cyclization[16] afforded the methyl substituted naphthodihydrofuran **7**. Intramolecular cyclisation of an aryl propargyl ether led to the naphthopyran **8**[17], followed by catalytic reduction gave the tetrahydronaphthalenic compound **10**[18], whereas magnesium in methanol only reduced the pyranic moiety to give **9**[19]. To access to the tetrahydronaphthalenic compound **12**, commercialy available 6,7-dimethoxytetralone was first demethoxylated with HBr to give the diphenol **11**[20]. Reaction of **11** with 1,2-dibromoethane led to a dioxanoketone, that permitted access to **12** using successively a Wadsworth-Emmons reaction with diethylcyanomethyl phosphonate[21] and catalytic reduction in the presence of acetic anhydride of the intermediary unsaturated nitrile. In these reactions, compounds **5**, **7**, **10**, **12** were obtained and then studied as a racemic mixture.

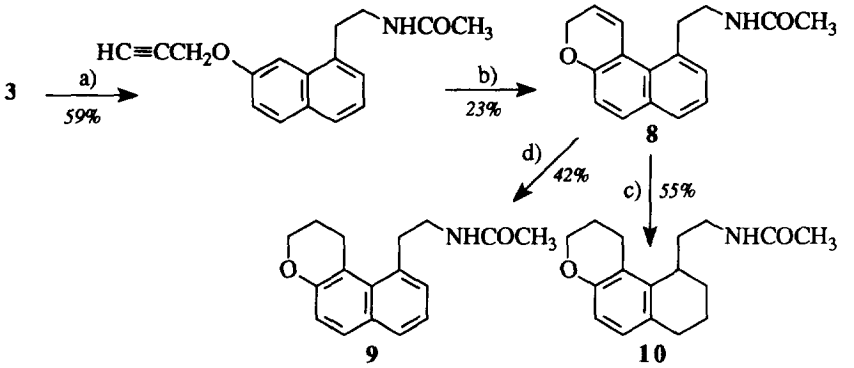
The binding affinity of the studied compounds was determined by a 2-[^{125}I]-melatonin radioligand binding assay in ovine pars tuberalis membranes and the results, shown in tables, are expressed in terms of Ki if the binding curve is monophasic or in terms of K_H and K_L if the curve is biphasic. Activity was evaluated for the agonists by the potential inhibition of cAMP production stimulated by forskolin[22,23]. In such conditions, some ligands induced potentialisation of the forskoline effects.



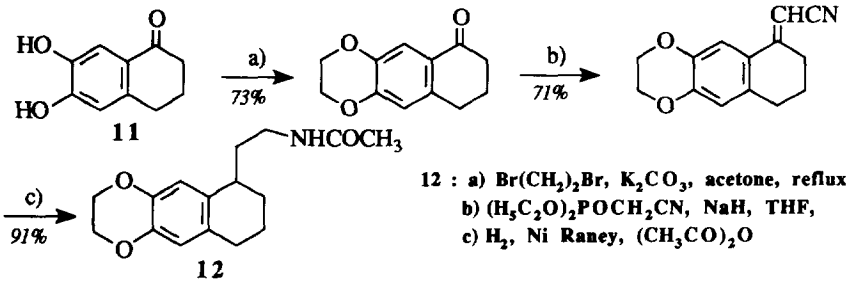
4, 5, 6 : a) $BrCH_2CO_2C_2H_5$, K_2CO_3, acetone, reflux; b) NaOH; c) polyphosphorique acid, heat; d) $NaBH_4$ (2 éq.), CH_3OH; e) $NaBH_4$ (4 éq.), HCl, CH_3OH



7 : a) $BrCH_2CH=CH_2$, K_2CO_3, acetone, reflux; b) CF_3CO_2H, $LiClO_4$, 60°C



8, 9, 10 : a) $TosCH_2C{\equiv}CH$, NaH, DMF; b) heat, triethylene glycol; c) H_2, Ni Raney, C_2H_5OH d) Mg, CH_3OH



12 : a) $Br(CH_2)_2Br$, K_2CO_3, acetone, reflux b) $(H_5C_2O)_2POCH_2CN$, NaH, THF, c) H_2, Ni Raney, $(CH_3CO)_2O$

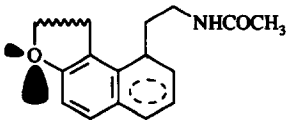
Compared to melatonin (Ki = 9.15 10^{-11}M) and **1** (Ki = 1.00 10^{-10} M) the naphthofuranic derivatives (**4-6**) show an agonist activity with a lower affinity for the ovine pars tuberalis melatonin receptor. From binding data, it is apparent that the degree of saturation and substitution of the furanic moiety has a significant effect on the affinity. While the dihydro compounds substituted by a ketonic (**4**) or an alcoholic oxygen (**5**) being the lowest ligands, the dihydro derivative **7** (racemic mixture) substituted by a methyl group is an agonist that shows a very high affinity (K_H = 6.9 10^{-15}M) referred to a biphasic curve.

Compd.	Ki (M)	K_H (M)	K_L (M)	Activity
4	1.39 10^{-8}			Agonist
5	1.30 10^{-7}			Agonist
6	7.80 10^{-10}			Agonist
7		6.90 10^{-15}	1.20 10^{-9}	Agonist
8	1.37 10^{-10}			Agonist
9	2.16 10^{-10}			Agonist
10	6.17 10^{-9}			1)
12	6.22 10^{-8}			1)

1) Potentialisation of forskoline stimulated cAMP production

The naphthopyrans **8** and **9** are agonists with an affinity equipotent to that of melatonin. In the racemic tetrahydronaphthalenic serie (**10,12**), whereas **2** is an agonist with an equipotent affinity as that of melatonin and **1**, incorporation of the C-7 oxygen in an heterocycle (**10**) leads to a diminution of the affinity compared to the naphthalenic analog (**8**) but especially to a completely different type of activity, i.e. a potentialisation of forskoline stimulation on cAMP production. The 6,7 disubstituted dioxan like derivative (**12**) has a lower affinity than that of **10** but the same type of activity.

Our work represents an important clue for the construction of a pharmacophoric model of the melatonin receptor. It provides a direction for further research involving other conformationally restricted analogs of melatonin. The results of this work suggest some important molecular recognition elements concerning ovine pars tuberalis melatonin receptor and their ligand's interaction. Since **7** shows a biphasic curve, it can be inferred that this compound interacts with two types of receptor. Otherwise, our binding results indicate first that the methoxy group of melatonin and related analogs is involved in the affinity and the activity. Then the orientation of the oxygen lone pairs of electrons interacting with an amino acid residue of the receptor is optimal for the 7,8-disubstituted naphthalenic (**4-9**) or tetrahydronaphthalenic (**10**) compounds. This hypothesis may then suggest that the dioxan **12**, which possesses the opposite directionality of the C-7 oxygen lone pairs of electrons should have a lower melatonin receptor affinity.



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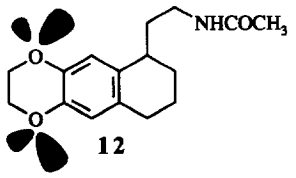

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An alternative hypothesis is that the low affinity of this compound might be a result of steric or electronic interferences involving the C-6 oxygen.

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