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SYNTHESIS OF BENZOCYCLOALKANE DERIVATIVES AS NEW CONFORMATIONALLY RESTRICTED LIGANDS FOR MELATONIN RECEPTORS

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Abstract: ***Benzocycloalkane derivatives 1-4 were synthesized as new conformationally restricted melatoninergic ligands. They were prepared by the reaction of the ketones 5 with diethylcyanophosphonate and the reduction of the corresponding cyano compounds or by the Wittig reaction and Curtius degradation to obtain the amines 8. The 1-Cyanobenzocyclobutane derivative was obtained by the benzyne cyclisation reaction. The amines 8 were acylated with acetyl, propionyl or butyryl groups. The affinity of the compounds for chicken brain melatonin receptors was evaluated using 2-[^{125}I]-iodomelatonin as the radioligand. The indanyl (2b,c), tetralin (3a-c) and benzocycloheptane (4c) derivatives were potent compounds with nanomolar affinity and an important enantioselectivity of the receptor was observed with the (+) enantiomers 2b and 3b.***

Melatonin (N-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone that is secreted during darkness[1]. It is now well recognized that it regulates the circadian rhythm[2] in a large number of animals and humans. It can be used to control diseases associated with circadian rhythm disorders. Melatonin alleviates jet-lag[3], regulates delayed sleep phase syndrome[4] and induces sleep[5]. Conversely, it has been implicated in seasonal and winter depression[6]. Melatonin controls the breeding cycle in photoperiodic species and can be used to induce reproduction outside of the breeding season[7]. In addition, melatonin has been shown to have antiproliferative effects on mammary cell lines[8].

It has been demonstrated that a number of the effects of melatonin are mediated through G protein-coupled receptors[9], the genes for which have been cloned[10] and coupling to one of the G_i family of G proteins appears to be the common signalling pathway for the receptors characterized to date.

Recently, considerable interest has evolved in the design of melatonin receptor ligands capable of mimicking or antagonizing the response to melatonin[11,12]. In particular, several constrained melatoninergic ligands have been reported[12], where the melatonin pharmacophore groups were incorporated in a ring . Several tricyclic structures were produced incorporating the alkoxy moiety and/or the side-chain in a ring[12]. Thus the indole derivatives described by Garratt[13] and Spadoni[14] possessed the partially constrained

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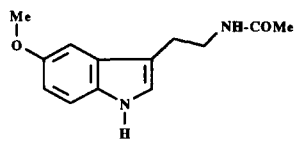
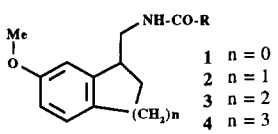
C-3 amidoethane side-chain. The SAR of these compounds showed the advantage of the partially constrained structures over the totally rigid structure. These results confirmed the model of the melatonin pharmacophore resulting from the 3D-QSAR studies reported by us[15], where it was shown that melatonin preferred to adopt the folded conformation in the receptor site. On the other hand, it was demonstrated that the indole and the bioisosteric naphthalene rings were not essential for a good recognition by the melatonin receptors as several alkylamides such as N-[2-(3-methoxyphenyl)ethyl]butyramide were described as potent ligands for melatonin receptors[16,17]. Recent reports about the tetralin derivative of S20098, a melatoninergic agonist[18], and the tricyclic indole derivatives[19] urge us to give the preliminary results obtained with a series of benzocycloalkane derivatives as melatonin receptor ligands. With the goal of preparing potent ligands, the [2-(3-methoxyphenyl)ethylamido] moiety was introduced into the bicyclic systems **1-4** with various ring size (n = 0, 1, 2, 3) and the partially constrained ethylamido chain. Preliminary modelling of these molecules showed that they had a suitable fit with the previously determined putative melatonin pharmacophore.



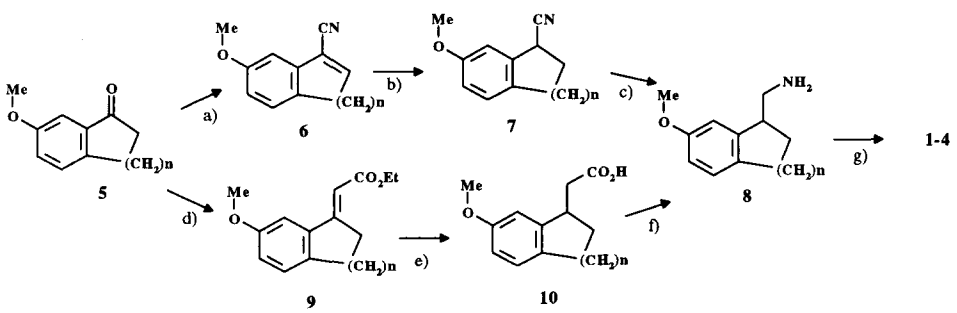
Melatonin



1 n = 0
2 n = 1
3 n = 2
4 n = 3

a R = Me
b R = Et
c R = Pr

The compounds **1-4** were evaluated on their affinity for the chicken brain melatonin receptors and compared to the reference compounds, melatonin and S 20098[20]. They were prepared from the amines **8** (scheme 1) synthesized following several methods.



Scheme 1. a) $(EtO)_2PO(CN)$, LiCN, THF, MsOH, toluene; b) $NaBH_4$, MeOH, $NaHCO_3$, H_2O; c) H_2, EtOH, Ni Raney, NH_3 aq.; d) $(EtO)_2POCH_2COOEt$, NaH, THF, r.t.; e) NaOH 10%, Ni-Al, Δ; f) NaN_3, ClCOOEt, Et_3N; HCl, aq., THF, Δ; g) $(RCO)_2O$, K_2CO_3, H_2O; CH_2Cl_2, r.t.

The compounds **2-4** (n = 1, 2, 3) were synthesized through the synthetic pathways described in the scheme 1. For n = 1 and 2, the commercially available ketones **5**, were reacted with diethylcyanophosphonate[21] in the presence of LiCN in a DMF/THF mixture to give, after hydrolysis by methanesulfonic acid in toluene, the unsaturated cyano compound **6** (n = 1, 2). They were reduced to the amines **8** (n = 1, 2) by a two steps process: the saturated nitrile **7** was obtained with $NaBH_4$ in MeOH, followed by catalytic reduction in the presence of Raney Nickel. The ketone **5** (n = 3) was prepared by a process previously reported[22] and it was transformed through the Wittig reaction to the acid **10** which gave the amino derivative **8** (n = 3) by the Curtius reaction. On the other hand, 1-cyano-5-methoxybenzocyclobutane **7** (n = 0) was synthesised by an alternative pathway using the cyclisation of 3-bromo-4-methoxyphenyl propionitrile in the presence of sodium amide (yield: 70%)[23]. Compound **7** (n = 0) was reduced to the amine **8** (n = 0) by catalytic hydrogenation with Raney Nickel as the catalyst. The amines **8** were acylated by the anhydride method, according to the processes already reported[16], to provide compounds **1-4** (R = Me, Et, Pr).

Compounds **1-4** were characterized by their NMR spectra and microanalysis. The (+) and (-) enantiomers of compounds **2b** (α_D = +11 ± 3° and α_D = -10 ± 3° respectively) and **3b** (α_D = + 32 ± 2° and α_D = -34 ± 2° respectively) were separated with a high enantiomeric purity by HPLC using the CHIROS-BOND chiral column.[24]

The affinity values (K_i) of compounds **1-4** for chicken brain melatonin receptors were evaluated in binding assays using 2-[^{125}I]-iodomelatonin according to the method already described[16] and the results are reported in Table 1.

The data demonstrated clearly that the affinities of the compounds were related to the ring size, the indan (n = 1) and tetralin (n = 2) moieties (compounds **2** and **3**) and the more flexible benzocycloheptane **4** being more favourable. In contrast, the rigid system such as the benzocyclobutane derivatives **1** was clearly less favourable. Furthermore, as has been reported previously the potency also depended upon the length of the amido chain, as the butyramido compounds were the most potent. Thus, derivatives **2c**, **3c** and **4c** (K_i = 7.6, 0.53 and 1 nM respectively) had nanomolar affinity. Moreover, the marked enantioselectivity of melatonin receptors for these compounds was clear as the activity of the enantiomers of **2b** and **3b** resided essentially in the (+) enantiomers (K_i = 3 and 0.45 nM respectively). These data agree with the results obtained previously with the partially constrained tricyclic indoles[19] with a β chiral center, where the (-) enantiomer was 2 orders of magnitude more potent than the (+) enantiomer. These results can be also compared to those reported on tetralinyl and indanyl ethylamides[18,25], the partially saturated analogues of the melatonin bioisosteres. According to the data reported recently by Lesieur[18] on the tetralinyl

ethylacetamido derivative, it appears that the affinity was not influenced by the length of the alkyl chain as the tetrahydro derivative of S 20098 was equipotent to **3a** with regard to the affinity given for melatonin.

AFFINITIES OF COMPOUNDS 1-4 FOR CHICKEN BRAIN MELATONIN RECEPTORS

Compound	n	R	[a]K_i (nM)
1a	0	Me	224 [157-321]
1b	"	Et	40 [29-55]
1c	"	Pr	49 [22-108]
2a	1	Me	77 [60-94]
(±) **2b**	"	Et	16 [9-22]
(+) **2b**	"	"	3 [2-5.5]
(-) **2b**	"	"	456 [356-553]
2c	"	Pr	7.6 [6.1-9.4]
3a	2	Me	4[2.7-3.7]
(±) **3b**	"	Et	0.53 [0.25-0.7]
(+) **3b**	"	"	0.45 [0.35-0.75]
(-) **3b**	"	"	>1000
3c	"	Pr	0.45 [0.35-0.57]
4a	3	Me	34 [25-45]
4b	"	Et	29 [22-37]
4c	"	Pr	1 [0.67-1.54]
S 20098			0.54 [0.4-0.67]
Melatonin			0.7 [0.4-1.2]
2-acetamido-8-methoxytetralin			161 ± 35

Table 1. a) 2-[^{125}I]-iodomelatonin was used as the radioligand and the binding assays were carried out using membranes prepared from chicken brain. Membrane aliquots (30 µL) were incubated in a total volume of 0.25 mL of Tris-HCl buffer (50 mM, pH 7.4) with 0.05 nM 2-[^{125}I]-iodomelatonin and seven concentrations of the compound under test. The incubation (25°C, 60 min) was stopped by the addition of 3 mL of ice-cold buffer and immediate filtration. Each binding assay was performed in triplicate. Non-specific binding was defined with 10 µM 2-iodomelatonin and represented about 10% of the total binding. $K_i$values are expressed in nM and were calculated using the Cheng-Prussof equation, 95% confidence limits are in brackets, except for 2-acetamido-8-methoxytetralin where the standart error of the mean (SEM) was calculated (PRISM software package). $K_i$values are the results of 2 separated determinations.

These data have demonstrated the interest of the simple bicyclic structure and the importance of the partially constrained side-chain to obtain potent melatonergic ligands. In particular, these compounds were more potent that the corresponding totally locked compounds derived from 2-amino tetralin[26] (Table 1) or phenalene[27]. They demonstrated also that the 3-methoxyphenyl moiety is an excellent bioisosteric group

for the indole ring as the compounds were equipotent for the chicken brain melatonin receptors to the structurally closely related tricyclic indole derivatives described recently[19]. These compounds constitute new molecular tools to improve the mapping of the melatonin receptor. On the other hand, the influence of this structural modification on the effect of these molecules on the adenylate cyclase activity and the aggregation of melanosomes of *Xenopus laevis* tadpoles is currently under investigation.

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