2-Amido-8-methoxytetralins: A Series of Nonindolic Melatonin-like Agents†

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A series of unsubstituted and methoxy-substituted 2-amidotetralins (**4a–q**) was prepared and evaluated for their ability to compete for 2-[^{125}I]iodomelatonin binding to chicken retinal membranes and for their potency to inhibit the calcium-dependent release of [^{3}H]dopamine from rabbit retina. The lead compound, 2-acetamido-8-methoxytetralin (**4j**), showed a moderate affinity (K_i = 46 nM) and potency (IC_{50} = 1.4 nM) at the melatonin receptor. The structural requirements necessary for optimal agonistic activity at the melatonin receptor are as follows. First, the amido group, which should have a small, nonbranched alkyl group, is essential for affinity, and second, the methoxy substituent at the 8-position of the 2-amidotetralin ring is essential for optimal agonistic activity at the melatonin receptor. We concluded that this series of unsubstituted and methoxy-substituted 2-amidotetralins constitutes a class of nonindolic melatonin-like agents that can be used as pharmacological tools to further characterize melatonin receptors and to elucidate the mode of action of melatonin.

Introduction

Considerable effort has been devoted to understand the mechanism of action of melatonin (**1**, Chart I)[1] since this hormone was isolated and identified as N-acetyl-5-methoxytryptamine by Lerner et al. in the late 1950's.[2] In vertebrates the primary sites of production of this hormone are the pinealocytes of the pineal gland[1e,3] and the photoreceptor cells of the retina.[4] Both organs synthesize melatonin from serotonin via a two-step biochemical pathway.[1e,3,4] The synthesis and secretion of melatonin follows a circadian rhythm reaching a maximum at night.

Melatonin is known to play a key role in the transduction of photoperiodic information[1e,5] and to modulate a variety of endocrinological, neurophysiological, and behavioral functions in vertebrates,[1c,4,6] including the regulation of reproduction,[6a–c] the control of circadian rhythms,[6c–d] and the modulation of retinal physiology.[4] The recent synthesis of 2-[^{125}I]iodomelatonin, a high-affinity radioligand,[7] and the development of quantitative *in vitro* receptor bioassays[8] have led to the localization of target sites for melatonin in discrete regions of the vertebrate brain, retina, and pituitary and to the pharmacological characterization of its receptor.[9]

These tools allow also the development of potent and selective melatonin agonists and antagonists. These agents can be used to further elucidate the mode of action of melatonin and may find application therapeutically in the synchronization of disrupted circadian rhythms as found in blindness, jet lag, shift-work syndromes, old age, and some affective disorders.[1c,e,10] Also, their influence on the reproductive system, other neuroendocrine functions, and retinal physiology could add to their therapeutic value.[1c,e,10]

To date, most of the known melatonin agonists are derivatives of melatonin itself, *e.g.* 2-iodomelatonin (**2a**), 6-chloromelatonin (**2b**), and 6,7-dichloro-2-methylmelatonin (**2c**), and contain as essential moieties the amido function and the 5-methoxyindole ring system.[7d,e,g–i,8c,11,12a] Recently, a series of melatonin analogues with a naphthalene nucleus instead of an indole nucleus was described.[13] On the other hand, *N*-acetyltryptamine (**3a**), a compound lacking the 5-methoxy group, appears to be a melatonin antagonist or a partial melatonin agonist.[7e,i,8b,c,11c] Attachment of a lipophilic group to the 2-position of the indole nucleus of *N*-acetyltryptamine (**3a**) produced the competitive melatonin antagonist luzindole (2-benzyl-*N*-acetyltryptamine, **3b**).[7i,12] On the basis of these findings Dubocovich[8c,9a] concluded that the *N*-acetyl group of melatonin is primarily responsible for affinity and the 5-methoxy group for intrinsic activity.

Closer examination of the melatonin structure shows that the side chain possesses rotational freedom, and consequently, many conformations with little difference in energy are possible.[14] This conformational flexibility is probably responsible for the broad spectrum of biological activities of melatonin. Rigid compounds, incorporating the essential moieties of melatonin, *i.e.* the amido function and the 5-methoxy group, in such a way that they can be

Chart I

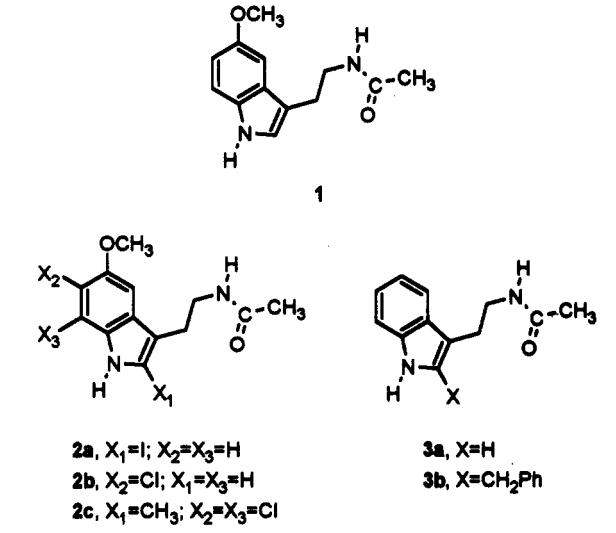

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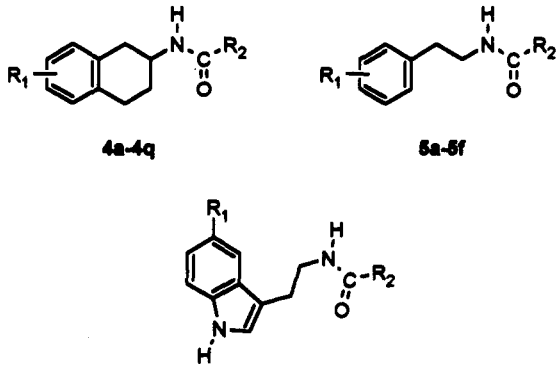
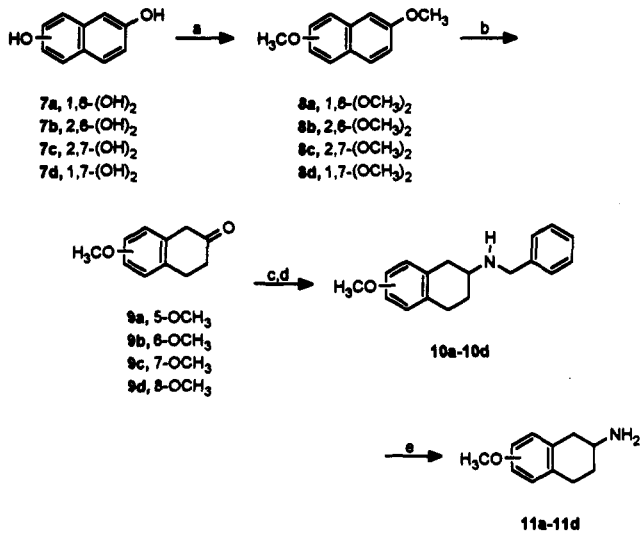
Chart II



Scheme I[a]



[a] Reagents: (a) $(CH_3)_2SO_4$, NaOH; (b) Na, EtOH, 2 N HCl; (c) $PhCH_2NH_2$, *p*-TsOH·H_2O; (d) PtO_2, H_2; (e) Pd–C (10%), H_2.

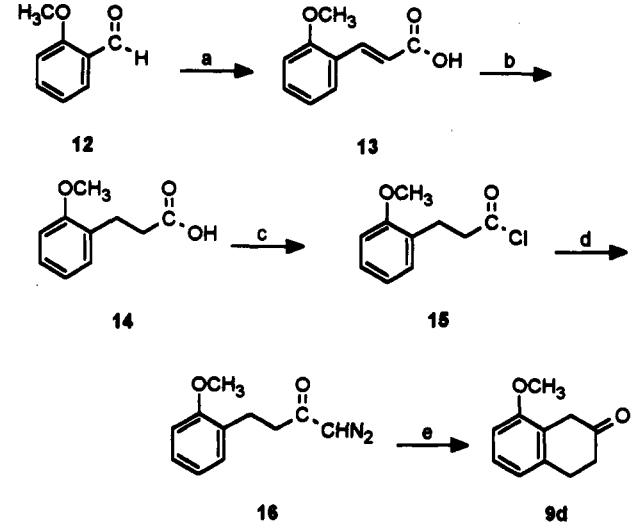
superimposed on the essential moieties of melatonin, when it adopts a low-energy conformation, may be melatonin agonists and perhaps more selective than melatonin itself, due to their conformational constraint. The successful development of the tetralin system as a structural base for the synthesis of rigid dopamine and serotonin agonists[15] prompted us to investigate this rigid structure as a template for nonindolic melatonin-like agents.

A series of unsubstituted and methoxy-substituted 2-amidotetralins **4a–q**[16,17] (Chart II) was synthesized. Their affinity and potency at the melatonin receptor were evaluated on 2-[^{125}I]iodomelatonin binding to chicken retinal membranes[7e] and calcium-dependent release of [^{3}H]-dopamine from rabbit retina,[7e,8a–c,12a] respectively. For comparative purposes, series of unsubstituted and methoxy-substituted phenethylamides **5a–f** and 5-methoxytryptamides **6a,b**[11a,11f] also were synthesized and evaluated.

Chemistry

Key intermediates in the synthesis of the amides **4a–6b** were the corresponding primary amines. For the synthesis of the amides **4a–f**, **5a–f**, and **6a,b** the primary amines were obtained from commercial sources. The precursors for the synthesis of the methoxy-substituted 2-amidotetralins **4g–q** were prepared according to known procedures, as outlined in Scheme I. Briefly, the appropriate dihydroxynaphthalenes **7a–d** were methylated and subsequently reduced according to a modification of the method of Cornforth et al.[18] to give the appropriate methoxy-2-tetralones **9a–d** upon acid hydrolysis.[18,19] These tetralones **9a–d** yielded in turn the desired methoxy-2-aminotetralins **11a–d** after condensation with benzylamine, a catalytic hydrogenation, and a catalytic debenzylation.[15b,d,20]

Scheme II[a]



[a] Reagents: (a) $CH_2(COOH)_2$, pyridine, piperidine; (b) Pd–C (10%), H_2; (c) $SOCl_2$; (d) CH_2N_2; (e) $[Rh(CH_3COO)_2]_2$, CF_3COOH.

Since 1,7-dihydroxynaphthalene (**7d**) is difficult to obtain commercially, we prepared 8-methoxy-2-tetralone (**9d**) via an alternate synthetic pathway, as outlined in Scheme II. This pathway has been used before by Nichols et al.[21] to synthesize 5,6-methylenedioxy-2-tetralone and 6,7-methylenedioxy-2-tetralone. The crucial step is the conversion of the diazoketone **16** to **9d** via a rhodium(II) acetate catalyzed cyclization, followed by a transformation under the influence of trifluoroacetic acid. This conversion has been reported previously by McKervey et al.[22] The yield of this conversion was maximally about 20%, which is much lower than the yield of McKervey (84%). In retrospect, synthesis of 8-methoxy-2-tetralone (**9d**) according to Scheme I is much more convenient. Hence, we used 8-methoxy-2-tetralone (**9d**) prepared according to Scheme I for the synthesis of 8-methoxy-2-aminotetralin (**11d**).

The preparation of the amides **4a–6b** (Table I) from the corresponding primary amines involved acylation by two different methods. The first utilized the appropriate anhydride in the presence of sodium acetate and the biphasic medium H_2O/EtOAc (method A), and the second employed the appropriate acyl chloride in the presence of sodium hydroxide and the biphasic medium H_2O/CH_2Cl_2 according to the Schotten–Baumann procedure (method B).

Pharmacology

The amides **4a–6b** were evaluated for their affinity at melatonin binding sites by competition with 2-[^{125}I]-iodomelatonin binding to chicken retinal membranes (Table II). This radioligand binding assay was conducted essentially as reported by Dubocovich and Takahashi.[7e] The HCl salt of amine **11d** was also tested in this radioligand binding assay (K_i > 100 000 nM). The amides **4a–6b** were also evaluated for their ability to inhibit the calcium-dependent release of [^{3}H]dopamine from rabbit retina (Table II) as described by Dubocovich.[8a–c]

Table I. Physical Properties of the Amides 4a–6b

compd	R_1	R_2	method of prep[a]	yield, %[b]	mp, °C	recrystn solvent[c]	anal. formula[d]
4a	H	CH_3	A	65	109–111	A/H	$C_{12}H_{15}NO$
4b	H	C_2H_5	A	86	99–101	A/H	$C_{13}H_{17}NO$
4c	H	n-C_3H_7	A[e]	81	81–82	A/H	$C_{14}H_{19}NO$
4d	H	CH_2Cl	B	56	131–133	A/H	$C_{12}H_{14}NOCl$[f]
4e	H	CH_2Ph	B	72	119–121	A/H	$C_{18}H_{19}NO$
4f	H	Ph	B	69	154–156	A/H	$C_{17}H_{17}NO$
4g[g]	5-OCH_3	CH_3	A	62	158–159	A/H	$C_{13}H_{17}NO_2$
4h	6-OCH_3	CH_3	A	64	115–116	A/H	$C_{13}H_{17}NO_2$[h]
4i	7-OCH_3	CH_3	A	51	105–108	A/H	$C_{13}H_{17}NO_2$
4j[g]	8-OCH_3	CH_3	A	79	156–157	A/H	$C_{13}H_{17}NO_2$
4k	8-OCH_3	C_2H_5	A	31	151–152	A/H	$C_{14}H_{19}NO_2$
4l	8-OCH_3	n-C_3H_7	A[e]	63	139–140	A/H	$C_{15}H_{21}NO_2$
4m	8-OCH_3	i-C_3H_7	B	71	167–168	A/H	$C_{15}H_{21}NO_2$
4n	8-OCH_3	c-C_3H_5	B	83	185–187	A/H	$C_{15}H_{19}NO_2$
4o	8-OCH_3	CH_2Cl	B	63	134–136	A/H	$C_{13}H_{16}NO_2Cl$
4p	8-OCH_3	CH_2Ph	B	61	154–156	A/H	$C_{19}H_{21}NO_2$
4q	8-OCH_3	Ph	B	84	173–175	A/H	$C_{18}H_{19}NO_2$
5a	H	CH_3	B	65	52–54	T	$C_{10}H_{13}NO$
5b	2-OCH_3	CH_3	A[i]	55	77–78	T	$C_{11}H_{15}NO_2$
5c	2-OCH_3	C_2H_5	B[i]	26	47–49	A/H	$C_{12}H_{17}NO_2$
5d	2-OCH_3	n-C_3H_7	A[i]	46	45–47	A/H	$C_{13}H_{19}NO_2$
5e	3-OCH_3	CH_3	A[i,j]	69			$C_{11}H_{15}NO_2$
5f	4-OCH_3	CH_3	A[i]	77	85–86	T	$C_{11}H_{15}NO_2$
6a[k]	OCH_3	C_2H_5	B	57	106–107	T	$C_{14}H_{18}N_2O_2$
6b[l]	OCH_3	n-C_3H_7	A	73	121–122	A/H	$C_{15}H_{20}N_2O_2$

[a] Method A: acylation of the HCl salt of the corresponding primary amine with the appropriate anhydride (see preparation of 4j in the Experimental Section). Method B: acylation of the HCl salt of the corresponding primary amine with the appropriate acyl chloride (see preparation of 4q in the Experimental Section). [b] All yields are unoptimized. [c] Recrystallization solvents: T, toluene; A/H, acetone/hexane. [d] All compounds were analyzed for C, H, and N and the results were within 0.4% of the theoretical values, except were noted. [e] After evaporation under reduced pressure, this compound gave a brown oil, which after addition of hexane partially solidified at −20 °C. After filtration and washing with hexane, the yield was a white solid, which was recrystallized. [f] C: calcd, 64.43; found, 63.91. [g] Previously described, ref 17. [h] C: calcd, 71.21; found, 70.70. [i] In this case the free primary amine was used instead of the HCl salt of the corresponding primary amine. [j] After evaporation under reduced pressure, this compound gave an oil, which after addition of hexane or toluene failed to solidify at −20 °C. Even after column chromatography a light yellow oil was obtained that could not be crystallized. [k] Previously described, ref 11a. [l] Previously described, ref 11a,f (mp 115 °C).

Results and Discussion

We have applied the rigid analogue approach in the development of agents which have melatonin-like potency but belong to another chemical class than melatonin itself. The use of the tetralin system as a structural base for the synthesis of rigid dopamine (DA) and serotonin (5-HT) agonists[15] prompted us to take this rigid system as a template to develop active analogues of melatonin. Especially, the discovery of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT, Chart III) as a selective 5-HT_{1a}-receptor agonist[15f,g,23] indicates that it is not always necessary to incorporate all the functional groups of a biologically active compound in a rigid compound to display some of its activities. In 8-OH-DPAT, the heterocyclic part of the indole nucleus of serotonin is omitted with retention of serotonin-like activity. The similarities and differences between serotonin and melatonin prompted us to synthesize 2-acetamido-8-methoxytetralin (4j) as a starting-point for a series of nonindolic melatonin-like agents (4a–q). The distance between the methoxy group and the amido function in compound 4j is comparable to the distance between these two moieties in a low-energy conformation of melatonin with the ethylamido side chain in a coplanar position (Figure 1).

Evaluation of the melatonin-like properties of 4j revealed that it competes for 2-[^{125}I]iodomelatonin binding to chicken retinal membranes with a K_i value of 46 nM and inhibits the calcium-dependent release of [^{3}H]dopamine from rabbit retina with an IC_{50} value of 1.4 nM with a maximal inhibitory effect of 80% at 1 μM.[16] Compared with the properties of melatonin (1) (K_i = 0.57 nM, IC_{50} = 17 pM with maximal inhibition of 80% at 1 nM),[8a] 4j displays an 80-fold lower affinity and also possesses an 80-fold lower potency. However, 4j can reach the same maximal inhibitory effect as melatonin in the [^{3}H]-dopamine release assay.

By slight alterations to the structure of 4j we tried to find the best melatonin agonist in this series of compounds. The importance of the 8-methoxy substituent on the aromatic nucleus of 4j for its melatonin-like properties was investigated by deleting the methoxy group or by changing its position on the aromatic nucleus. Removal of the 8-methoxy group led to a compound (4a) displaying an almost 15-fold lower affinity (K_i = 665 nM) than 4j in the 2-[^{125}I]iodomelatonin binding assay and possessing a 37-fold lower potency (IC_{50} = 52 nM) than 4j in the [^{3}H]-dopamine release assay. Since 4a reaches only a maximal inhibition of 50% in the latter assay,[16] the intrinsic activity of 4a is less than 65% of that of melatonin and 4j. On the basis of these melatonin-like properties of 4a and 4j, we conclude that for the 2-amidotetralins the methoxy group is more important for melatonin-like potency/intrinsic activity than for melatonin-like affinity. This conclusion agrees well with that drawn from prior studies with indolic melatonin-like agents (2a–3b), especially N-acetyltryptamine (3a).[7e,8c,11c]

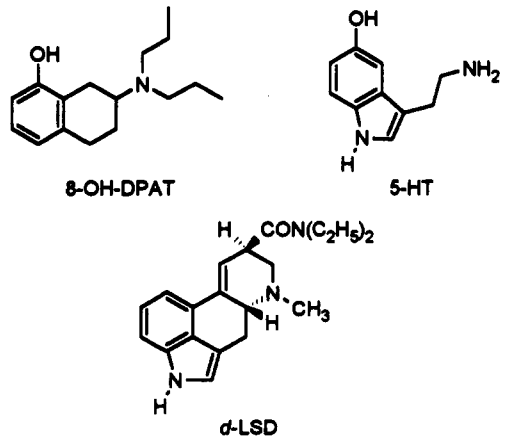
By changing the position of the methoxy group we obtained compounds without (4h), with low (4g), and with moderate (4i) melatonin-like affinity and potency. These results can well be accounted for, when we assume that the biologically active conformation of melatonin is the one in which the flexible side chain is folded in the same way as the flexible side chain in the conformation of serotonin (5-HT), mimicking the structure of the serotonergic agent d-lysergic acid diethylamide (d-LSD).[15g] Superimposing the acetamido groups of the methoxy-

Table II. Pharmacological Evaluation of the Amides 1–2c and 4a–6b

compound	competition for 2-[^{125}I]iodomelatonin binding[a]		inhibition of [^{3}H]dopamine overflow[d]	
	K_i, nM[b]	relative affinity[c]	IC_{50}, nM[e]	relative potency[f]
1[g]	0.57	1.00	0.017	1.0
2a[g]	0.13	0.23	0.005	0.3
2b[g]	0.34	0.60	0.040	2.4
2c[g]	0.23	0.40	0.010	0.6
4a	665	1170	52	3060
4b	145	254	8.1	476
4c	44.4	78	1.0	59
4d	95.1	167	1.3	76
4e	NE[h]		ND[i]	
4f	NE		ND	
4g	1950	3420	6.5	382
4h	NE		ND	
4i	121	212	1.6	94
4j	46.3	81	1.4	82
4k	7.40	13	0.48	28
4l	3.60	6.3	1.2	71
4m	312	547	7.9	465
4n	141	247	2.5	147
4o	3.75	6.6	0.063	3.7
4p	NE		NE	
4q	23100	40500	22	1290
5a	NE		ND	
5l	420	737	3.0	176
5c	789	1380	NE	
5d	748	1310	ND	
5e	581	1020	ND	
5f	NE		ND	
6a	0.27	0.47	ND	
6b	0.73	1.28	ND	

[a] Competition for 2-[^{125}]iodomelatonin binding to chicken retinal membranes by various concentrations (0.1 nM-0.1 mM) of the test compounds. [b] K_i values were calculated, from IC_{50} values obtained from competition curves, by the method of Cheng and Prusoff.[37] Results are mean values of at least three independent determinations in duplicate. [c] Relative affinity of the test compounds to compete for 2-[^{125}I]iodomelatonin in chicken retina (K_i x/K_i 1). [d] Inhibition by various concentrations of the test compounds (1 pM–1 μM) of the calcium-dependent release of [^{3}H]dopamine from rabbit retina *in vitro*. [e] IC_{50} values were determined graphically from concentration-effect curves. [f] Relative potency of the test compounds to inhibit calcium-dependent [^{3}H]dopamine release from rabbit retina (IC_{50}x/IC_{50}1). [g] See also refs 7e, 8c and 12a. [h] No effect. [i] Not determined.

Chart III



substituted 2-acetamidotetralins 4g–j on this conformation of melatonin (Figure 1) makes it clear that the 7-methoxy derivative 4i and the 8-methoxy derivative 4j, which have the highest affinity and potency for the melatonin receptor, give the best fit with regard to the methoxy group.

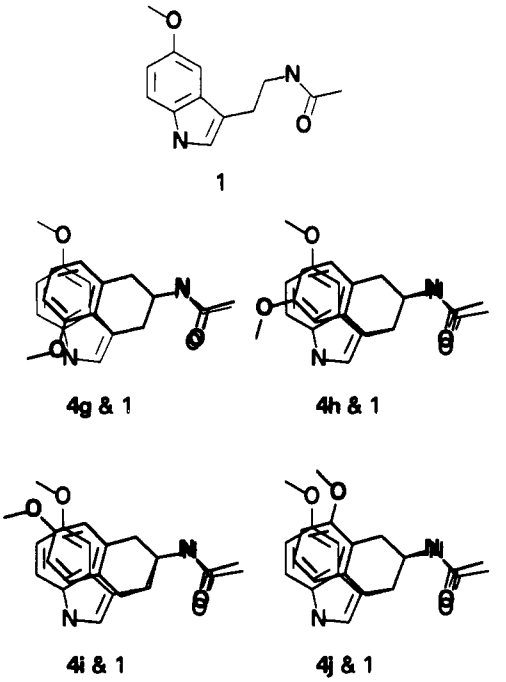


Figure 1. Representations of superimpositions of methoxy-substituted 2-acetoamidotetralins 4g–j (heavy lines) on the possible biological conformation of melatonin (1) (thin lines), which is comparable to the conformation of serotonin (5-HT), mimicking the structure of *d*-LSD.

The influence of the acetamido group of 4j on its melatonin-like properties was investigated by deleting the *N*-acetyl group of 4j, giving the amine 11d, or substituting the methyl group of the N-acetyl group of 4j with other alkyl and aryl groups. The HCl salt of amine 11d failed to compete for 2-[^{125}I]iodomelatonin binding to chicken retinal membranes (K_i > 100 000 nM). Therefore, we conclude that in the series of 2-amido-8-methoxytetralins, like in the series of 5-methoxy-tryptamides, the *N*-acetyl group is very important for binding to a melatonin receptor.[7e,8c,11c]

N-Propionyl-5-methoxytryptamine (6a) and *N*-*n*-butyryl-5-methoxytryptamine (6b) are potent analogues of melatonin.[11a,f] Therefore, we substituted the methyl group of the *N*-acetyl group of 4j with an ethyl (4k) and a *n*-propyl group (4l). The *N*-propionyl analogue 4k shows the highest potency in inhibiting [^{3}H]dopamine release (IC_{50} = 0.48 nM; 30-fold lower potency than melatonin) and the *N*-*n*-butyryl analogue 4l shows the highest affinity for 2-[^{125}I]-iodomelatonin binding (K_i = 3.60 nM; 6-fold lower affinity than melatonin).

Substitution of the methyl group of the *N*-acetyl group of 4j with a more bulky alkyl group, like isopropyl (4m) or cyclopropyl (4n), gave rise to analogues, which have moderate affinity and potency for the melatonin receptor. Substitution of the methyl group with an aryl group, like benzyl (4p) or phenyl (4q), led to analogues with no or very low affinity for the melatonin receptor. These results are in good agreement with those found by Frohn et al. for 5-methoxytryptamides.[12f] They showed that substitution of the methyl group of the *N*-acetyl group of melatonin with a bulky alkyl group, like *tert*-butyl, or an aryl group, like phenyl, led to compounds that could not mimic the activity of melatonin in their *in vivo* bioassay.

Another substitution was the replacement of the methyl group of the *N*-acetyl group of 4j with a chloromethyl group (4o). This compound competes for 2-[^{125}I]iodome-

latonin binding to chicken retinal membranes with almost the same K_i value (K_i = 3.75 nM; 6.5-fold lower affinity than melatonin) as **4l**, the 2-amido-8-methoxytetralin with the highest affinity, and inhibits the calcium-dependent release of [^{3}H]dopamine from rabbit retina with an IC_{50} value of 0.063 nM, which is almost the same potency as that of melatonin (IC_{50} = 0.017 nM). With this substitution, we introduced a chemicaly reactive, electrophilic moiety into the 2-amido-8-methoxytetralin system, which may form a covalent bond with a nucleophile near the active site of the melatonin binding site, resulting in irreversible attachment.

Most of the above substitutions were also carried out on the 2-amidotetralin **4a**. The 2-amidotetralins that were obtained (**4b–f**) showed the same tendencies in their affinities for the chicken retinal melatonin binding site as the 2-amido-8-methoxytetralins **4k–q**. We conclude that unsubstituted and 8-methoxy-substituted 2-amidotetralins require a small, nonbranched acyl group, like acetyl, haloacetyl, propionyl, or *n*-butyryl, to display optimal melatonin-like properties.

The importance of the rigidity of **4j** for its melatonin-like properties was investigated by testing the flexible analogue *N*-acetyl-2-methoxyphenethylamine (**5b**). This phenethylamide **5b** shows a 9-fold lower affinity (K_i = 420 nM) than **4j** in the 2-[^{125}I]iodomelatonin binding assay and possesses a 2-fold lower potency (IC_{50} = 3.0 nM) than **4j** in the [^{3}H]dopamine release assay. An explanation for the lower affinity and potency for the melatonin receptor of this ring-opened analogue of **4j** could be that internal hydrogen bonding between the hydrogen atom of the amide and the oxygen atom of the methoxy group alters the conformation of the side chain in such a way that this compound cannot mimic the active conformation of **4j**. A similar explanation has been proposed by Glennon to account for the lower serotonergic potency of 2-hydroxy-*N*,*N*-di-*n*-propylphenethylamine, a ring-opened analogue of 8-OH-DPAT, compared with that of 8-OH-DPAT.[23c] Some of the alterations made in the structure of 2-amidotetralin **4j** were also applied to the structure of the ring-opened analogue **5b**, including deletion of the methoxy group (**5a**), changing the position of the methoxy group in the aromatic nucleus (**5e/f**) and substitution of the methyl group of the N-acetyl group with an ethyl group (**5c**) or a *n*-propyl group (**5d**). Also in these flexible phenethylamides, a well-positioned methoxy group and a small acyl group are structural requirements for optimal melatonin-like properties.

In summary, the amido group of the unsubstituted and methoxy-substituted 2-amidotetralins should have a small, nonbranched alkyl group in order to bind to the melatonin receptor with high affinity, and the 2-amidotetralin ring needs a methoxy subtituent at the 8-position in order to show maximal agonistic activity.

Conclusion

The series of unsubstituted and methoxy-substituted 2-amidotetralins constitutes a class of nonindolic melatonin-like agents that can be applied as pharmacological tools to further characterize melatonin receptors and to elucidate the mode of action of melatonin. The 2-amido-8-methoxytetralins **4j–l**, which are melatonin agonists of moderate to high potency, can probably be used as lead compounds in further structure–activity relationships and for the development of therapeutic agents that act through melatonin receptors.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries on an electrothermal digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Philips PU 9706 spectrophotometer or on a Beckman AccuLab 2 spectrophotometer, and only the important absorptions are given. ^{1}H NMR spectra were recorded on a 60-MHz Hitachi Perkin-Elmer R-24 B spectrometer or on a 300-MHz Varian VXR-300 spectrometer. Chemical shifts are reported in δ units (parts per million) relative to $(CH_3)_4Si$ as an internal standard or via δ $CDCl_3$ (7.24) or $(CD_3)_2SO$ (2.49). ^{13}C NMR spectra were recorded at 75 MHz on a Varian VXR-300 spectrometer. Chemical shifts were obtained in δ units (parts per million) using the solvent as internal standard, relative to $(CH_3)_4Si$, by using δ $CDCl_3$ (77.0) or $(CD_3)_2SO$ (39.7). Mass spectra were obtained with a Finnegan 3300 system. Elemental analyses for new substances were performed at the Department of Chemistry, University of Groningen. Where elemental analyses are indicated, obtained results were within 0.4% of the theoretical values.

General Method for the Synthesis of the Dimethoxynaphthalenes 8a–d. The method adopted for the synthesis of **1,7-dimethoxynaphthalene (8d)** is described.

Dimethyl sulfate (40 mL, 0.42 mol) was added at once to a vigorously stirred solution of 1,7-dihydroxynaphthalene (**7d**) (31.5 g, 0.197 mol) in 2 N NaOH (180 mL). The temperature of the reaction mixture increased to 50 °C and the reaction mixture became acidic. Immediately 2 N NaOH (135 mL) was added to obtain a basic reaction mixture followed by another portion of dimethyl sulfate (20 mL, 0.21 mol). The basic reaction mixture was stirred for 2 h at 55 °C and subsequently heated at reflux for 2 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL). The CH_2Cl_2 layer was washed with 2 N NaOH (3 × 75 mL) and a saturated solution of NaCl (1 × 75 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residual oil was purified on an Al_2O_3 90 active, neutral (Merck) silica gel 60 (Merck) column with CH_2Cl_2 as the eluent to yield 30.1 g (0.160 mol, 81%) of **8d** as a colorless, viscous oil: bp 88–90 °C (0.01 mbar) [lit.[24,25] bp 123–130 °C (0.4 mmHg); bp 124–127 °C (0.7 mmHg), solid at room temperature]; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 6.6–7.8 (m, 6H, ArH).

Similarly **8a** [mp 58–59 °C, EtOH (lit.[25,26] bp 123–126 °C (0.8 mmHg), solid at room temperature; mp 60–61 °C, petroleum ether)], **8b** [mp 151–152, EtOH (lit.[27,28] mp 149–150.5 °C, petroleum ether; mp 153–154 °C)], and **8c** [mp 138–139 °C, EtOH (lit.[25,29] mp 136–137 °C, EtOH; mp 138 °C EtOH)] were obtained from the suitable starting dihydroxynaphthalenes **7a–c**.

General Method for the Synthesis of the Methoxy-2-tetralones 9a–d. The method adopted for the synthesis of **8-methoxy-2-tetralone (9d)** is described.

Dimethoxynaphthalene **8d** (27.1 g, 0.144 mol) was added to boiling absolute EtOH (250 mL) under mechanical stirring. Sodium (25 g), cut in little pieces, was added as rapidly as possible (45 min) to the nitrogen-flushed solution. After addition of another portion of absolute EtOH (70 mL), refluxing was continued until all the sodium had disappeared (1 h). The reaction mixture was cooled to 10 °C and then 2 N HCl (470 mL) was added dropwise until pH 6 was obtained (the colour of the reaction mixture changed from white to yellow). More 2 N HCl (30 mL) was added and the reaction mixture was refluxed for 30 min. After cooling, the reaction mixture was extracted with Et_2O (125 mL) and the H_2O/EtOH layer was concentrated under reduced pressure until only H_2O remained. This H_2O layer was extracted with Et_2O (3 × 125 mL), and the Et_2O layers were combined. The resulting Et_2O layer was washed with a saturated solution of NaCl (3 × 75 mL) and dried over $MgSO_4$. After *in vacuo* evaporation of the Et_2O, a viscous, brown-orange oil was afforded. The crude oil was purified by vacuum distillation to yield 15.8 g (0.090 mol, 62%) of **9d** as a light yellow oil, which solidified on standing: bp 104–106 °C (0.02 mbar). Recrystallization from petroleum ether (bp 40–60 °C) gave **9d** as fine white needles: mp 56.6–57.5 °C [lit.[24,25] mp 58–59 °C, light petroleum;

bp 120–123 °C (1.0 mmHg), solid at room temperature]; IR (cm^{-1}, neat) 2840 (OCH_3), 1715 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.5 (t, 2H, CH_2), 3.0 (t, 2 H, CH_2), 3.4 (s, 2 H, CH_2), 3.8 (s, 3H, OCH_3), 6.5–7.5 (m, 3H, ArH).

Similarly **9a** [bp 112–114 °C (0.01 mbar), solid at room temperature (lit.[25,30] bp 118–124 °C (1.1 mmHg); mp 36–37 °C)], **9b** [mp 34–35 °C, petroleum ether (bp 40–60 °C) (lit.[18] mp 36 °C, light petroleum)], and **9c** [mp 26–27 °C, petroleum ether (bp 40–60 °C) (lit[25,31] bp 130–136 °C (2.3 mmHg); mp 27–28 °C, bp 124–126 °C (1.5 mmHg))] were obtained from the dimethoxynaphthalenes **8a–c**.

2-Methoxy-*trans*-cinnamic Acid (13). A well-stirred mixture of 2-methoxybenzaldehyde (**12**) (20.4 g, 0.15 mol), malonic acid (31.2 g, 0.30 mol), and piperidine (2.2 mL) in pyridine (70 mL) was heated for 2 h at 85 °C and then refluxed for 2 h at 110 °C. The mixture was cooled and poured with stirring into an excess of cold 1N HCl (1.0 L). The flocculent white precipitate was collected by suction filtration and washed by resuspension and stirring for 15 min in cold H_2O (300 mL). The precipitate was collected by suction filtration, dried in a vacuum desiccator, and recrystallized from 2-butanone. The yield was 25.0 g (0.14 mol, 93%) of **13** as long white crystals: mp 186–188 °C (lit.[32] mp 186 °C, H_2O); IR (cm^{-1}, KBr) 1685 (C=O), 1625 (C=C); ^1H NMR (60 MHz, $(CD_3)_2SO$) δ 3.8 (s, 3H, OCH_3), 6.45 (d, 1H, CHCO, J = 16 Hz), 6.7–7.7 (m, 4H, ArH), 7.85 (d, 1H, ArCH, J = 16 Hz).

3-(2-Methoxyphenyl)propionic Acid (14). Acid **13** (9.90 g, 55.6 mmol) was taken up into 96% EtOH (400 mL) and hydrogenated overnight over 10% Pd–C (1.25 g) in a Parr shaker apparatus under a H_2 pressure of 3.5 atm. The reduction mixture was filtered and the solvent was evaporated *in vacuo* to yield 9.60 g (53.3 mmol, 96%) of **14**. An analytical sample was recrystallized from 2-butanone to provide white crystals: mp 88–90 °C (lit.[32,33] mp 92 °C, H_2O); IR (cm^{-1}, KBr) 1715 (C=O); ^1H NMR (60 MHz, $(CD_3)_2SO$) δ 2.3–2.8 (m, 4H, CH_2CH_2), 3.7 (s, 3H, OCH_3), 6.7–7.2 (m, 4H, ArH).

3-(2-Methoxyphenyl)propionyl Chloride (15). $SOCl_2$ (4.2 mL, 58 mmol) was added to a stirred solution of **14** (9.50 g, 52.8 mmol) in benzene (125 mL). After refluxing for 3 h and cooling of the reaction mixture, the volatiles were evaporated under reduced pressure to yield the crude acyl chloride **15**. This acyl chloride was purified by vacuum distillation. The yield was 9.86 g (49.7 mmol, 94%) of **15** as a colorless, viscous oil: bp 99–100 °C (0.01 mbar) [lit.[34] bp 165 °C (40 mmHg)]; IR (cm^{-1}, neat) 1810 (C=O).

1-Diazo-4-(2-methoxyphenyl)-2-butanone (16). A solution of acyl chloride **15** (9.80 g, 49.4 mmol) in anhydrous Et_2O (160 mL) was added dropwise over a period of 0.5 h to a stirred solution of freshly prepared CH_2N_2 (~6.6 g) in dry Et_2O (380 mL)[35] at 5 °C and under an atmosphere of nitrogen. After the reaction mixture had reached room temperature, it was allowed to stand overnight under an atmosphere of nitrogen. Removal of the solvent under reduced pressure yielded 9.87 g (48.3 mmol, 98%) of **16** as a yellow oil, which solidified in the refrigerator: IR (cm^{-1}, neat) 2860 (OCH_3), 2120 (CHN_2), 1650 (C=O); MS (CI with NH_3) m/z 205 (M + 1), 222 (M + 18).

8-Methoxy-2-tetralone (9d). Diazo ketone **16** (2.20 g, 10.8 mmol) was dissolved in CH_2Cl_2 (50 mL) and this solution was added slowly (30 min) to a rapidly stirred solution of $[Rh(CH_3COO)_2]_2$ (5 mg) in CH_2Cl_2 (25 mL) under an atmosphere of nitrogen. After refluxing for 10 min, 1 drop of CF_3COOH was added and refluxing was continued for 15 min. After cooling, the reaction mixture was washed with saturated aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. *In vacuo* evaporation of the CH_2Cl_2 yielded a brown oil. The crude oil was purified by a Kugelrohr vacuum distillation to yield 0.37 g (2.1 mmol, 19%) of **9d** as a light-yellow oil, which solidified on standing: bp 102–108 °C (0.01 mbar) [lit.[24,25] mp 58–59 °C, light petroleum; bp 120–123 °C (1.0 mmHg), solid at room temperature]; IR (cm^{-1}, neat) 2840 (OCH_3), 1715 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.5 (t, 2H, CH_2), 3.0 (t, 2H, CH_2), 3.4 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 6.5–7.5 (m, 3H, ArH); MS (CI with NH_3) m/z 177 (M + 1), 194 (M + 18).

General Method for the Synthesis of 2-(Benzylamino)-methoxytetralins 10a–d. The method adopted for the synthesis of **2-(benzylamino)-8-methoxytetralin (10d)** is described.

Under an atmosphere of nitrogen, a solution of tetralone **9d** (5.30 g, 30.1 mmol), benzylamine (4.35 mL (4.27 g), 39.8 mmol), and *p*-toluenesulfonic acid monohydrate (0.07 g, 0.4 mmol) in dry benzene (70 mL) was refluxed for 17 h under continuous removal of H_2O using a Dean–Stark apparatus. The benzene and the excess benzylamine were removed under reduced pressure and the residue (in this case a solid enamine) was dissolved in absolute EtOH (100 mL). After transferring the solution to a Parr hydrogenation flask, PtO_2 (50 mg) was added as a catalyst and the mixture was hydrogenated for 2.5 h under a H_2 pressure of 2 atm. The catalyst was filtered off and the solvent was evaporated under reduced pressure to yield the brown, oily amine **10d**. After converting the crude amine to its HCl salt, the salt was dissolved in EtOH and decolorized with charcoal. Recrystallization ($EtOH/Et_2O$) gave 6.58 g (21.7 mmol, 72%) of **10d**·HCl: mp 219–220 °C (lit.[15g] mp 218.5–219.5 °C, $MeOH/Et_2O$); IR (cm^{-1}, KBr) 2850–2300 (NH_2^+), 775, 750, and 700 (ArH); MS (CI with NH_3) m/z 268 (M + 1) (M, free amine).

Similarly **10a**·HCl, **10b**·HCl, and **10c**·HCl were obtained from the methoxy-2-tetralones **9a–c**.

General Method for the Synthesis of 2-Aminomethoxytetralins 11a–d. The method adopted for the synthesis of **2-amino-8-methoxytetralin (11d)** is described.

2-(Benzylamino)-8-methoxytetralin (**10d**) (2.12 g, 7.94 mmol) was dissolved in absolute EtOH (60 mL), 10% Pd–C catalyst (1.6 g) was added, and the solution was debenzylated in a Parr hydrogenation flask for 1 h at 45 °C under a H_2 pressure of 3 atm. After filtering off of the catalyst, the volatiles were removed under reduced pressure to give a dark brown oil, which became solid at room temperature. This solid was taken up in $EtOH/Et_2O$ and precipitated as its HCl salt by Et_2O saturated with dry HCl. After decolorization with charcoal, recrystallization from $EtOH/Et_2O$ yielded 1.17 g (5.48 mmol, 69%) of **11d**·HCl as fine white needles: mp 281–282 °C dec (lit.[17,25,36] mp >275 °C; mp 273–275 °C dec; mp 275–278 °C, $EtOH/Et_2O$); IR (cm^{-1}, KBr) 3160–2420 (NH_3^+), 2060 (NH_3^+), 770 and 710 (ArH); MS (CI with NH_3) m/z 178 (M + 1) (M, free amine).

Similarly **11a**·HCl [mp 265–268 °C dec, $EtOH/Et_2O$ (lit.[15e,17,25] mp 266–267 °C, $EtOH/Et_2O$; 260–264 °C dec; 258–260 °C dec)], **11b**·HCl [mp 248–250 °C dec, $EtOH/Et_2O$ (lit.[25] mp 243–246 °C dec)] and **11c**·HCl [mp 218–221 °C dec, $MeOH/Et_2O$ (lit.[25] mp 213–214 °C dec)] were obtained from the 2-(benzylamino)-methoxytetralins **10a–c**.

General Methods for the Synthesis of the Amides 4a–6b. Method A. The method adopted for the synthesis of **2-acetamido-8-methoxytetralin (4j)**[17] is described.

Acetic anhydride (0.84 mL, 8.9 mmol) was added dropwise at room temperature to a well-stirred mixture of 2-amino-8-methoxytetralin hydrochloride (**11d**·HCl) (0.30 g, 1.4 mmol), NaOAc (0.65 g), EtOAc (15 mL), and H_2O (5 mL). After 3 h of stirring and after diluting of the mixture with H_2O (10 mL), the phases were separated, and the H_2O layer was extracted twice with EtOAc (15 mL). Subsequently the EtOAc layers were combined and washed with saturated solutions of $NaHCO_3$ (3 × 20 mL) and NaCl (1 × 20 mL) and then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure yielded a white solid. Recrystallization from acetone/hexane gave a yield of 0.24 g (1.1 mmol, 79%) of **4j** as fine white needles: mp 156–157 °C; IR (cm^{-1}, KBr) 3320 (NH), 2850 (OCH_3), 1640 (C=O, amide I), 1540 (C=O, amide II); ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 1H, CHCN), 1.97 (s, 3H, $COCH_3$), 2.02 (m, 1H, CHCN), 2.44 (dd, 1H, $ArCH_{ax}$, J = 17.2 Hz, 7.7 Hz), 2.85 (m, 2H, $ArCH_2$), 3.05 (dd, 1H, $ArCH_{eq}$, J = 17.4 Hz, 5.3 Hz), 3.79 (s, 3H, OCH_3), 4.26 (m, 1H, $CH_{ax}N$), 5.48 (bs, 1H, NH), 6.66 (d, 1H, ArH, J = 8.1 Hz), 6.72 (d, 1H, ArH, J = 7.7 Hz), 7.11 (t, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.52 ($COCH_3$), 27.06, 28.05, 29.64, (C-1, C-3, C-4), 44.91 (C-2), 55.12 (OCH_3), 106.86, 120.83, 126.34 (C-5, C-6, C-7), 122.83, 136.76, 157.33 (C-4a, C-8, C-8a), 169.32 ($COCH_3$); MS (CI with NH_3) m/z 220 (M + 1), 237 (M + 18). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

The physical characteristics of the amides prepared according to method A are reported in Table I.

Method B. The method adopted for the synthesis of **2-benzamido-8-methoxytetralin (4q)** is described.

Benzoyl chloride (0.55 mL, 4.7 mmol) was added dropwise at room temperature to a rigorously stirred mixture of 2-amino-

8-methoxytetralin hydrochloride (11d·HCl) (0.40 g, 1.9 mmol), CH_2Cl_2 (20 mL) and 10% NaOH (12 mL). After 3 h of stirring, the reaction mixture was poured into H_2O (50 mL), and the phases were separated. Subsequently the H_2O layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (3 × 20 mL) and H_2O (1 × 20 mL), dried over $MgSO_4$, and then evaporated under reduced pressure to yield a light yellow solid. Recrystallization from acetone/hexane yielded 0.45 g (1.6 mmol, 84%) of **4q** as white crystals: mp 173–175 °C; IR (cm^{-1}, KBr) 3310 (NH), 2840 (OCH_3), 1630 (C=O, amide I), 1580 (Ar), 1530 (C=O, amide II); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 1H, CHCN), 2.15 (m, 1H, CHCN), 2.57 (dd, 1H, $ArCH_{ax}$, J = 17.2 Hz, 8.1 Hz), 2.93 (m, 2H, $ArCH_2$), 3.20 (dd, 1H, $ArCH_{eq}$, J = 17.2 Hz, 5.5 Hz), 3.82 (s, 3H, OCH_3), 4.49 (m, 1H, $CH_{ax}N$), 6.12 (bs, 1H, NH), 6.69 (d, 1H, ArH, J = 8.1 Hz), 6.76 (d, 1H, ArH, J = 7.7 Hz), 7.13 (t, 1H, ArH), 7.45 (m, 3H, ArH), 7.76 (m, 2H, ArH); MS (CI with NH_3) m/z 282 (M + 1). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

The physical characteristics of the amides prepared according to method B are reported in Table I.

Pharmacology. Competition for 2-[^{125}I]Iodomelatonin Binding to Chicken Retinal Membranes. This radioligand binding assay was conducted essentially as reported by Dubocovich and Takahashi,[7e] except for the incubation temperature, which was 25 °C instead of 0 °C.

Inhibition of Calcium-Dependent Release of [^{3}H]Dopamine from Rabbit Retina. This *in vitro* assay was performed as described by Dubocovich.[8a-c]

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