Synthesis of a Novel Series of Benzocycloalkene Derivatives as Melatonin Receptor Agonists

Kohji Fukatsu, Osamu Uchikawa,* Mitsuru Kawada, Toru Yamano, Masayuki Yamashita, Koki Kato, Keisuke Hirai, Shuji Hinuma, Masaomi Miyamoto, and Shigenori Ohkawa

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan

Received March 12, 2002

We synthesized a novel series of benzocycloalkene derivatives and evaluated their binding affinities to melatonin receptors. To control the spatial position of the amide group, one of the important pharmacophores, we incorporated an *endo* double bond, an *exo* double bond (*E*- and *Z*-configurations), and a chiral center (*R*- and *S*-configurations) at position 1. The indan derivatives with the *S*-configuration at position 1 were the most promising in terms of potency and selectivity for the human melatonin receptor (MT_1 site), while compounds with the *R*-configuration showed little potential. Our next attempt was to investigate the most favorable conformation of the methoxy group, the other important pharmacophore for binding to the MT_1 receptor. The introduction of a methyl group at position 5 of the indene ring conserved affinity; however, at position 7, it caused a decrease in affinity. These results suggested that the substitution at position 7 forced the methoxy group to adopt an unfavorable orientation. The optimization of the condensed ring size and substituents led to (*S*)-**8d** [(*S*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]propionamide], which had high affinity for the human MT_1 receptor (K_i = 0.041 nM) but no significant affinity for the hamster *MT*$_3$ receptor (K_i = 3570 nM). In addition, a practical synthetic method of chiral *N*-[2-(2,3-dihydro-1*H*-inden-1-yl)ethyl]-alkanamides employing asymmetric hydrogenation with (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl−Ru has been established.

Introduction

Sleep disorders are commonly caused by exposure to stress, and it was reported that they affect one-third of Americans.[1] Benzodiazepines are normally used for the treatment of sleep disorders since they have fewer side effects than barbiturates. However, the administration of benzodiazepines to the elderly is restricted because it can cause rebound insomnia,[2] muscle relaxation,[3] and amnesia.[4] We therefore attempted to develop a new type of agent for sleep disorders, focusing on the natural hormone melatonin (**1**).

The pineal hormone melatonin plays a key role in modulating circadian and seasonal rhythms.[5] A large number of studies on melatonin for the treatment of circadian rhythm disorders such as delayed sleep phase syndrome[6] and jet lag[7] have been reported. However, the effect of melatonin is limited by its short half-life in the human body,[8] and the safety of melatonin when it is administered chronically has yet to be tested. Melatonin receptors can be classified into MT_1, MT_2, and *MT*$_3$ subtypes, and melatonin is suggested to exert its regulatory function through MT_1 and MT_2 receptors.[9] The expression of the MT_1 receptor mRNA was observed throughout the human brain, while the expression of the MT_2 receptor mRNA was observed in the retina with much lower expression in the brain and hippocampus.[10] For this reason, it was thought that interaction with the MT_1 receptor was a potential target for the regulation of sleep disorders. Recently, the *MT*$_3$ binding site has been identified as a melatonin sensitive form of the quinone reductase 2 (QR_2, EC 1.6.99.2), but the physiological function of this enzyme has not been well-characterized.[11] Thus, to avoid unknown potential side effects, we have investigated compounds that have affinity for the MT_1 receptor but do not affect the *MT*$_3$.

According to reports on indolic and nonindolic melatonin receptor ligands, several models of the docking between ligands and receptors have been proposed[12] and a comparative molecular field analysis of melatonin receptor ligands was investigated.[13] These studies and the structures of the ligands suggested that the pyrrole unit of melatonin was not essential for receptor binding. Furthermore, it was also suggested that the amide group in the side chain and the methoxy group on the benzene ring were important ligand pharmacophores. With a view to altering the conformation of the side chain and the methoxy group, we chose benzocycloalkenes (indan, tetraline, and benzocycloheptene) as versatile scaffolds and attempted to elevate the affinity and selectivity for the MT_1 receptor.

Structural modifications to the benzocycloalkene derivatives **2** included the introduction of (a) an *endo* double bond as in melatonin, (b) an *exo* double bond followed by *E*/*Z* separation, and (c) a chiral center to control the spatial positioning of the amide side chain. Additionally, we modified the substituents on the benzene ring to clarify the most favorable conformation for the methoxy group on the benzene ring. These strategies are illustrated in Figure 1.

Chemistry

Benzocycloalkene derivatives having a 2-amidoethyl side chain were synthesized according to the general

* To whom correspondence should be addressed. Tel: +81-6-6300-6546. Fax: +81-6-6300-6306. E-mail: uchikawa_osamu@takeda.co.jp.

10.1021/jm020114g CCC: $22.00
Published on Web 08/15/2002

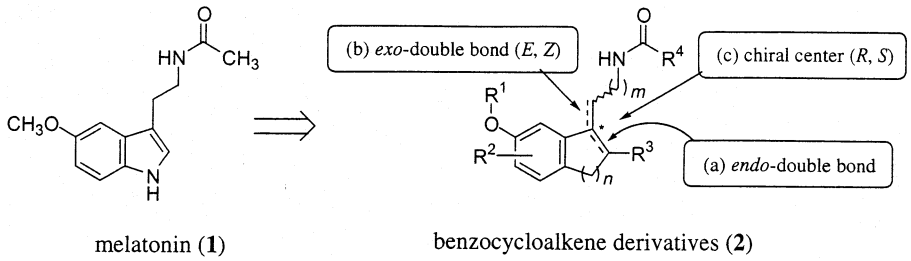
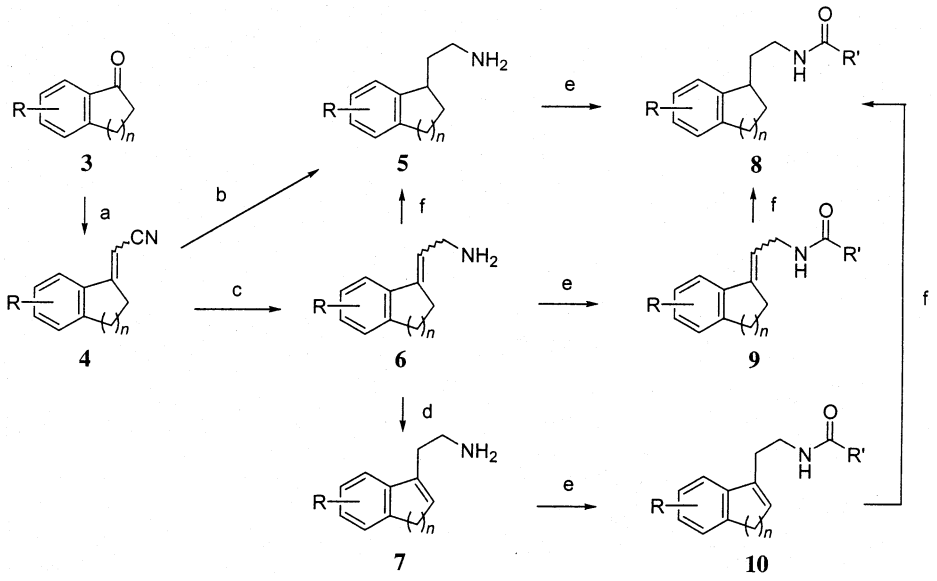


Figure 1. Design of benzocycloalkene derivatives (**2**) for melatonin receptor agonists. The structure shows (a) introduction of an *endo* double bond, (b) introduction of an *exo* double bond followed by *E*/*Z* separation, and (c) introduction of a chiral center. Substitution (R^2) on the benzene ring to restrict the conformation of the alkoxy group (OR^1). In addition, ring size (*n*), substituents (R^1, R^3, and R^4), and the length of the side chain (*m*) are represented.

Scheme 1. Synthesis of Benzocycloalkene Derivatives Having a 2-Amidoethyl Side Chain[a]



[a] Reagents: (a) $(C_2H_5O)_2P(O)CH_2CN$, NaH (method A) or CH_3CN, $LiN(TMS)_2$ and then *p*-TsOH/toluene (method B). (b) H_2/Raney-Ni, NH_3/C_2H_5OH (method C). (c) H_2/Raney-Co, NH_3/C_2H_5OH (method D). (d) HCl/C_2H_5OH (method E). (e) R′CO-X, $(C_2H_5)_3N$ (method F) or R′CO-X, aqueous NaOH (method G). (f) H_2/Pd-C (method H).

route outlined in Scheme 1. The starting ketones **3** were cyanomethylenated employing Horner−Emmons olefination (method A) or an Aldol type reaction with acetonitrile followed by dehydration (method B) to afford **4**, which could be separated into isomeric pure forms (*E* and *Z*) by column chromatography. Hydrogenation of **4** using Raney-nickel as a catalyst provided 2-aminoethyl derivatives **5** (method C). Raney-cobalt-catalyzed hydrogenation of **4** and selective reduction of the cyano group[14] afforded 2-aminoethylidene derivatives **6** (method D), which could be converted into *endo* olefins **7** under acidic conditions (method E). The amines **5**−**7** thus obtained were acylated in the presence of triethylamine (method F) or under Schotten−Baumann conditions (method G) to afford **8**−**10**, respectively. Compound **8** was also obtained by catalytic hydrogenation of olefins **9** or **10** (method H).

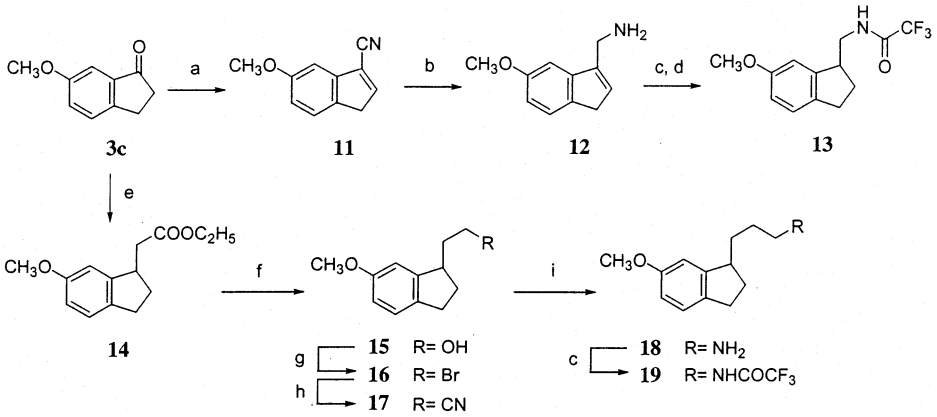
The synthetic routes to the compounds having an amidomethyl (**13**) or a 3-amidopropyl side chain (**19**) are shown in Scheme 2. Hydrocyanation of ketone **3c** using trimethylsilyl cyanide followed by dehydration afforded cyanoindene **11** (method I). Hydrogenation of the cyano group of **11** using Raney-cobalt provided aminomethyl compound **12**, which was trifluoroacetylated and hydrogenated to afford **13**. Compound **19** was also synthesized from **3c**. Horner−Emmons olefination of **3c** followed by hydrogenation gave acetate **14** (method J), which was converted into 2-cyanoethyl compound **17** with a three step sequence: lithium aluminum hydride reduction of the ethoxycarbonyl group (method K), bromination of the resulting alcohol **15** (method L), and cyanation using sodium cyanide (method M). Finally, Raney-nickel-catalyzed hydrogenation of **17** followed by trifluoroacetylation provided **19**.

The modification of the methoxy group at position 6 is summarized in Scheme 3. A methyl ether group of methoxyindan **8d** was cleaved with boron tribromide to afford phenol **20** (method N), which was alkylated to yield alkoxy compounds **21a**−**c** (method O).

Hydrazinolysis of chiral acetamide (*S*)-**8c**, which was obtained by optical resolution utilizing chiral high-performance liquid chromatography (HPLC) (method P), gave chiral amine (*S*)-**5c** (method Q) (Scheme 4). Absolute stereochemistry was determined by X-ray crystallographic analysis of *p*-bromobenzamide (*S*)-**8o**, which was prepared from (*S*)-**5c**. Compound (*S*)-**5c** was acylated to give chiral amides (*S*)-**8d**, (*S*)-**8e**, and (*S*)-**8h**. The corresponding *R*-isomers ((*R*)-**8d**, (*R*)-**8e**, and (*R*)-**8h**) were obtained in the same manner.

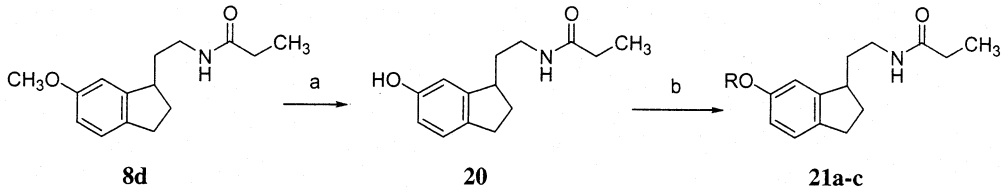
To obtain chiral compounds on a large scale, we planned to establish a practical method using asymmetric hydrogenation. There have been only a few reports on the asymmetric hydrogenation of (amidomethyl)olefins, and these substrates contained allylic

Scheme 2. Synthesis of Benzocycloalkene Derivatives Having Amidomethyl or a 3-Amidopropyl Side Chain[a]



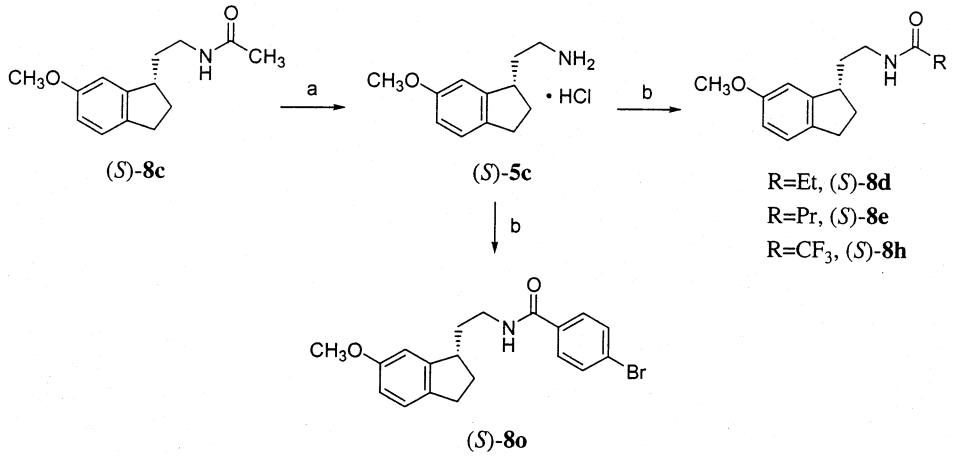
[a] Reagents: (a) TMSCN, ZnI_2 and then CF_3COOH/toluene (method I). (b) H_2/Raney-Co, NH_3/C_2H_5OH (method D). (c) $(CF_3CO)_2O$, $(C_2H_5)_3N$ (method F). (d) H_2/Pd-C (method H). (e) $(C_2H_5O)_2P(O)CH_2COOC_2H_5$, NaH and then H_2/Pd-C (method J). (f) $LiAlH_4$ (method K). (g) PBr_3 (method L). (h) NaCN (method M). (i) H_2/Raney-Ni, NH_3/C_2H_5OH (method C).

Scheme 3. Modification of the Alkoxy Group[a]



[a] Reagents: (a) BBr_3 (method N). (b) R-X, K_2CO_3 (method O).

Scheme 4. Synthesis of the Chiral Compounds[a]



[a] Reagents: (a) $NH_2NH_2 \cdot H_2O$ and then HCl (method Q). (b) RCO-X (method F or G).

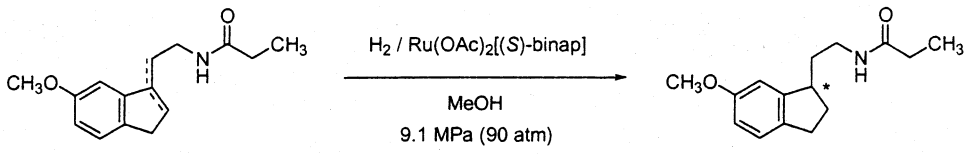
alcohol or unsaturated carboxylic acid to improve the efficiency of enantioselective hydrogenation.[15] We attempted to apply readily available $Ru(OAc)_2$[(*S*)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (binap)] to indan derivatives (*E*)-**9a**, (*Z*)-**9a**, and **10a** (Table 1). We have found that hydrogenation of *E*-olefin (*E*)-**9a** successfully afforded (*S*)-**8d** having the *S*-configuration in 98% yield with 95% ee, and optically pure (*S*)-**8d** was isolated in 83% yield (method R). In contrast, *Z*-olefin (*Z*)-**9a** was hydrogenated to yield the corresponding *R*-isomer (*R*)-**8d** in 95% yield with 80% ee. These *exo* olefins were versatile materials for the synthesis of chiral *N*-[2-(2,3-dihydro-1*H*-inden-1-yl)ethyl]alkanamides. However, hydrogenation of **10a** having an *endo* double bond afforded (*S*)-**8d** with an unsatisfactory enatioselectivity. All of the synthesized compounds are listed in Table 2.

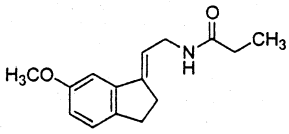
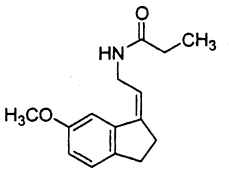
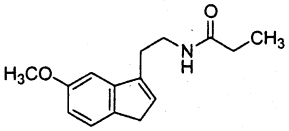
Biological Results and Discussion

Affinities for the MT_1 receptor were evaluated for the competition of 2-[^{125}I]iodomelatonin with human melatonin receptors expressed in Chinese hamster ovary (CHO) cells, and affinities for the MT_3 receptor were evaluated with Syrian hamster brain and peripheral organs. The K_i values of the compounds tested are listed in Table 3. Evaluation of melatonin revealed that it competes with 2-[^{125}I]iodomelatonin to bind the MT_1 receptor with a K_i value of 0.082 nM and also the MT_3 receptor with a K_i value of 28 nM.

Because the amide moiety of melatonin was considered to be an important hydrogen bond donor and acceptor for interaction with the MT_1 receptor, we attempted to change the spatial conformation of the amide group to potentiate the affinity for the MT_1

Table 1. Asymmetric Hydrogenation of Olefins **9a** and **10a** Using (*S*)-binap as a Chiral Auxiliary



Starting materials		Products	% ee	% yield
(*E*)-**9a**		(*S*)-**8d**	95	98
(*Z*)-**9a**		(*R*)-**8d**	80	95
10a		(*S*)-**8d**	10	16

receptor and to elevate MT_1/MT_3 selectivity. Initially, we introduced an *exo* (*E*, *Z*) or *endo* double bond to restrict the conformation of the side chain. A comparison of the *E*- and *Z*-configurations of the *exo* double bond revealed the indan derivative (*E*)-**9a** having the *E*-configuration to show higher affinity for the MT_1 receptor than (*Z*)-**9a**. Moving the amide group toward the benzene ring seemed to attenuate the affinity for the MT_1 receptor. On comparison between the *exo* and the *endo* double bond, *endo* compound **10a** was found to exhibit higher affinity for the MT_1 receptor than (*E*)-**9a**. Notably, the 2-phenyindene derivative **10c** had the highest affinity for the MT_1 receptor. In the structure−activity relationships of melatonin derivatives, a similar effect of substitution of the phenyl group at position 2 was reported. However, introduction of the benzyl group at position 2 of the indene ring (**10d**) reduced affinity for the MT_1 receptor.

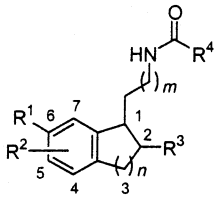
We also attempted to reduce the double bond and separate the resulting enantiomers. Although a marked difference was not observed on reduction of the double bond of **10a**,**b** (**8d**,**h**), reduction of **10c** attenuated the affinity for the MT_1 receptor (**8m**). However, these enantiomers were the most promising. In the MT_1 binding assay, the compounds possessing the *S*-configuration ((*S*)-**8c**, (*S*)-**8d**, (*S*)-**8e**, and (*S*)-**8h**) had more than 100-fold the affinity of the corresponding *R*-isomers ((*R*)-**8c**, (*R*)-**8d**, (*R*)-**8e**, and (*R*)-**8h**), and the *S*-isomers showed less affinity for the MT_3 receptor than the *R*-isomers. The MT_1/MT_3 selectivity of *S*-isomers overwhelmed that of the compounds having an *endo* double bond, **10a**−**d**, and melatonin.

The methoxy group of melatonin was defined as another important pharmacophore.[12] To clarify the most favorable conformation of the methoxy group in our series, a methyl group was introduced at the ortho position of the methoxy group. The compound having a methyl group at position 5 of the indan nucleus (**8j**) showed a higher affinity than the compound having a methyl group at position 7 (**8i**). In a homology modeling study based on the structure of *Bacterio rhodopsine*, it was suggested that His_{195} in helix five forms a hydrogen bond with a methoxy oxygen in melatonin, and the methyl group on the oxygen points toward position 4 of melatonin.[12a] In order for a hydrogen bond to form between the histidine residue and the methoxy oxygen of benzocycloalkene derivatives, the direction of the methyl group on the oxygen should be restricted. The methyl group at position 7 of the indan nucleus orients the methyl group on the oxygen toward position 5 by steric repulsion and orients oxygen lone pairs toward position 7 (Figure 2B). In contrast, the methyl group at position 5 settles lone pairs of the methoxy oxygen in the appropriate conformation for interaction with the MT_1 receptor (Figure 2A). The same explanation might be applied to dimethoxy compounds **8k**,**l**.[16]

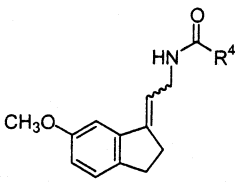
Additionally, the effect of changing the size of the annelating ring was examined. The affinity for the MT_1 receptor of the compound having a five-membered ring (**8h**) was almost 2-fold that of the compound having a six-membered ring (**8b**). The compound having a seven-membered ring (**8a**) had markedly decreased affinity (**8a** vs **8h**).[17] Chain extension of the amide alkyl group increased the affinity of the ethyl (propionamide **8d**) and propyl (butyramide **8e**) group. In contrast, incorporation of the branched alkyl group (**8g**) reduced affinity. Incorporation of a halogen atom into the amide alkyl group (trifluoroacetamide **8h**) increased affinity in comparison with acetamide **8c**.

Changing the length of the side chain as the spacer greatly influenced the affinity. 3-Amidopropyl derivative **19** had about 20-fold less affinity than 2-amidoethyl derivative **8h**, and the amidomethyl side chain (**13**) markedly reduced affinity in comparison with the

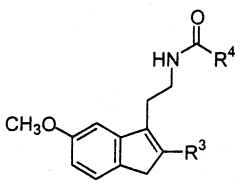
Table 2. Method of Preparation and Intermediates of Benzocycloalkene Derivatives



8a-n, 13, 19, 20 21a-c



(*E*)-**9a**, (*Z*)-**9a**



10a-d

no.[a]	R^1	R^2	R^3	R^4	*n*	*m*	method of preparation[b]	intermediates[c]
8a	CH_3O	H	H	CF_3	3	1	A, D, F, H	**3a**, **4a**, (*E*)-**6a**, (*E*)-**9c**
8b	CH_3O	H	H	CF_3	2	1	A, D, F, H	**3b**, **4b**, **6b**, (*E*)-**9b**
8c	CH_3O	H	H	CH_3	1	1	A, C, G	**3c**, (*E*)-**4c**, **5c**
(*S*)-**8c**							P	**8c**
(*R*)-**8c**							P	**8c**
8d	CH_3O	H	H	C_2H_5	1	1	A, C, G	**3c**, (*E*)-**4c**, **5c**
(*S*)-**8d**							Q, G, or R	(*S*)-**8c**, (*S*)-**5c**, or (*E*)-**9a**
(*R*)-**8d**							Q, G	(*R*)-**8c**, (*R*)-**5c**
8e	CH_3O	H	H	$(CH_2)_2CH_3$	1	1	A, C, G	**3c**, (*E*)-**4c**, **5c**
(*S*)-**8e**							Q, G	(*S*)-**8c**, (*S*)-**5c**
(*R*)-**8e**							Q, G	(*R*)-**8c**, (*R*)-**5c**
8f	CH_3O	H	H	$(CH_2)_3CH_3$	1	1	A, C, F	**3c**, (*E*)-**4c**, **5c**
8g	CH_3O	H	H	$CH(CH_3)_2$	1	1	A, C, G	**3c**, (*E*)-**4c**, **5c**
8h	CH_3O	H	H	CF_3	1	1	A, C, F	**3c**, (*E*)-**4c**, **5c**
(*S*)-**8h**							Q, F	(*S*)-**8c**, (*S*)-**5c**
(*R*)-**8h**							Q, F	(*R*)-**8c**, (*R*)-**5c**
8i	CH_3O	7-CH_3	H	CF_3	1	1	A, D, F, H	**3d**, (*E*)-**4d**, (*E*)-**6d**, (*E*)-**9d**
8j	CH_3O	5-CH_3	H	CF_3	1	1	A, D, F, H	**3e**, (*E*)-**4e**, (*E*)-**6e**, (*E*)-**9e**
8k	CH_3O	7-CH_3O	H	CH_3	1	1	A, D, G, H	**3f**, (*E*)-**4f**, (*E*)-**6f**, **5f**
8l	CH_3O	5-CH_3O	H	CH_3	1	1	A, C, F	**3g**, **4g**, **5g**
8m	CH_3O	H	C_6H_5	CF_3	1	1	H	**10c**
8n	H	H	H	CF_3	1	1	A, D, F, H	**3h**, **4h**, (*E*)-**6h**, (*E*)-**9h**
(*S*)-**8o**	CH_3O	H	H	C_6H_4-4-Br	1	1	Q, G	(*S*)-**8c**, (*S*)-**5c**
(*E*)-**9a**				C_2H_5			A, D, F	**3c**, (*E*)-**4c**, (*E*)-**6c**
(*Z*)-**9a**				C_2H_5			A, D, F	**3c**, (*Z*)-**4c**, (*Z*)-**6c**
10a			H	C_2H_5			A, D, E, F	**3c**, (*E*)-**4c**, (*E*)-**6c**, **7c**
10b			H	CF_3			A, D, E, F	**3c**, (*E*)-**4c**, (*E*)-**6c**, **7c**
10c			C_6H_5	CF_3			B, D, F	**3i**, (*E*)- **4i**, **7i**
10d			$CH_2C_6H_5$	CF_3			B, D, E, F	**3j**, **4j**, **6j**, **7j**
13	CH_3O	H	H	CF_3	1	0	I, D, F, H	**3c**, **11**, **12**
19	CH_3O	H	H	CF_3	1	2	J, K, L, M, C, F	**3c**, **14**−**18**
20	HO	H	H	C_2H_5	1	1	N	**8d**
21a	C_2H_5O	H	H	C_2H_5	1	1	O	**20**
21b	$CH_3(CH_2)_2O$	H	H	C_2H_5	1	1	O	**20**
21c	$(CH_3)_2CHO$	H	H	C_2H_5	1	1	O	**20**

[a] All of the target compounds listed in the table were analyzed correctly (±0.4%) for C, H, and N. [b] A combination of methods. [c] The chemical names of intermediates are given in the Experimental Section.

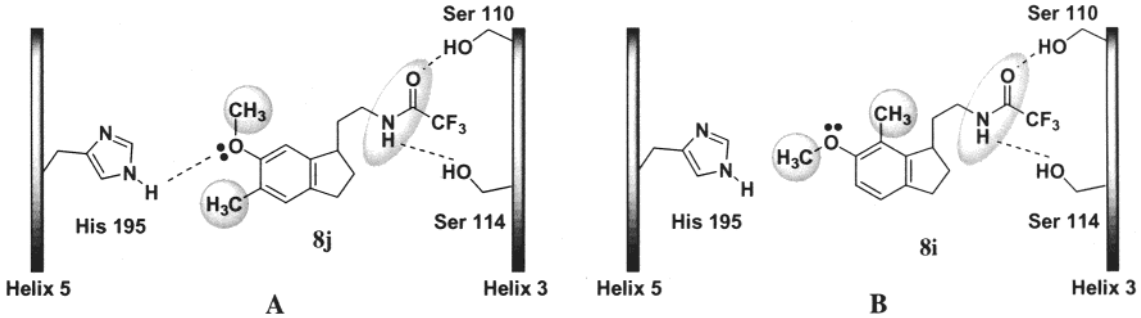


Figure 2. Schematic models of interaction between the indan derivatives and the histidine residue of the MT_1 receptor. Compound **8j** (A) exhibited higher affinity than **8i** (B).

2-amidoethyl side chain (**8h**). Replacing the methoxy group with an ethoxy (**21a**), a propoxy (**21b**), and an isopropoxy (**21c**) group led to a decrease in affinity.[18] The contribution of the methoxy group was also demonstrated by the weak activity seen with hydroxy (**20**) and deoxy (**8n**).

Conclusion

We designed and synthesized a novel series of benzocycloalkene derivatives focusing on the conformation of the amide side chain and the methoxy group. In receptor binding assays, it was revealed that indan

Table 3. Affinities of Benzocycloalkene Derivatives for Human Melatonin Receptor (MT_1 Site) and Syrian Hamster Brain Melatonin Receptor (MT_3 Site)

	receptor binding[a]	
no.	MT_1,[b] K_i (nM)	MT_3,[c] K_i (nM)
melatonin	0.0823 ± 0.0021	27.6 ± 0.3
8a	1.65 ± 0.49	>10 000
8b	0.0469 ± 0.0125	608 ± 372
8c	0.131 ± 0.038	316 ± 166
(*S*)-**8c**	0.0733 ± 0.0201	4180 ± 118
(*R*)-**8c**	10.6 ± 0.5	372 ± 35
8d	0.0728 ± 0.0186	686 ± 202
(*S*)-**8d**	0.0410 ± 0.0102	3570 ± 760
(*R*)-**8d**	30.1 ± 3.2	561 ± 161
8e	0.0553 ± 0.0054	946 ± 301
(*S*)-**8e**	0.0321 ± 0.0064	2230 ± 248
(*R*)-**8e**	43.7 ± 10.3	785 ± 207
8f	1.32 ± 0.32	837 ± 489
8g	0.250 ± 0.041	2270 ± 813
8h	0.0225 ± 0.0059	497 ± 205
(*S*)-**8h**	0.0123 ± 0.0033	1550 ± 387
(*R*)-**8h**	6.43 ± 0.34	374 ± 83
8i	28.5 ± 1.9	2600 ± 687
8j	0.0984 ± 0.0096	4580 ± 1480
8k	46.7 ± 9.3	3150 ± 1050
8l	4.09 ± 0.79	782 ± 237
8m	1.60 ± 0.18	1770 ± 442
8n	12.3 ± 3.4	>10 000
(*E*)-**9a**	0.208 ± 0.021	1190 ± 439
(*Z*)-**9a**	0.927 ± 0.336	467 ± 128
10a	0.0231 ± 0.0041	48.6 ± 8.7
10b	0.0408 ± 0.0098	9.09 ± 2.90
10c	0.006 02 ± 0.000 52	48.0 ± 17.7
10d	6.84 ± 1.80	2450 ± 948
13	28.6 ± 8.0	428 ± 125
19	0.526 ± 0.136	353 ± 147
20	23.8 ± 3.4	1810 ± 54
21a	0.100 ± 0.029	760 ± 238
21b	0.425 ± 0.066	812 ± 121
21c	1.45 ± 0.23	5490 ± 1390

[a] The K_i values were calculated from IC_{50} values. IC_{50} values were obtained from the molar concentration of test compound required to inhibit by 50% the 2-[^{125}I]iodomelatonin specific binding. [b] Human melatonin receptor expressed in CHO cells. [c] Syrian hamster brain and peripheral organs and were calculated by log-probit analysis.

derivatives having an *S*-configuration at position 1 showed greater affinity for the MT_1 receptor than compounds with the *R*-configuration or with a double bond (*endo*, *exo*). Because the *S*-compounds, e.g., (*S*)-**8d**, exhibited little affinity for the MT_3 receptor, the *S*-configured chiral center in benzocycloalkene derivatives was significant on account of the selectivity toward the MT_1 receptor.[19] To obtain *S*-compounds practically, we examined the asymmetric synthesis of (*S*)-**8d**. We clarified that hydrogenation of (*E*)-**9a** with an *exo E* double bond using $Ru(OAc)_2$[(*S*)-binap] as a catalyst gave (*S*)-**8d** conveniently and efficiently.

It was also revealed that the conformation of the methoxy group of indan derivatives, in relation to the orientation of oxygen lone pairs, is important for affinity. The chiral indan derivatives reported herein exhibited no significant affinity for other receptors and enzymes and exhibited agonistic activity toward melatonin receptors in experiments on forskolin-induced adenosine cyclic 3′,5′-phosphate (cAMP) production in CHO cells expressing the human MT_1 receptor (see the Supporting Information). These results would be a basis for further investigation.

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz), with tetramethylsilane as the internal standard. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Thin-layer chromatography (TLC) analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses of the target compounds were carried out by Takeda Analytical Research Laboratories, Ltd. Tetrahydrofuran (THF) was distilled over calcium hydride prior to use, and other solvents and reagents were used without purification. The Raney-cobalt used was commercially available as ODHT-60 (Kawaken Finechemical Co. Ltd.), and was washed with distilled water (three times) and EtOH (once) prior to use. Solutions in organic solvents were dried over anhydrous $MgSO_4$, and concentration of the organic solution was carried out under reduced pressure. Chromatographic purification was carried out on silica gel columns (Merck Kieselgel 60, 0.063−0.200 mm). Yields were not maximized.

Method A. (*E*)-(2,3-Dihydro-6-methoxy-1*H*-inden-1-ylidene)acetonitrile ((*E*)-4c) and (*Z*)-(2,3-Dihydro-6-methoxy-1*H*-inden-1-ylidene)acetonitrile ((*Z*)-4c). To a solution of diethyl cyanomethylphosphonate (9.4 g, 53 mmol) in THF (60 mL) was added 66% NaH (1.9 g, 53 mmol; dispersion in oil), and the mixture was cooled in an ice-water bath before it was stirred at room temperature for 30 min. After the mixture was cooled again in an ice-water bath, a suspension of 2,3-dihydro-6-methoxy-1*H*-inden-1-one (**3c**) (7.9 g, 48 mmol) in THF (40 mL) was added with stirring, and the stirring was continued at room temperature for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was crystallized from EtOAc−hexane, and the solid was collected by filtration to yield 4.9 g (55% yield) of (*E*)-**4c**; mp 95−96 °C. ^{1}H NMR ($CDCl_3$): δ 3.01−3.18 (m, 4H), 3.83 (s, 3H), 5.61 (t, 1H, J = 2.4 Hz), 6.96−7.03 (m, 2H), 7.27 (d, 1H, J = 8.8 Hz). The filtrate was concentrated, and the residue was purified by column chromatography (hexane:EtOAc 23:2) to afford 1.3 g (15% yield) of (*Z*)-**4c**; mp 68−69 °C (EtOAc−hexane). ^{1}H NMR ($CDCl_3$): δ 2.97 (s, 4H), 3.86 (s, 3H), 5.31 (s, 1H), 7.00 (dd, 1H, J = 2.6 Hz, 8.4 Hz), 7.24 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, J = 2.6 Hz). Further elution afforded 1.7 g (18% yield) of (*E*)-**4c**. With a similar procedure, the following compounds were prepared (6,7,8,9-tetrahydro-3-methoxy-5*H*-benzocyclohepten-5-ylidene)acetonitrile (**4a**), (3,4-dihydro-7-methoxy-1(2*H*)-naphthalenylidene)-acetonitrile (**4b**), (*E*)-(5-bromo-2,3-dihydro-6-methoxy-7-methyl-1*H*-inden-1-ylidene)acetonitrile ((*E*)-**4d**), (*E*)-(7-bromo-2,3-dihydro-6-methoxy-5-methyl-1*H*-inden-1-ylidene)acetonitrile ((*E*)-**4e**), (*E*)-(2,3-dihydro-6,7-dimethoxy-1*H*-inden-1-ylidene)-acetonitrile ((*E*)-**4f**), (2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-ylidene)acetonitrile (**4g**), and (2,3-dihydro-1*H*-inden-1-ylidene)-acetonitrile (**4h**).

Method B. (*E*)-(2,3-Dihydro-6-methoxy-2-phenyl-1*H*-inden-1-ylidene)acetonitrile ((*E*)-4i). To a solution of 1,1,1,3,3,3-hexamethyldisilazane (2.9 mL, 14 mmol) in THF (80 mL) was added dropwise 1.6 M *n*-BuLi hexane solution (8.7 mL, 14 mmol) at −78 °C under an argon atmosphere, and the mixture was stirred for 15 min. To the mixture was added dropwise acetonitrile (0.65 mL, 12 mmol), and stirring was continued for 20 min; then, a solution of 2,3-dihydro-6-methoxy-2-phenyl-1*H*-inden-1-one (**3i**)[20] (2.7 g, 11 mmol) in THF (30 mL) was added dropwise. After the reaction mixture was stirred for 1 h, water was added and the mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in toluene (100 mL), and 10-camphorsulfonic acid (0.50 g) was added to the resulting solution. The mixture was stirred under reflux with an azeotropic water-removing system for 1 h. After the reaction mixture was cooled, water was added and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was crystallized

from EtOAc−diisopropyl ether to recover 1.0 g of the starting material **3i**. The mother liquid was concentrated, and the residue was again crystallized from EtOAc−diisopropyl ether to afford 0.47 g (16% yield) of (*E*)-**4i**; mp 112−114 °C. ^{1}H NMR ($CDCl_3$): δ 3.03 (d, 1H, J = 17.0 Hz), 3.59 (dd, 1H, J = 8.2 Hz, 17.0 Hz), 3.86 (s, 3H), 4.49 (d, 1H, J = 8.2 Hz), 5.69 (d, 1H, J = 2.6 Hz), 6.95−7.32 (m, 8H). By a similar procedure, [2,3-dihydro-6-methoxy-2-(phenylmethyl)-1*H*-inden-1-ylidene]acetonitrile (**4j**) was prepared.

Method C. 2,3-Dihydro-6-methoxy-1*H*-inden-1-ethanamine (5c) and 5c Hydrochloride. To a solution of (*E*)-**4c** (4.0 g, 22 mmol) in EtOH (80 mL) were added Raney-nickel (4.0 g; W2) and 4 M NH_3/EtOH (40 mL), and the mixture was stirred under a hydrogen atmosphere (0.4 MPa) at room temperature for 5 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH 97:3, followed by $CHCl_3$:MeOH:Et_3N 90:7:3) to afford 3.3 g (80% yield) of **5c** as an oily product. ^{1}H NMR ($CDCl_3$): δ 1.50−1.76 (m, 2H), 1.90−2.08 (m, 1H), 1.22−1.34 (m, 1H), 2.65−3.20 (m, 5H), 3.79 (s, 3H), 6.71 (dd, 1H, J = 2.6 Hz, 8.2 Hz), 6.76 (1H, br s), 7.12 (d, 1H, J = 8.2 Hz), hidden (2H). Hydrochloride of **5c** was prepared from **5c** and 4 M HCl/EtOH and recrystallized from EtOH−diethyl ether; mp 147−148 °C. ^{1}H NMR (DMSO-d_6): δ 1.57−1.88 (m, 2H), 2.01−2.36 (m, 2H), 2.62−2.92 (m, 4H), 3.07−3.23 (m, 1H), 3.73 (s, 3H), 6.68−6.78 (m, 2H), 7.12 (d, 1H, J = 8.2 Hz), 8.14 (br s, 2H). A similar procedure was employed to prepare the following compounds: 2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-ethanamine hydrochloride (**5g**) and 2,3-dihydro-6-methoxy-1*H*-indene-1-propanamine (**18**).

Method D. (*E*)-2-(2,3-Dihydro-6-methoxy-1*H*-inden-1-ylidene)ethanamine ((*E*)-6c). To a solution of (*E*)-**4c** (2.0 g, 11 mmol) in EtOH (20 mL) were added Raney-cobalt (2.0 g) and 4 M NH_3/EtOH (10 mL), and the mixture was stirred under a hydrogen atmosphere (0.4 MPa) at 40 °C for 6 h. The mixture was filtered, and the filtrate was concentrated to afford 2.0 g (96% yield) of (*E*)-**6c** as an oily product. ^{1}H NMR ($CDCl_3$) δ 1.38 (br s, 2H), 2.70−2.80 (m, 2H), 2.89−2.98 (m, 2H), 3.48 (d, 2H, J = 7.0 Hz), 3.81 (s, 3H), 5.92−6.01 (m, 1H), 6.78 (dd, 1H, J = 2.4 Hz, 8.2 Hz), 6.97 (d, 1H, J = 2.4 Hz), 7.14 (d, 1H, J = 8.2 Hz). A similar procedure was used to prepare the following compounds: (*E*)-2-(6,7,8,9-tetrahydro-3-methoxy-5*H*-benzocyclohepten-5-ylidene)ethanamine ((*E*)-**6a**), 2-(3,4-dihydro-7-methoxy-1(2*H*)-naphthalenylidene)ethanamine (**6b**), (*Z*)-2-(2,3-dihydro-6-methoxy-1*H*-inden-1-ylidene)ethanamine ((*Z*)-**6c**), (*E*)-2-(5-bromo-2,3-dihydro-6-methoxy-7-methyl-1*H*-inden-1-ylidene)ethanamine ((*E*)-**6d**), (*E*)-2-(7-bromo-2,3-dihydro-6-methoxy-5-methyl-1*H*-inden-1-ylidene)-ethanamine ((*E*)-**6e**), (*E*)-2-(2,3-dihydro-6,7-dimethoxy-1*H*-inden-1-ylidene)ethanamine ((*E*)-**6f**), (*E*)-2-(2,3-dihydro-1*H*-inden-1-ylidene)ethanamine ((*E*)-**6h**), 2-[2,3-dihydro-6-methoxy-2-(phenylmethyl)-1*H*-inden-1-ylidene]ethanamine (**6j**), 5-methoxy-2-phenyl-1*H*-inden-3-ethanamine hydrochloride (**7i**), and 2,3-dihydro-6-methoxy-1*H*-indene-1-methanamine (**12**).

Method E. 5-Methoxy-2-(phenylmethyl)-1*H*-inden-3-ethanamine Hydrochloride (7j). A solution of **6j** (6.4 g, 23 mmol) in 4 M HCl/EtOH (60 mL) was stirred at 70 °C for 13 h. After the reaction mixture was cooled, the deposited powder was collected by filtration, washed with diethyl ether, and dried to afford 1.8 g (24% yield) of **7j**. The filtrate was concentrated, and the residue was crystallized from EtOH−diethyl ether to afford 3.6 g (50% yield) of **7j**; mp 217−219 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 2.96 (br s, 4H), 3.15 (s, 2H), 3.79 (s, 3H), 3.82 (s, 2H), 6.68 (dd, 1H, J = 2.2 Hz, 8.1 Hz), 7.06 (d, 1H, J = 2.2 Hz), 7.15−7.40 (m, 6H), 8.13 (br s, 2H). By a similar procedure, 5-methoxy-1*H*-inden-3-ethanamine (**7c**) was prepared.

Method F. (*E*)-*N*-[2-(2,3-Dihydro-6-methoxy-1*H*-inden-1-ylidene)ethyl]propionamide ((*E*)-9a). To a stirring solution of (*E*)-**6c** (3.0 g, 16 mmol) and triethylamine (2.4 g, 24 mmol) in THF (35 mL) was added dropwise propionyl chloride (1.9 g, 21 mmol) in an ice-water bath, and the stirring was continued for 15 min. The reaction mixture was poured into water, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (EtOAc) followed by recrystallization with EtOAc to afford 2.3 g (59% yield) of (*E*)-**9a**; mp 129−131 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, J = 7.5 Hz), 2.24 (q, 2H, J = 7.5 Hz), 2.73−2.86 (m, 2H), 2.90−3.00 (m, 2H), 3.81 (s, 3H), 4.04 (t, 2H, J = 6.2 Hz), 5.55 (br s, 1H), 5.88 (m, 1H), 6.79 (dd, 1H, J = 2.4 Hz, 8.1 Hz), 6.93 (d, 1H, J = 2.4 Hz), 7.14 (d, 1H, J = 8.1 Hz). Anal. ($C_{15}H_{19}NO_2$) C, H, N. A similar procedure was used to prepare the following compounds: *N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]pentanamide (**8f**), *N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide (**8h**), (*S*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide ((*S*)-**8h**), (*R*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide ((*R*)-**8h**), *N*-[2-(2,3-dihydro-6,7-dimethoxy-1*H*-inden-1-yl)ethyl]acetamide (**8k**), *N*-[2-(2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-yl)ethyl]acetamide (**8l**), (*Z*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-ylidene)ethyl]propionamide ((*Z*)-**9a**), (*E*)-*N*-[2-(3,4-dihydro-7-methoxy-1(2*H*)-naphthalenylidene)ethyl]-2,2,2-trifluoroacetamide ((*E*)-**9b**), (*E*)-2,2,2-trifluoro-*N*-[2-(6,7,8,9-tetrahydro-3-methoxy-5*H*-benzocyclohepten-5-ylidene)ethyl]acetamide ((*E*)-**9c**), (*E*)-*N*-[2-(5-bromo-2,3-dihydro-6-methoxy-7-methyl-1*H*-inden-1-ylidene)-ethyl]-2,2,2-trifluoroacetamide ((*E*)-**9d**), (*E*)-*N*-[2-(7-bromo-2,3-dihydro-6-methoxy-5-methyl-1*H*-inden-1-ylidene)ethyl]-2,2,2-trifluoroacetamide ((*E*)-**9e**), (*E*)-*N*-[2-(2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-2,2,2-trifluoroacetamide ((*E*)-**9h**), *N*-[2-(5-methoxy-1*H*-inden-3-yl)ethyl]propionamide (**10a**), 2,2,2-trifluoro-*N*-[2-(5-methoxy-1*H*-inden-3-yl)ethyl]acetamide (**10b**), 2,2,2-trifluoro-*N*-[2-(5-methoxy-2-phenyl-1*H*-inden-3-yl)ethyl]acetamide (**10c**), 2,2,2-trifluoro-*N*-[2-[5-methoxy-2-(phenylmethyl)-1*H*-inden-3-yl]ethyl]acetamide (**10d**), *N*-[(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)methyl]-2,2,2-trifluoroacetamide (**13**), and *N*-[3-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)propyl]-2,2,2-trifluoroacetamide (**19**).

Method G. *N*-[2-(2,3-Dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]acetamide (8c). To a suspension of **5c** hydrochloride (16 g, 71 mmol) in THF (100 mL) was added 1 M aqueous NaOH (180 mL) in an ice-water bath followed by acetic anhydride (8.7 g, 85 mmol) with vigorous stirring. After it was stirred for 15 min, the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was recrystallized from EtOAc−hexane to yield 16 g (94% yield) of **8c**; mp 80−81 °C. ^{1}H NMR ($CDCl_3$): δ 1.50−1.80 (m, 2H), 1.98 (s, 3H), 1.99−2.14 (m, 1H), 2.21−2.40 (m, 1H), 2.66−2.94 (m, 2H), 3.03−3.17 (m, 1H), 3.38 (dd, 2H, J = 7.4 Hz, 13.2 Hz), 3.78 (s, 3H), 5.53 (br s, 1H), 6.68−6.75 (m, 2H), 7.11 (d, 1H, J = 8.0 Hz). Anal. ($C_{14}H_{19}NO_2$) C, H, N. A similar procedure was used to prepare the following compounds: *N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]propionamide (**8d**), (*S*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]propionamide ((*S*)-**8d**), (*R*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]propionamide ((*R*)-**8d**), *N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]butanamide (**8e**), (*S*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]butanamide ((*S*)-**8e**), (*R*)-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)-ethyl]butanamide ((*R*)-**8e**), *N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]-2-methylpropionamide (**8g**), and (*S*)-4-bromo-*N*-[2-(2,3-dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]benzamide ((*S*)-**8o**).

Method H. 2,2,2-Trifluoro-*N*-[2-(6,7,8,9-tetrahydro-3-methoxy-5*H*-benzocyclohepten-5-yl)ethyl]acetamide (8a). To a solution of (*E*)-**9c** (1.5 g, 4.8 mmol) was added 5% Pd−C (0.40 g, water 50%), and the mixture was stirred under a hydrogen atmosphere (normal pressure) until the theoretical amount of hydrogen gas was consumed. The reaction mixture was filtered, and the filtrate was concentrated. The residue was recrystallized from diisopropyl ether−hexane to afford 1.5 g (97% yield) of **8a**; mp 77−78 °C. ^{1}H NMR ($CDCl_3$): δ 1.65−1.96 (m, 7H), 2.08−2.25 (m, 1H), 2.72−2.89 (m, 3H), 3.22−3.38 (m, 1H), 3.40−3.60 (m, 1H), 3.78 (s, 3H), 6.18 (br s, 1H), 6.61−6.68 (m, 2H), 7.02 (t, 1H, J = 8.0 Hz). Anal. ($C_{16}H_{20}F_3NO_2$) C, H, N. A similar procedure was employed to prepare the following compounds: 2,2,2-trifluoro-*N*-[2-(1,2,3,4-tetrahy-

dro-7-methoxy-1-naphthalenyl)ethyl]acetamide (**8b**), 2,3-dihydro-6,7-dimethoxy-1*H*-inden-1-ethanamine (**5f**), *N*-[2-(2,3-dihydro-6-methoxy-7-methyl-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide (**8i**), *N*-[2-(2,3-dihydro-6-methoxy-5-methyl-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide (**8j**), *N*-[2-(2,3-dihydro-6-methoxy-2-phenyl-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide (**8m**), and *N*-[2-(2,3-dihydro-1*H*-inden-1-yl)ethyl]-2,2,2-trifluoroacetamide (**8n**).

Method I. 5-Methoxy-1*H*-indene-3-carbonitrile (11). To a solution of **3c** (10 g, 62 mmol) and ZnI_2 (0.8 g, 2.5 mmol) in CH_2Cl_2 (200 mL) was added dropwise trimethylsilyl cyanide (7.3 g, 74 mmol), and the mixture was stirred under an argon atmosphere at 40 °C for 20 h. The reaction mixture was washed with water and brine and filtered through Celite. The filtrate was concentrated. The residue was suspended in toluene (200 mL), and trifluoroacetic acid (14 mL, 0.18 mol) was added. The mixture was stirred under refluxing for 1.5 h and then cooled. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc 9:1) to afford 4.5 g (42% yield) of **11** as an oily product. ^{1}H NMR ($CDCl_3$): δ 3.57 (d, 2H, J = 2.2 Hz), 3.87 (s, 3H), 6.90 (dd, 1H, J = 2.2 Hz, 8.2 Hz), 7.11 (d, 1H, J = 2.2 Hz), 7.32−7.35 (m, 1H), 7.39 (d, 1H, J = 8.2 Hz).

Method J. 2,3-Dihydro-6-methoxy-1*H*-indene-1-acetic Acid Ethyl Ester (14). To a suspension of 60% NaH (1.8 g, 46 mmol; dispersion in oil) in THF (200 mL) was added triethyl phosphonoacetate (10 g, 46 mmol) in an ice-water bath, and the mixture was stirred until it became homogeneous. To the mixture was added a suspension of **3c** (7.1 g, 44 mmol) in THF (30 mL), and the stirring was continued at room temperature for 2 h and then at 70 °C for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was diluted with EtOH (200 mL), and 5% Pd−C (2.5 g, water 50%) was added. The mixture was stirred under a hydrogen atmosphere (normal pressure) at 50 °C for 1.5 h. It was then filtered, and the filtrate was concentrated. The residue was purified by column chromatography (hexane:EtOAc 97:3, followed by 4:1) to afford 6.6 g (64% yield) of **14** as an oily product. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.2 Hz), 1.67−1.83 (m, 1H), 2.30−2.47 (m, 2H), 2.69−2.95 (m, 3H), 3.47−3.62 (m, 1H), 3.78 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 6.69−6.75 (m, 2H), 7.11 (d, 1H, J = 8.6 Hz).

Method K. 2,3-Dihydro-6-methoxy-1*H*-indene-1-ethanol (15). To a stirring suspension of lithium aluminum hydride (1.1 g, 28 mmol) in THF (150 mL) was added dropwise a solution of **14** (6.5 g, 28 mmol) in THF (20 mL) in an ice-water bath, and the stirring was continued for 15 min. To the reaction mixture was added water (1.0 mL), EtOAc, $MgSO_4$, and Celite, and then, the mixture was filtered. The filtrate was concentrated to afford 5.0 g (93% yield) of **15** as an oily product. ^{1}H NMR ($CDCl_3$): δ 1.35 (br s, 1H), 1.60−1.82 (m, 2H), 2.06−2.41 (m, 2H), 2.69−2.96 (m, 2H), 3.15−3.28 (m, 1H), 3.75−3.88 (m, 2H), 3.79 (s, 3H), 6.68−6.79 (m, 2H), 7.12 (d, 1H, J = 8.0 Hz).

Method L. 1-(2-Bromoethyl)-2,3-dihydro-6-methoxy-1*H*-indene (16). To a stirring solution of **15** (5.0 g, 26 mmol) in CH_2Cl_2 (100 mL) was added phosphorus tribromide (0.86 mL, 27 mmol) at −5 °C, and the stirring was continued for 30 min. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc 7:3, followed by 1:1) to afford 1.8 g (27% yield) of **16** as an oily product. ^{1}H NMR ($CDCl_3$): δ 1.60−1.78 (m, 1H), 1.88−2.06 (m, 1H), 2.24−2.41 (m, 2H), 2.70−2.96 (m, 2H), 3.21−3.38 (m, 1H), 3.41−3.60 (m, 2H), 3.79 (s, 3H), 6.68−6.78 (m, 2H), 7.12 (d, 1H, J = 7.6 Hz).

Method M. 2,3-Dihydro-6-methoxy-1*H*-indene-1-propanenitrile (17). To a solution of **16** (1.8 g, 6.9 mmol) in dimethyl sulfoxide (80 mL) was added sodium cyanide (0.35 g, 7.2 mmol), and the mixture was stirred at 60 °C for 40 min. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc 85:15) to afford 1.3 g (93% yield) of **17** as an oily product. ^{1}H NMR ($CDCl_3$): δ 1.62−1.89 (m, 2H), 2.03−2.48 (m, 4H), 2.71−2.96 (m, 2H), 3.18−3.33 (m, 1H), 3.80 (s, 3H), 6.72−6.78 (m, 2H), 7.13 (d, 1H, J = 9.0 Hz).

Method N. *N*-[2-(2,3-Dihydro-6-hydroxy-1*H*-inden-1-yl)ethyl]propionamide (20). To a stirring solution of **8d** (5.6 g, 22 mmol) in CH_2Cl_2 (200 mL) was added dropwise boron tribromide (11 g, 45 mmol) in an ice-water bath, and the stirring was continued for 2 h. The reaction mixture was poured into ice-water, and the mixture was stirred at room temperature for 15 h and then extracted with EtOAc. The extract was concentrated, and the residue was purified by column chromatography (EtOAc:MeOH 95:5) and recrystallized from EtOAc−hexane to afford 5.2 g (quantitative yield) of **20**; mp 119−121 °C. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J = 7.6 Hz), 1.50−1.80 (m, 2H), 1.87−2.10 (m, 1H), 2.22 (q, 1H, J = 7.6 Hz), 2.20−2.38 (m, 1H), 2.65−2.90 (m, 2H), 2.97−3.15 (m, 1H), 3.38 (q, 2H, J = 7.0 Hz), 5.67 (br s, 1H), 6.68 (dd, 1H, J = 2.9 Hz, 8.0 Hz), 6.74 (d, 1H, J = 2.9 Hz), 7.05 (d, 1H, J = 8.0 Hz). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

Method O. *N*-[2-(6-Ethoxy-2,3-dihydro-1*H*-inden-1-yl)-ethyl]propionamide (21a). To a suspension of **20** (1.0 g, 4.3 mmol) and potassium carbonate (3.0 g, 21 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise iodoethane (6.7 g, 43 mmol), and the mixture was stirred under reflux for 1.5 h. After it was cooled, the reaction mixture was poured into water and extracted with EtOAc. The extract was concentrated, and the residue was purified by column chromatography (EtOAc:hexane 85:15) and recrystallized from EtOAc−hexane to afford 0.86 g (77% yield) of **21a**; mp 87−89 °C. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.7 Hz), 1.31 (t, 3H, J = 7.0 Hz), 1.39−1.71 (m, 2H), 1.80−2.00 (m, 1H), 2.07 (q, 2H, J = 7.7 Hz), 2.15−2.33 (m, 1H), 2.59−2.89 (m, 2H), 2.91−3.08 (m, 1H), 3.14 (q, 2H, J = 7.7 Hz), 3.97 (q, 2H, J = 7.0 Hz), 6.66 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 2.4 Hz), 7.07 (d, 1H, J = 8.1 Hz), 7.79 (br s, 1H). Anal. ($C_{16}H_{23}NO_2$) C, H, N. A similar procedure was used to prepare the following compounds: *N*-[2-(2,3-dihydro-6-propoxy-1*H*-inden-1-yl)ethyl]propionamide (**21b**) and *N*-[2-[2,3-dihydro-6-(1-methylethoxy)-1*H*-inden-1-yl]ethyl]propionamide (**21c**).

Method P. (*S*)-*N*-[2-(2,3-Dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]acetamide ((*S*)-8c) and (*R*)-*N*-[2-(2,3-Dihydro-6-methoxy-1*H*-inden-1-yl)ethyl]acetamide ((*R*)-8c). The racemate **8c** was resoluted with HPLC to afford optically pure (*S*)-**8c** and (*R*)-**8c** [column, Ceramospher RU-1 (6.0 mm × 250 mm), 50 °C; eluent, MeOH; flow rate, 0.6 mL/min; detect, 290 nm; t_R of (*S*)-**8c**, 50.3 min; t_R of (*R*)-**8c**, 45.9 min]. Compound (*S*)-**8c**: $[\alpha]_D^{20}$ −1.5° (*c* 0.35, $CHCl_3$); $[\alpha]_{Hg365}^{20}$ +80.7° (*c* 0.35, $CHCl_3$); mp 93−94 °C (EtOAc/hexane). Anal. ($C_{14}H_{19}NO_2$) C, H, N. Compound (*R*)-**8c**: $[\alpha]_D^{20}$ +1.2° (*c* 0.30, $CHCl_3$); $[\alpha]_{Hg365}^{20}$ −61.3° (*c* 0.30, $CHCl_3$); mp 95−96 °C (EtOAc/hexane). Anal. ($C_{14}H_{19}NO_2$) C, H, N. ^{1}H NMR data of the chiral compounds were identical with those of **8c**.

Method Q. (*R*)-2,3-Dihydro-6-methoxy-1*H*-indene-1-ethanamine Hydrochloride ((*R*)-5c). Under an argon atmosphere, a mixture of (*R*)-**8c** (1.0 g, 4.3 mmol) and hydrazine monohydrate (20 mL) was stirred under reflux for 24 h. To the reaction mixture was added brine, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was diluted with EtOH (1 mL), and 4 M HCl/EtOH (1.5 mL) was added. To the solution was added diethyl ether, and the solid that precipitated was collected by filtration. The crude solid was recrystallized from EtOH−diethyl ether to afford 0.78 g (80% yield) of (*R*)-**5c**; $[\alpha]_D^{20}$ +32.6° (*c* 0.18, H_2O); mp 183−185 °C. ^{1}H NMR data of (*R*)-**5c** were identical with those of **5c** hydrochloride. The enantiomeric excess of (*R*)-**5c** was determined by HPLC as >99% [column, CHIRAL-AGP (4.0 mm × 100 mm), room temperature; eluent, 10 mM phosphate buffer (pH 7.0)−acetonitrile (9:1); flow rate, 0.5 mL/min; detect, 280 nm; t_R of (*R*)-**5c**, 19.2 min; t_R of (*S*)-**5c** (enantiomer of (*R*)-**5c**), 23.6 min]. A similar procedure was used to prepare compound (*S*)-**5c**.

Method R. Asymmetric Hydrogenation. (*S*)-8d. A mixture of (*E*)-**9a** (3.5 g, 14 mmol) and $Ru(OCOCH_3)_2$[(*S*)-binap] (0.12 g, 14 mmol) in degasified absolute methanol (70 mL) was stirred at 70 °C for 3 h in an autoclave (hydrogen pressure, 9.1 MPa). The reaction mixture was concentrated, and the residue was purified by column chromatography (hexane: EtOAc 1:9) and recrystallized from EtOAc−hexane to yield 2.9 g (83%) of (*S*)-**8d**: $[\alpha]_D^{20}$ −7.0° (*c* 1.00, EtOH); mp 76−77 °C. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J = 7.8 Hz), 1.50−1.80 (m, 2H), 1.98−2.40 (m, 2H), 2.20 (q, 2H, J = 7.6 Hz), 2.68−2.97 (m, 2H), 3.04−3.20 (m, 1H), 3.39 (dd, 2H, J = 7.2 Hz, 13.2 Hz), 3.79 (s, 3H), 5.45 (br s, 1H), 6.68−6.76 (m, 2H), 7.12 (d, 1H, J = 8.0 Hz). Anal. ($C_{15}H_{21}NO_2$) C, H, N. The enantiomeric excess of (*S*)-**8d** was determined by HPLC as >99% [column, CHIRALPAK AS (4.6 mm × 250 mm), room temperature; eluent, hexane-2-propanol-trifluoroacetic acid (90:10:0.1); flow rate, 1.0 mL/min; detect, 290 nm; t_R of (*S*)-**8d**, 28.0 min; t_R of (*R*)-**8d** (enantiomer of (*S*)-**8d**), 23.6 min].

Affinity for the MT_1 Receptor Expressed in CHO Cells. cDNA encoding the human melatonin receptor gene was introduced into CHO cells. A cell line stably expressing the MT_1 receptor (CHO-hMelR7) was selected and cultured in Eagle's minimum essential medium-α (MEM-α) supplemented with 10% dialyzed fetal bovine serum (dFBS). Cells were harvested, homogenized in 50 mM Tris-HCl (pH 7.7), aliquoted, and sedimented by centrifugation at 44 000*g* for 10 min. The resulting pellet was stored at −30 °C until use. The frozen pellet was thawed, homogenized in assay buffer (50 mM Tris-HCl, pH 7.7), and used for the binding assay. An aliquot of the homogenate was incubated with 40 pM 2-[^{125}I]iodomelatonin and the test compound at 25 °C for 150 min in a total volume of 1 mL. The reaction was terminated by addition of 3 mL of ice-cold assay buffer followed by rapid vacuum filtration on Whatman GF/B. The filter was washed twice with 3 mL of ice-cold buffer and placed in a polystyrene tube. The radioactivity was then measured with a γ-counter. Nonspecific binding was determined in the presence of 10 μM melatonin. IC_{50} values were calculated from three experiments by log-probit analysis, and the inhibition constant (K_i) values were obtained from the IC_{50} by the method of Cheng and Prusoff.[21]

Affinity for *MT_3* Site in Syrian Hamster Brain and Peripheral Organs. The brain, liver, kidney, and spleen were dissected from male Syrian hamsters (7−8 weeks old) and homogenized in 50 mM Tris-HCl (pH 7.4 at 4 °C). After connective tissues were removed by filtration using a quadruple layer of cotton gauze, the homogenate was centrifuged at 48 000*g* for 10 min. The resultant pellet was washed twice with ice-cold buffer by resuspension and recentrifugation, and the final pellet was suspended in the same buffer. An aliquot of the homogenate was incubated with 100 pM 2-[^{125}I]iodomelatonin and the test compound at 4 °C for 60 min in a total volume of 250 μL. The reaction was terminated by addition of 3 mL of ice-cold assay buffer followed by rapid vacuum filtration on Whatman GF/B. The filter was washed a further two times with 3 mL of ice-cold buffer and placed in a polystyrene tube, and the radioactivity was measured with a γ-counter. Nonspecific binding was determined in the presence of 100 μM melatonin. IC_{50} values were calculated from three experiments by log-probit analysis, and the inhibition constants (K_i) were obtained from the IC_{50} by the method of Cheng and Prusoff.[21]

Acknowledgment. We thank Mr. Akira Fujishima and Ms. Keiko Higashikawa for X-ray crystallographic analysis. Thanks also to Mr. Nobuhiro Fujii and Mr. Masaki Setoh for technical assistance.

Supporting Information Available: X-ray crystallographic data of (*S*)-**8o**; detailed information on the synthesis and characterization of the target compounds listed in Table 2; a list of receptors and enzymes tested for (*S*)-**8d**; the inhibitory effect of (*S*)-**8d** on forskolin-induced cAMP production in CHO cells expressing the human MT_1 receptor. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Posting. This manuscript was released ASAP on 8/15/2002 with an error in the leftmost structure in Table 2. The correct version was posted on 9/5/2002.

References

(1) Mellinger, G. D.; Balter, M. B.; Uhlenhuth, E. H. Insomnia and its Treatment. *Arch. Gen. Psychiatry* **1985**, *42*, 225−232.
(2) Kales, A.; Scharf, M. B.; Kales, J. D. Rebound Insomnia: A New Clinical Syndrome. *Science* **1978**, *201*, 1039−1041.
(3) Herings, R. M. C.; Stricker, B. H. C.; de Boer, A.; Bakker, A.; Strumans, F. Benzodiazepines and the Risk of Falling leading to Femur Fractures. Dosage More Important than Elimination Half-life. *Arch. Intern. Med*. **1995**, *155*, 1801−1807.
(4) (a) Roth, T.; Hartse, K. M.; Saab, P. G.; Piccione, P. M.; Kramer, M. The Effects of Flurazepam, Lorazepam and Triazolam on Sleep and Memory. *Psychopharmacology* **1980**, *70*, 231−237. (b) Lister, R. G. The Amnesic Action of Benzodiazepines in Man. *Neurosci. Biobehav. Rev*. **1985**, *9*, 87−94.
(5) Reiter, R. J. Pineal Melatonin: Cell Biology of its Synthesis and of its Physiological Interactions. *Endocr. Rev*. **1991**, *12*, 151−180.
(6) Wehr, T. A. The Durations of Human Melatonin Secretion and Sleep Respond to Changes in Daylength (Photoperiod). *J. Clin. Endocrinol. Metab*. **1991**, *73*, 1276−1280.
(7) (a) Arendt, J. Melatonin in Humans: Jet-lag and After. *Adv. Pineal Res*. **1991**, *5*, 299−302. (b) Nickelsen, T.; Lang, A.; Bergau, L. The Effect of 6-, 9- and 11-Hour Time Shifts on Circadian Rhythms: Adaptation of Sleep Parameters and Hormonal Patterns following the Intake of Melatonin or Placebo. *Adv. Pineal Res*. **1991**, *5*, 303−306.
(8) Claustrat, B.; Le Bards, D.; Brun, J.; Thivolle, P.; Mallo, C.; Arendt, J.; Chazot, G. Plasma and Brain Pharmacokinetic Studies in Human after Intravenous Administration of Cold or ^{11}C Labeled Melatonin. *Adv. Pineal Res*. **1989**, *3*, 305−310.
(9) (a) *TiPS Receptor and Ion Channel Nomenclature Supplement*; Alexander, S. P., Peter, J. A., Eds.; Elsevier: 2001; Vol. 12, p 72. (b) Reppert, S. M.; Weaver, D. R.; Godson, C. Melatonin Receptors Step into the Light: Cloning and Classification of Subtypes. *Trends Pharmacol. Sci*. **1996**, *17*, 100−102. (c) Liu, C.; Weaver, D. R.; Jin, X.; Shearman, L. P.; Pieschl, R. L.; Gribkoff, V. K.; Reppert, S. M. Molecular Dissection of Two Distinct Actions of Melatonin on the Suprachiasmatic Circadian Clock. *Neuron* **1997**, *19*, 91−102. (d) Dubocovich, M. L.; Yun, K.; Al-Ghoul, W. M.; Benloucif, S.; Masana, M. I. Selective MT_2 Melatonin Receptor Antagonists Block Melatonin-Mediated Phase Advances of Circadian Rhythms. *FASEB J*. **1998**, *12*, 1211−1220.
(10) Reppert, S. M.; Godson, C.; Mahle, C. D.; Weaver, D. R.; Slaugenhaupt, S. A.; Gusella, J. F. Molecular Characterization of a Second Melatonin Receptor Expressed in Human Retina and Brain: The Mel_{1b} Melatonin Receptor. *Proc. Natl. Acad. Sci. U.S.A*. **1995**, *92*, 8734−8738.
(11) (a) Nosjean, O.; Ferro, M.; Cogé, F.; Beauverger, P.; Henlin, J.-M.; Lefoulon, F.; Fauchère, J.-L.; Delagrange, P.; Canet, E.; Boutin, J. A. Identification of the Melatonin-binding site MT_3 as the Quinone Reductase 2. *J. Biol. Chem*. **2000**, *275*, 31311−31317. (b) Nosjean, O.; Nicolas, J.-P.; Klupsch, F.; Delagrange, P.; Canet, E.; Boutin, J. A. Comparative Pharmacological Studies of Melatonin Receptors: MT_1, MT_2 and MT_3/QR_2. Tissue Distribution of MT_3/QR_2. *Biochem. Pharmacol*. **2001**, *61*, 1369−1379.
(12) (a) Grol, C. J.; Jansen, J. M. The High Affinity Melatonin Binding Site Probed with Conformationally Restricted Ligands−II. Homology Modeling of the Receptor. *Bioorg. Med. Chem*. **1996**, *4*, 1333−1339. (b) Spadoni, G.; Stankov, B.; Duranti, A.; Biella, G.; Lucini, V.; Salvatori, A.; Fraschini, F. 2-Substituted 5-Methoxy-*N*-acyltryptamines: Synthesis, Binding Affinity for the Melatonin Receptor, and Evaluation of the Biological Activity. *J. Med. Chem*. **1993**, *36*, 4069−4074. (c) Sugden, D.; Chong, N. W. S.; Lewis, D. F. V. Structure Requirements at the Melatonin Receptor. *Br. J. Pharmacol*. **1995**, *114*, 618−623.
(13) Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V.; Spadoni, G.; Diamantini, G.; Balsamini, C.; Tarzia, G.; Fraschini, F.; Lucini, V.; Nonno, R.; Stankov, B. M. Melatonin Receptor Ligands: Synthesis of New Melatonin Derivatives and Comprehensive Comparative Molecular Field Analysis (CoMFA) Study. *J. Med. Chem*. **1998**, *41*, 3831−3844.

(14) Reeve, W.; Eareckson, W. M., III. Preparation of Homopiperonylamine by Hydrogenation of 3,4-Methylenedioxybenzyl Cyanide over Raney Cobalt Catalyst. *J. Am. Chem. Soc.* **1950**, *72*, 3299−3300.

(15) (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP−Ruthenium(II) Complexes. *J. Org. Chem.* **1987**, *52*, 3174−3176. (b) Kitamura, M.; Nagai, K.; Hsiao, Yi; Noyori, R. Stereoselective Synthesis of a Precursor of 1β-Methylcarbapenems. *Tetrahedron Lett.* **1990**, *31*, 549−552.

(16) (a) Leclerc, V.; Depreux, P.; Lesieur, D.; Caignard, D. H.; Renard, P.; Delagrange, P.; Guardiola-Lemaitre, B.; Morgan, P. Synthesis and Biological Activity of Conformationally Restricted Tricyclic Analogues of the Hormone Melatonin. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1071−1076. (b) Marot, C.; Chavatte, P.; Morin-Allory, L.; Viaud, M. C.; Guillaumet, G.; Renard, P.; Lesieur, D.; Michel, A. Pharmacophoric Search and 3D-QSAR Comparative Molecular Field Analysis Studies on Agonists of Melatonin Sheep Receptors. *J. Med. Chem.* **1998**, *41*, 4453−4465.

(17) Kloubert, S.; Mathé-Allainmat, M.; Andrieux, S.; Langlois, S. M. Synthesis of Benzocycloalkane Derivatives as New Conformationally Restricted Ligands for Melatonin Receptors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3325−3330.

(18) Fourmaintraux, E.; Depreux, P.; Lesieur, D.; Guardiola-Lemaître, B.; Bennejean, C.; Delagrange, P.; Howell, H. E. Tetrahydronaphthalenic Derivatives as New Agonist and Antagonist Ligands for Melatonin Receptors. *Bioorg. Med. Chem.* **1998**, *6*, 9−13.

(19) (a) Jansen, J. M.; Copinga, S.; Gruppen, G.; Molinari, E. J.; Dubocovich, M. L.; Grol, C. J. The High Affinity Melatonin Binding Site Probed with Conformationally Restricted Ligands−I. Pharmacophore and Minireceptor Models. *Bioorg. Med. Chem.* **1996**, *4*, 1321−1332. (b) Davies, D. J.; Garratt, P. J.; Tocher, D. A.; Vonhoff, S.; Davies, J.; Teh, M.-T.; Sugden, D. Mapping the Melatonin Receptor. 5. Melatonin Agonists and Antagonists Derived from Tetrahydrocyclopent[*b*]indoles, Tetrahydrocarbazoles and Hexahydrocyclohept[*b*]indoles. *J. Med. Chem.* **1998**, *41*, 451−467.

(20) Lednicer, D.; Babcock, J. C.; Marlatt, P. E.; Lyster, S. C.; Duncan, G. W. Mammalian Antifertility Agents. I. Derivatives of 2,3-Diphenylindenes. *J. Med. Chem.* **1965**, *8*, 52−57.

(21) Cheng, Y. C.; Prusoff, W. H. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor which Causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

JM020114G