purified by silica gel chromatography using hexane–ether (70:30) as eluant to give **42** and **43**. Diastereoisomer I as a white solid (0.15 g, 38%): $[\alpha]^{22}_D$ = +69° (c = 0.5, $CHCl_3$); IR (film) 2910 and 1687 (C=O urethane) cm^{-1}; NMR ($CDCl_3$) δ 1.3 (4 H, m, 2 × CH_2), 1.4–2.1 (17 H, m, adamantane, CH_3), 2.7 (2 H, m, CH_2Ph), 3.1 (1 H, d, J = 14 Hz, one of CH_2-indole), 3.5 (1 H, d, J = 14 Hz, one of CH_2-indole), 3.6 (1 H, m, CH), 4.6 (1 H, br, OH), 4.7 (1 H, s, urethane NH), 4.8 (1 H, s, adamantane H-2), 7.0–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.6 (1 H, d, J = 8 Hz, indole H-4), 8.2 (1 H, s, indole NH), MS *m/e* (FAB) 501 (17) (M^+ + H), 135 (100), 130 (99). Diastereoisomer II as a white solid (0.18 g, 46%): $[\alpha]^{22}_D$ = +43° (22 °C, c = 0.5, $CHCl_3$); IR (film) 2912 and 1690 (C=O urethane) cm^{-1}; NMR ($CDCl_3$) δ 1.3 (4 H, m, 2 × CH_2), 1.5–2.1 (17 H, m, adamantane, CH_3), 2.7 (2 H, m, CH_2Ph), 2.9 (1 H, d, J = 14 Hz, one of CH_2-indole), 3.2 (1 H, d, J = 14 Hz, one of CH_2-indole), 3.8 (1 H, m, CH), 4.0 (1 H, br, OH), 4.7 (1 H, s, urethane NH), 4.8 (1 H, s, adamantane H-2), 6.9–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.6 (1 H, d, J = 8 Hz, indole H-4), 8.1 (1 H, br, indole NH); MS *m/e* (FAB) 501 (12) (M^+ + H), 370 (30), 135 (100), 130 (99).

Tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R,*S**)]-[1-[4,5-Dihydro-4-(phenylmethyl)-2-thiazolyl]-2-(1*H*-indol-3-yl)-1-methylethyl]carbamate (45).** To a solution of **44**[7a] (0.1 g, 0.2 mmol) in toluene (10 mL) was added Lawesson's reagent (0.10 g, 0.25 mmol), and the mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to ambient temperature and was purified by silica gel chromatography using CH_2Cl_2–ether as eluant to give **45** as a white solid (0.07 g, 70%): $[\alpha]^{22}_D$ = −20° (c = 0.5, $CHCl_3$); IR (film) 2910, 1697 (C=O urethane), and 1620 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 1.3 (3 H, s, CH_3), 1.4–2.1 (14 H, m, adamantane), 2.2 (1 H, br, one of CH_2Ph), 2.8 (1 H, br, one of CH_2Ph), 2.9 (1 H, m, one of CH_2S), 3.2 (1 H, m, one of CH_2S), 3.4 (1 H, d, J = 14 Hz, one of CH_2-indole), 3.7 (1 H, d, J = 14 Hz, one of CH_2-indole), 4.6 (1 H, m, CH), 4.9 (1 H, br, adamantane H-2), 5.8 (1 H, br, urethane NH), 6.9–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.7 (1 H, d, J = 8 Hz, indole H-4), 8.1 (1 H, br, indole NH); MS *m/e* (FAB) 529 (47) (M^+ + H), 398 (44), 130 (100).

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Communications to the Editor

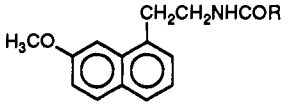
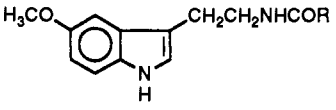
Novel Naphthalenic Ligands with High Affinity for the Melatonin Receptor

Introduction

The neurohormone melatonin (5-methoxy-*N*-acetyltryptamine), which is synthesized principally in the pineal gland, is putatively involved in several physiological axes. These include the entrainment of both seasonal (reproduction)[1] and circadian (activity)[2] rhythms. The role of melatonin in the human is still controversial, but it is thought to be involved in the regulation of sleep,[3,4] seasonal disorders,[4] depression,[4] and ageing.[5] The lack of rigorous data in this regard has often led to conflicting and confusing reports.[4] Nevertheless, the localization of 2-[^{125}I]-iodomelatonin binding sites in the suprachiasmatic nucleus (SCN) of the human hypothalamus,[6] which is the biological clock of the brain, enhances the argument for a physiological role in man.

The recent development of a radioligand binding assay for melatonin receptors using ovine pars tuberalis membranes of the pituitary enables the rapid screening of melatonin analogues for their receptor binding potency.[7]

Table I. Structure Binding Characteristics of 2-(7-Methoxy-1-naphthyl)ethylamides for the Melatonin Receptor

compd	R	mp, °C	K_d:[a] mean ± SEM	order of potency
				
5	CH_3	109–110	(1.00 ± 0.353) × 10^{-10}	7
6	CH_2CH_3	103	(2.19 ± 0.897) × 10^{-11}	5
7	$(CH_2)_2CH_3$	96–97	(6.15 ± 0.178) × 10^{-12}	4
8	$(CH_2)_3CH_3$	90	(3.43 ± 2.430) × 10^{-12}	3
9	$(CH_2)_4CH_3$	84–85	(2.83 ± 0.211) × 10^{-7}	12
10	$(CH_2)_5CH_3$	68–70	(2.33 ± 0.815) × 10^{-6}	15
11	isopropyl	77–78	(2.29 ± 0.745) × 10^{-9}	8
12	$CH{=}CHCH_3$	119–120	(8.47 ± 0.793) × 10^{-9}	9
13	cyclopropyl	91–92	(4.18 ± 0.870) × 10^{-13}	1
14	cyclobutyl	75–76	(2.42 ± 0.536) × 10^{-8}	10
15	cyclohexyl	105–106	(1.59 ± 0.792) × 10^{-7}	11
16	benzyl	101–102	(1.95 ± 0.397) × 10^{-6}	14
17	phenyl	128–130	(4.99 ± 4.360) × 10^{-6}	16
18	$C_6H_3Cl_2$(*m*)	138	(1.13 ± 0.856) × 10^{-5}	17
19	2-indolyl	198–199	(1.17 ± 0.781) × 10^{-6}	13
				
melatonin	CH_3	116–118	(9.15 ± 3.980) × 10^{-11}	6
20	cyclopropyl	101–102	(4.97 ± 0.928) × 10^{-13}	2

[a] K_d's are the means of three independent experiments, calculated as inverse K_a's from single-site fit of untransformed data to equations describing the law of mass action,[10] using a K_a for 2-[^{125}I]iodomelatonin of 3.3 × 10^{10} L/mol. The protocol for the synthesis and purification of the radioligand 2-[^{125}I]iodomelatonin and the receptor-binding assay using ovine pars tuberalis membranes were as described previously.[7]

Fifteen naphthalenic bioisosteres of melatonin with variations on the *N*-acylamino group have been synthesized.

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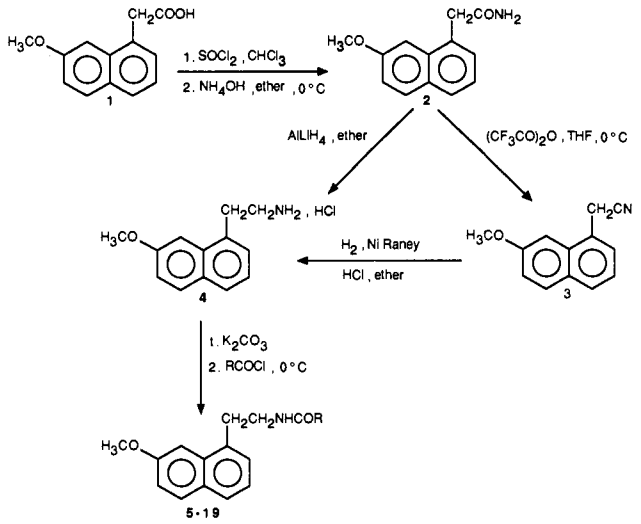
Scheme I



This group was selected for chemical modification, as it has been reported that the *N*-acetyl substituent has primary importance to the efficacy of binding, whereas the 5-methoxy group of the indole nucleus has greater importance to biological activity.[8] Furthermore, it was also decided to test whether the indole nucleus of melatonin could be substituted by a naphthalene structure, as such a modification may afford a longer biological half-life to the molecular bioisosteres. The results of this study not only provide new and useful information about the structure–binding relationships and mode of interaction at the melatonin receptor but also introduce new tools for examining the physiological importance of melatonin.

Chemistry

The synthetic pathways for the compounds listed in Table I are outlined in Scheme I. (7-Methoxy-1-naphthyl)acetic acid (1) was synthesized as described previously.[9] This was reacted with thionyl chloride in $CHCl_3$, and the crude acid chloride was treated with aqueous ammonia to produce amide **2**. Reduction of this amide with metallic hydrides resulted in low yields, so an improved method was used to prepare the corresponding amine. Dehydration of **2** with trifluoroacetic anhydride in THF at 0 °C gave nitrile **3**, which was converted to the desired amine **4** by catalytic hydrogenation (Raney Ni) with an overall yield of 66%. Amides **5–19** were prepared by acylating the hydrochloride of **4** with the appropriate acid chlorides in the presence of potassium carbonate and a biphasic (H_2O–$CHCl_3$) medium.

Compound **20**, the indolic analogue of **13**, was obtained using the same experimental conditions from (5-methoxyindol-3-yl)ethylamine and cyclopropanecarbonyl chloride.

Results and Discussion

The comparisons of each structure and their binding characteristics are summarized in Table I. It is important to note from compound **5** that the indole nucleus of melatonin can be substituted by naphthalene without loss of binding potency. Structural variations of the acylamino group cause major changes in the affinity of the drug for the melatonin receptor. By increasing the chain length of the acyl substituent, binding affinity is increased with the optimum being achieved with propyl (**7**) and butyl (**8**) substitutions. Further homologation, as seen in compounds **9** and **10**, results in dramatically lowered affinity. Loss in affinity also results from branching of the side-chain substitution (**11** and **12**) and from introduction of the larger phenyl (**17**) and benzyl groups (**16**). The compound with the highest binding affinity within this series is structure **13** (K_d, 3×10^{-13}), which has a cyclopropyl substituted at the carbonyl group of the acylamino chain. Expansion of this cyclic ring to include four (**14**) or six (**15**) carbons results in decreased affinity. The importance of the cyclopropyl group to increased binding affinity is demonstrated by compound **20**, which is the indolyl analogue of compound **13**. As for compound **13**, substitution of the methyl group on the *N*-acylamino chain of melatonin by a cyclopropyl group (compound **20**) increases the affinity for the melatonin receptor 100-fold. This observation further emphasizes the ability of naphthalene to fully substitute for the indole nucleus.

Overall these results clearly confirm the crucial role played by the *N*-acyl side chain on the binding affinity for the melatonin receptor. The enhanced affinity displayed by compounds **7**, **8**, **13**, and **20** and the decreased affinity shown by compounds **9**, **10**, **18**, and **19** suggest that there is an optimal size for the acyl group. This predicts that the receptor site has a hydrophobic pocket of relatively small size, which is important to ligand binding.

In conclusion, some of the ligands described in the present paper show greater affinities for the melatonin receptor than melatonin itself. Furthermore, preliminary experimentation in vivo has shown that in rats these compounds present similar biological activities to melatonin. Studies on ability of these compounds to re-entrain activity rhythms in rats are currently under evaluation.

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Supplementary Material Available: Experimental details and tables listing the physicochemical and ^1H NMR spectral data for the 2-(7-methoxy-1-naphthyl)ethylamides (6 pages). Ordering information is given on any current masthead page.

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Registry No. 1, 6836-22-2; 2, 138113-07-2; 3, 138113-08-3; 4, 139525-77-2; 5, 138112-76-2; 6, 138112-79-5; 7, 138112-99-9; 8, 138112-80-8; 9, 139525-78-3; 10, 139525-79-4; 11, 138112-78-4; 12, 139525-80-7; 13, 138113-03-8; 14, 138113-13-0; 15, 138113-02-7; 16, 138112-77-3; 17, 138112-87-5; 18, 138112-91-1; 19, 138112-95-5; 20, 139564-01-5; $CH_3CH{=}CHC(O)Cl$, 10487-71-5; $CH_3C(O)Cl$, 75-36-5; $CH_3CH_2C(O)Cl$, 79-03-8; $CH_3(CH_2)_2C(O)Cl$, 141-75-3; $CH_3(CH_2)_3C(O)Cl$, 638-29-9; $CH_3(CH_2)_4C(O)Cl$, 142-61-0; $CH_3(CH_2)_5C(O)Cl$, 2528-61-2; $(CH_3)_2CHC(O)Cl$, 79-30-1; c-$C_6H_{11}C(O)Cl$, 2719-27-9; $PhCH_2C(O)Cl$, 103-80-0; PhC(O)Cl, 98-88-4; cyclopropanecarbonyl chloride, 4023-34-1; 5-methoxytryptamine, 608-07-1; melatonin, 73-31-4; cyclobutanecarbonyl chloride, 5006-22-4; 3,5-dichlorobenzoyl chloride, 2905-62-6; 1*H*-indole-2-carbonyl chloride, 58881-45-1.

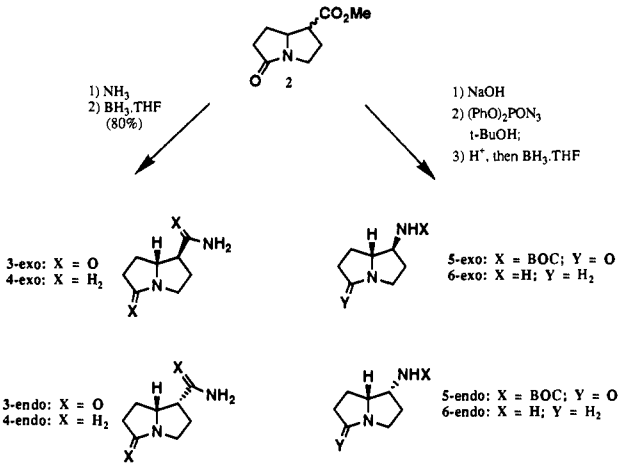
SC-53116: The First Selective Agonist at the Newly Identified Serotonin 5-HT_4 Receptor Subtype†

Serotonin acts as a neurotransmitter, neuromodulator, and hormone in mammals, and it is known to exhibit profound pharmacological activities in the central nervous system, autonomic nervous system, enteric nervous system, and cardiovascular system.[1] Among monoamine neurotransmitters, serotonin is unsurpassed in the number of receptor subtypes identified. Until recently, serotonin was thought to act through receptors subtyped as 5-HT_1, 5-HT_2, and 5-HT_3. Furthermore, even these subtypes have been subclassed to now include 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{3A}, 5-HT_{3B}, and 5-$HT3_{3C}$.[2]

Metoclopramide (Reglan) is a gastrointestinal agent which has been known for some time. Its clinical utilities as an antiemetic and as an upper GI prokinetic agent were originally thought to be due to antagonism at dopamine D_2 receptors (K_i = 113 nM). However, more recently it has been identified as a serotonin 5-HT_3 antagonist (K_i = 240 nM); it is now well established that its utility as an antiemetic (emesis secondary to cytotoxic drugs) is due to its 5-HT_3 antagonist properties.[3,4] Indeed, its interaction with dopamine D_2 receptors is viewed as a clinical liability, causing increased prolactin release and extrapyramidal-like symptoms in medical practice. Regarding utility as a gastrointestinal prokinetic agent, however, interaction with serotonin 5-HT_3 receptors does not adequately explain metoclopramide's activity. Another significant gastroprokinetic agent, cisapride, is believed to act via a serotonergic mechanism in the enteric nervous system. However, its activity does not correlate with interaction at 5-HT_1, 5-HT_2, or 5-HT_3 receptors.[5]

Very recently, Bockaert[6] and Clarke[7] independently reported a new serotonin receptor subtype (5-HT_4) in brain and gut tissues, respectively. Serotonin is quite potent (EC_{50} = 109 nM,[6] 2.8 nM[7]) as an agonist at this receptor, which is positively coupled to adenylate cyclase. Bockaert et al. reported that the gastroprokinetic activity of several agents, including metoclopramide, zacopride, cisapride, and renzapride, could be correlated with agonist activity at this 5-HT_4 receptor.[8] Clarke et al. have described several functional models for the 5-HT_4 receptor in gut tissues,[9,10] and the activities of gastroprokinetic agents were attributed to agonism at this new serotonin receptor.[11] Regarding CNS pharmacology of the 5-HT_4 receptor, Bockaert has identified functional 5-HT_4 receptors in the guinea pig hippocampus,[12] and Boddeke and Kalkman have demonstrated that activation of 5-HT_4 receptors in rat hippocampal regions induce an increase in EEG energy.[13] The design of agents selectively potent

Scheme I. Preparation of Racemic Pyrrolizidine Side Chains



† Dedicated to Professor Lester A. Mitscher on the occasion of his sixtieth birthday.

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