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Tetrahydroisoquinoline derivatives as melatonin MT_2 receptor antagonists

George N. Karageorge,* Stephen Bertenshaw, Lawrence Iben, Cen Xu, Nathan Sarbin, Anthony Gentile and Gene M. Dubowchik

Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT 06492-7660, USA

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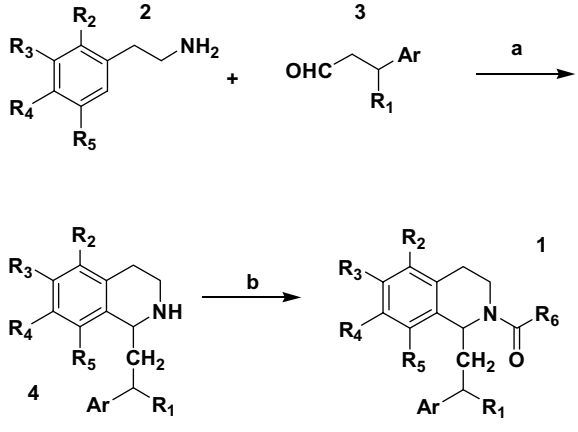
Abstract—A series of tetrahydroisoquinolines has yielded potent MT_2 receptor antagonists, which are selective versus the MT_1 receptor.

Melatonin (*N*-acetyl-5-methoxytryptamine) has been shown to exert its biological effects through binding to specific G-protein coupled receptors in the brain.[1] Cloning of several melatonin receptor genes has revealed at least three melatonin receptor proteins. Two of these receptors are G-protein coupled receptors and have been designated as MT_1 and MT_2.[2,3] Specific 2-[^{125}I]iodomelatonin binding within the hypothalamus in the brain is completely localized to the suprachiasmatic nucleus, the area in the brain thought to regulate the body's internal clock. Further evidence suggests that the melatonin subtype primarily responsible for this action is the MT_2 receptor.[4] This hypothesis has been further strengthened by recent studies showing that MT_2 receptor agonists advance circadian rhythms[5] while MT_2 antagonists block melatonin-mediated phase advances of circadian rhythms.[6]

Accordingly, this body of evidence suggests that selective MT_2 receptor agonists should be particularly useful for the treatment of sleep and chronobiotic disorders, including jet lag and work shift syndrome.[7,8] By focusing on selective MT_2 receptor antagonism, other effects of endogenously secreted melatonin should not be interrupted. This is important as melatonin has also been thought to be involved in seasonal affective disorder[9,10] immune disorders, premenstrual syndrome, and reproductive disorders.[11]

Limited previous research has led to the identification of a small number of selective MT_1 or MT_2 melatoninergic ligands. Furthermore, much of this earlier work focused on MT_1 receptor ligands.[12] Few reports have appeared on selective MT_2 receptor agonists.[13–15] and MT_2 receptor antagonists.[16–18] In this paper we present a novel series of MT_2 receptor antagonists. This series of compounds was discovered via directed high-throughput screening, and the central feature around which we focused our initial SAR efforts was the tetrahydroisoquinoline scaffold as shown in compound **4** (Scheme 1).



Scheme 1. Reagents and conditions: (a) formic acid 95 °C, ~50% yield; (b) $R_6(C{=}O)Cl$, Et_3N, CH_2Cl_2 or $R_6(C{=}O)Cl$, poly(4-vinylpyridine), dichloroethane, Wa21J (Supelco) polyamine scavenging resin, rt (42–88% yield).

Keywords: Melatonin; Antagonist.
* Corresponding author. Tel.: +1 203 677 6351; fax: +1 203 677 7702; e-mail: karageog@bms.com

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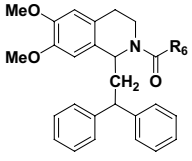
The general synthetic route to these compounds is described in Scheme 1. Pictect–Spengler[19] reaction of amine **2** with aldehyde **3** in formic acid afforded intermediate **4** in approximately 50% yield. Acylation of compound **4** using an appropriate activated acyl derivative was accomplished either singly or in parallel fashion using automated high-speed synthesis techniques to yield amide **1**.

Using the methodology described above with 3,3-diphenylproprionaldehyde (i.e., R_1 and Ar = Ph in **4**) and 3,4-dimethoxyphenethylamine, a diverse set of racemic compounds (**1a**–**o**) were prepared and evaluated for their melatonergic properties (Table 1) in a human MT_1 and MT_2 receptor binding assay.[20,21] Acetamide **1a** had the most potent MT_2 receptor binding affinity with a greater than 100-fold selectivity for the MT_2 receptor. Urea **1g**, formamide **1b**, and carbamate **1i** were also potent MT_2 receptor ligands. However, the latter two possessed less selectivity versus the MT_1 receptor, when compared to **1a**. Larger substituents at R_6 (i.e., pentyl **1l**, hexyl **1o**, and *c*-hexyl **1k**) had significantly reduced MT_2 receptor affinity. These results indicated that MT_2 receptor affinity could be achieved with small substituents at R_6, but selectivity versus MT_1 receptor binding was optimized with a specific substitution pattern found in **1a**.

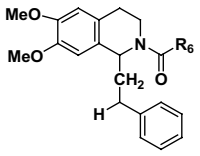
Removal of one of the side-chain phenyl rings was investigated. Using the methodology described in Scheme 1 with 3-phenylproprionaldehyde (i.e., R_1 = H and Ar = Ph in **4**), afforded compounds **1p**–**u** (Table 2). When R_6 = Me (**1p**), the removal of the phenyl group (i.e., R_1 = H) led to a decrease in MT_2 receptor affinity. For example, compound **1a** has an MT_2 affinity of 9.7 nM (Table 1), while des-phenyl analog **1p** had an IC_{50} of 76 nM (Table 2). However, when R_6 was larger (**1q**), there was an increase in MT_2 affinity. For example, *c*-Bu derivative **1j** had an IC_{50} = 310 nM (Table 1), whereas, des-phenyl analog **1q** had an IC_{50} of 24 nM (Table 2). These results suggest that the lipophilic binding pocket occupied by the second phenyl ring in **1a** is adjacent to the area where R_6 binds, and that a larger R_6 may be able to partially fill that pocket when the phenyl ring is removed.

Table 1. Melatonin receptor binding of compounds **1a**–**o**



Example	R_6	MT_2 IC_{50} (nM)	MT_1 IC_{50} (nM)	MT_1/MT_2
1a	Me	9.7	>1000	>103
1b	H	9.9	621	62
1c	Et	62	>1000	>16
1d	Pr	79	>1000	>12
1e	Ph	120	>1000	>8
1f	CF_3	100	>1000	>9
1g	NH_2	30	>1000	>33
1h	NHMe	60	>1000	>17
1i	OMe	22	673	30
1j	*c*-Bu	310	—	—
1k	*c*-Hex	370	—	—
1l	Pentyl	280	—	—
1m	*c*-Bu	240	—	—
1n	4-CF_3Ph	810	—	—
1o	Hexyl	400	—	—

Table 2. Melatonin receptor binding of compounds **1p**–**u**



Example	R_6	MT_2 IC_{50} (nM)	MT_1 IC_{50} (nM)	MT_1/MT_2
1p	Me	76	>1000	>13
1q	*c*-Bu	24	—	—
1r	*c*-Hex	220	—	—
1s	4-CF_3Ph	1000	—	—
1t	H	83	>1000	>12
1u	NH_2	160	>1000	>6

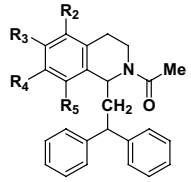
Finally, substitution on the aromatic phenyl ring of the tetrahydroisoquinoline was evaluated. This was accomplished with a variety of phenethylamines **2** in the Pictect–Spengler reaction (Scheme 1). The results of these efforts are shown in Table 3.

Proper substitution of the phenyl ring of the tetrahydroisoquinoline was necessary for potent affinity at the MT_2 receptor. The absence of substitution on the phenyl ring led to no affinity for the MT_1 and MT_2 receptor (i.e., **1w**). Substitution at R_2 was uniformly deleterious to MT_2 and MT_1 receptor affinity (i.e., **1x**,**ab**, and **1ad**). In contrast, substitution at R_4 led to potent MT_2 receptor ligands (i.e., **1a**,**z**, **1ae**). In fact, **1z** with only a single methoxy substituent at R_4 is the most potent compound encountered in this study, and it was reasonably selective versus the MT_1 receptor.

Additional substitution at R_3 had significant effects on selectivity. Addition of a second methoxy substituent at R_3 (**1a**) improved selectivity, while addition of bromine (**1ae**) diminished selectivity. This diminution of selectivity for **1ae** was a result of both increased MT_1 receptor affinity and a loss of MT_2 receptor affinity.

Compounds **1a**,**b**,**e**, and **1f** were selected for evaluation of their functional activity at the MT_2 receptor. Agonism of MT_2 receptors leads to inhibition of adenylate cyclase, leading to a decrease in intracellular cAMP. Thus, inhibition of forskolin-stimulated cAMP accumulation in NIH-3T3 cells stably expressing the MT_2 receptor was used as our functional assay.[5] Compounds **1a**, **1b**, **1e**, and **1f** demonstrated full antagonism in this assay (intrinsic activity = 0), indicating these compounds, as representatives of the series, are full MT_2 receptor antagonists.

Table 3. Melatonin receptor binding of amides **1v–ae**



Example	R_2	R_3	R_4	R_5	MT_2 IC_{50} (nM)	MT_1 IC_{50} (nM)	MT_1/MT_2
1a	H	OMe	OMe	H	9.7	>1000	>103
1w	H	H	H	H	130	>1000	>7
1x	OMe	H	H	H	>1000	>1000	—
1y	H	OMe	H	H	270	>1000	>3
1z	H	H	OMe	H	5.5	512	93
1aa	H	OMe	H	OMe	45	>1000	>22
1ab	OMe	OMe	H	H	>1000	>1000	—
1ac	H	F	H	H	140	>1000	>7
1ad	CH_2CH_2O		H	H	>1000	>1000	—
1ae	H	Br	OMe	H	24	230	9

In summary, we have identified a novel series of tetrahydroisoquinolines,[22] which are potent and selective MT_2 receptor antagonists. In particular, compound **1a** demonstrated single-digit nanomolar binding affinity, $a > 100$-fold selectivity for the MT_2 receptor versus the MT_1 receptor, and functional antagonism for the MT_2 receptor. This compound represents a useful pharmacological tool to further investigate the chronobiotic function of the MT_2 receptor. Behavioral aspects will be disclosed in further publications.

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22. Selected spectral data. Compound **1a**: ^{1}H NMR ($CDCl_3$) (approx. 1.8:1 ratio of rotomers, A:B, respectively): δ 7.32 (rotomers A and B, m, 10H), 6.62 (rotomer A, s, 1H), 6.60 (rotomer B, s, 1H), 6.53 (rotomer A, s, 1H), 6.38 (rotomer B, s 1H), 5.68 (rotomer A, m, 1H), 4.60 (rotomer B, m, 1H), 4.12 (rotomer B, t, 1H), 4.03 (rotomer A, m, 1H), 3.92 (rotomer A, s, 3H), 3.88 (rotomers A and B, s, 3H), 3.77 (rotomer B, s, 3H), 3.43 (rotomers A and B, m, 1H), 3.21 (rotomer A, m, 1H), 2.94 (rotomer A, m, 1H), 2.80 (rotomers A and B, m, 1H), 2.67 (rotomer A, m, 1H), 2.54 (rotomer A, m, 1H), 2.35 (rotomer B, m, 1H), 1.96 (rotomer B, s, 3H), 1.65 (rotomer A, s, 3H). Mass spec. 416 $(MH)^+$. Anal. Calcd for $C_{27}H_{29}NO_3$–2/3H_2O: C, 75.85; H, 7.15; N, 3.28. Found: C, 75.89; H, 7.03; N, 3.24. Compound **1b**: ^{1}H NMR ($CDCl_3$) (approx. 1.8:1 mixture of rotomers A:B, respectively): δ 8.09 (rotomer B, s, 1H), 7.89 (rotomer A, s, 1H), 7.30 (rotomers A and B, m, 10H), 6.61 (rotomer A, s, 1H), 6.55 (rotomer B, s, 1H), 6.47 (rotomer A, s, 1H), 6.30 (rotomer B, s, 1H), 5.40 (rotomer B, q, 1H), 4.52 (rotomer A, q, 1H), 4.22 (rotomer A, q,

1H), 4.16 (rotomer B, t, 1H), 4.01 (rotomer A, q, 1H), 3.89 (rotomer A, s, 3H), 3.86 (rotomer A, s, 3H), 3.83 (rotomer B, s, 3H), 3.74 (rotomer B, s, 3H), 3.48 (rotomer A, m, 1H), 2.80 (rotomers A and B, m, 4H). Mass spec. 402 $(MH)^+$. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.74, H, 6.93; N, 3.30. Compound **1c**: ^1H NMR ($CDCl_3$) (approx. 2:1 ratio of A:B rotomers, respectively): δ 7.34 (rotomers A and B, m, 10H), 6.60 (rotomers A and B, s, 1H), 6.52 (rotomer A, s, 1H), 6.30 (rotomer B, s, 1H), 5.69 (rotomer B, t, 1H), 4.64 (rotomer A, m, 1H), 4.10 (rotomer B, t, 1H), 4.01 (rotomer A, q, 1H), 3.90 (rotomer A, s, 3H), 3.87 (s, 3H), 3.71 (rotomer B, s, 2H), 3.44 (rotomer B, m, 2H), 2.80 (rotomers A and B, m, 4H), 2.33 (rotomer A, m, 2H), 2.17 (rotomer B, m, 2H), 1.80 (rotomer A, m, 4H), 1.14 (rotomer B, t, 3H), 0.91 (rotomer A, t, 3H). Mass spec. 430 $(MH)^+$. Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.12; H, 7.23; N, 3.15. Compound **1d**: ^1H NMR ($CDCl_3$) (approx. 2:1 ratio of rotomers): δ 7.32 (rotomers A and B, m, 10H), 6.58 (rotomers A and B, s, 1H), 6.51 (rotomer A, s, 1H), 6.30 (rotomer B, s, 1H), 5.67 (rotomer B, t, 1H), 4.66 (rotomer A, s, 1H), 4.15 (rotomer B, t, 1H), 4.00 (rotomer A, q, 1H), 3.90 (rotomer A, s, 3H), 3.85 (rotomers A and B, s, 3H), 3.68 (rotomer B, s, 3H), 3.43 (rotomer B, m, 2H), 2.80 (rotomers A and B, m, 4H), 2.31 (rotomer A, m, 2H), 2.15 (rotomer B, m, 2H), 1.78 (rotomer A, m, 1H), 1.18 (rotomers A and B, m, 2H), 1.05 (rotomer B, t, 3H), 0.87 (rotomer A, t, 3H). Mass spec. 442 $(MH)^+$. Anal. Calcd for $C_{29}H_{33}NO_3$–1/3H_2O: C, 77.55; H, 7.55; N, 3.12. Found: C, 77.38; H, 7.50; N, 3.19. Compound **1f**: ^1H NMR ($CDCl_3$): δ 7.30 (m, 10H), 6.59 (s, 1H), 6.29 (s, 1H), 5.50 (q, 1H), 4.07 (t, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.62 (m, 1H), 2.83 (m, 4H), 2.45 (m, 1H). Mass spec. 470 $(MH)^+$. Anal. Calcd for $C_{27}H_{26}NO_3F_3$: C, 69.07; H, 5.58; N, 2.98. Found: C, 68.90; H, 5.58; N, 2.91.