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SYNTHESIS AND RECEPTOR BINDING STUDIES OF QUINOLINIC DERIVATIVES AS MELATONIN RECEPTOR LIGANDS

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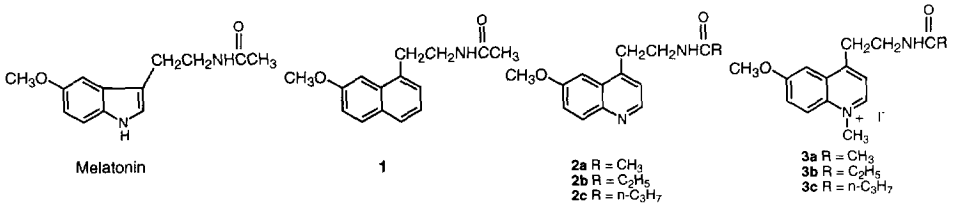
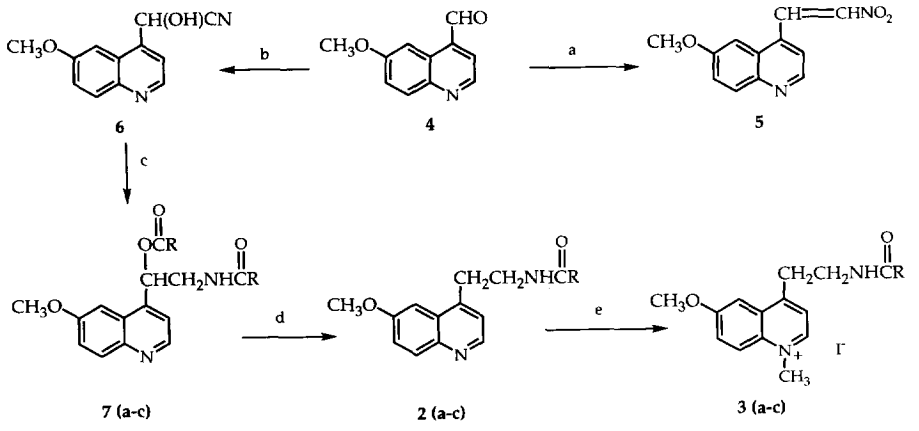
Abstract: We report the development of melatonin receptor ligands containing a quinolinic nucleus. Ligands containing a neutral moiety within the nucleus displayed high affinity for melatonin receptors while those analogs containing a permanently charged nucleus had very low affinity for melatonin receptors. © 1997 Elsevier Science Ltd.

Melatonin is a hormone that is involved in circadian rhythms, retinal physiology, seasonal breeding, cardiovascular regulation, and oncogenesis.[1-4] Even though melatonin receptors are classified as either ML_1 or ML_2 based on pharmacological profiles, molecular cloning has revealed the existence of only the ML_1 types (Mel_{1a}, Mel_{1b}, Mel_{1c}).[5-8] Since melatonin mediates its actions by binding to different receptor subtypes, development of agonists or antagonists for the melatonin receptors is important to investigate the roles of melatonin in a variety of physiological functions.

Several groups such as naphthalenic,[9] amidotetralin,[10] and amido indane[11] can serve as a bioisostere of the indole nucleus of melatonin. The naphthalenic analog **1** was reported to have the same affinity for the melatonin receptor as melatonin.[9]

We report herein the synthesis and melatonin receptor binding affinities of quinolinic bioisosteres of melatonin. The quinolinic derivatives **2 (a-c)** are structurally related to both melatonin and the naphthalenic analog **1**. Also, these quinolinic derivatives of melatonin can be converted to derivatives **3 (a-c)**, which contain permanent charges in their quinolinic nuclei. Because analogs with charged substituents cannot penetrate membrane barriers, such compounds could be used for investigating the role internalization plays in melatonin receptor regulation.





Reagents and Conditions: a. CH_3NO_2, NH_4OAc, reflux (<10 % yield); b. Acetone Cyanohydrin, K_2CO_3, CH_3OH, rt, 18 h; c. (i) $LiAlH_4$, THF, 55 °C, 18 h; (ii) Ac_2O (or C_2H_5COCl or n-C_3H_7COCl), Et_3N, DMAP, CH_2Cl_2, rt, 20 h, 20-40 % overall yield (2 steps); d. H_2, 5% Pd-C, CH_3OH, rt, 18 h, 80-85 % yield; e. CH_3I, acetone, rt, 2 days, 91-92 %.

The syntheses of **2 (a-c)** and **3 (a-c)** are shown above. 6-Methoxyquinoline-4-carboxaldehyde **4** was used as the starting material. Aldehyde **4** was obtained by selenium dioxide oxidation of 6-methoxyepidine,[12] which in turn was synthesized from *p*-anisidine and ethyl acetoacetate as first described by Rabe[13] and later modified by Elderfield and coworkers.[14] Condensation of aldehyde **4** with nitromethane in the presence of ammonium acetate[15] gave very low yield (<10%) of the desired nitroethylene derivative **5**. The low yield may be due to the polymerization of nitroalkene **5**.[16] Another method to introduce CH_2NH_2 group into compound **4** was to introduce a cyano group followed by reduction. Treatment of aldehyde **4** with acetone cyanohydrin in a methanolic solution of K_2CO_3 gave the cyanohydrin **6**. Compound **6** was then reduced with $LiAlH_4$ followed by acylation of the resulting α-hydroxyamine with acetic anhydride, propionyl chloride or butyryl chloride in the presence of 4-dimethylaminopyridine (4-DMAP), yielded the corresponding diacylated products **7 (a-c)**[17] (20-24 % overall yield). Deacyloxylation of compounds **7 (a-c)** under hydrogenation led to the target compound **2 (a-c)**[18] (80-85 % yield). Target compouds **3 (a-c)** were obtained by stirring **2 (a-c)** with iodomethane in acetone at room temperature.

The affinities of compounds **2 (a-c)** and **3 (a-b)** for melatonin receptors were evaluated in vitro and in duplicate (n = 3-5 experiments per compound) by competition binding analysis using the

radioligand 2-[^{125}I]-iodomelatonin (80-100 pM; DuPont, Boston, MA) as described previously.[19] All three quinolinic derivatives of melatonin **2 (a-c)** displayed high affinity for both the Mel_{1a} and Mel_{1b} melatonin receptors which suggests that the indole nucleus of melatonin can be substituted by a quinolinic nucleus without a loss of binding affinity (Table 1). In addition, increasing the chain length of the linear acyl substituents (from N-acetyl to N-propionyl), resulted in an increase in affinity of the analogs for the melatonin receptors. Such binding characteristics were also observed for the indole and napthalenic analogs.[10,15] Quinolinic analogs that underwent N-methylation **3 (a-c)**, had a substantial decrease in binding affinity to melatonin receptors (i.e, >1 μM affinity) which could be due to either steric and/or electronic effects. Electronic effects appear to be more significant than steric effects because N-methylation of quinolinic analogs, which converts the quinolinic nucleus from a neutral to a permanently charged molecule, resulted in binding affinities that were profoundly less (i.e., >10,000-fold less) than melatonin's affinity for the receptors (Table 1). In contrast, N-methylation of melatonin, which does not change the neutrality of the indole nucleus, produced only mild decreases (i.e., 500-fold less) than melatonin's affinity for the melatonin receptor.[20] In conclusion, these studies are the first to report the development of quinolinic bioisosteres of melatonin with variations on the N-acylamino group, including analogs with permanent charges, which could be used in future studies to investigate whether or not internalization of melatonin receptors occurs in vitro.

Table 1. Competition of Melatonin and Quinolinic Analogs for 2-[^{125}I]-iodomelatonin Binding to Human Mel_{1a} or Mel_{1b} Melatonin Receptors Stably Expressed in CHO Cells

	Receptor Binding, (K_i) nM (range of SEM)	
Compound #	Mel_{1a}	Mel_{1b}
2a	5.9 (3.6-9.5)	1.4 (1.2-1.6)
2b	6.9 (3.8-13)	0.96 (0.86-1.1)
2c	2.2 (1.2-4.1)	0.41 (0.30-0.55)
3a	>1,000	>1,000
3b	>1,000	>1,000
Melatonin	0.13 (0.09-0.18)	0.23 (0.14-0.37)

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References and Notes

1. Morgan, P. J.; Barrett, P.; Howell, H. E.; Helliwell, R. *Neurochem. Int.* **1994**, *24*, 101.

2. Dubocovich, M. L. *Trends Pharmacol. Sci.* **1995**, *16*, 50.

3. Krause, D. N.; Barrios, V. E.; Duckles, S. P. *Eur. J. Pharmacol.* **1995**, *276*, 207.

4. Brzezinski, A. *N. Engl. J. Med.* **1997**, *336*, 186.

5. Reppert, S. M.; Weaver, D. R.; Ebisawa, T. *Neuron* **1994**, *13*, 1177.

6. Reppert, S. M.; Godson, C.; Mahle, C. D.; Weaver, D. R.; Slaugenhaupt, S. A.; Gusella, J. F. *Natl. Acad. Sci.* **1995**, *92*, 8734.

7. Slaugenhaupt, S.; Roca, A. L.; Liebert, C. B.; Altherr, M. R.; Gusella, J. F.; Reppert, S. M. *Genomics* **1995**, *27*, 355.

8. Reppert, S. M.; Weaver, D. R.; Godson, C. *TIPS* **1996**, *17*, 100.

9. Yous, S.; Andrieux, J.; Howell, H. E.; Morgan, P. J.; Renard, P.; Pfeiffer, B.; Lesieur, D.; Guardiola-Lemaitre, B. *J. Med. Chem.* **1992**, *35*, 1484.

10. Copinga, S.; Tepper, P. G.; Grol, C. J.; Horn, A. S.; Dubocovich, M. L. *J. Med. Chem.* **1993**, *36*, 2891.

11. Jansen, J. M.; Copinga, S.; Gruppen, G.; Molinar, E. J.; Dubocovich, M. L.; Grol, C. J. *Bioorg. Med. Chem.* **1996**, *4*, 1321.

12. Kwartler, C. E.; Lindwall, H. G. *J. Amer. Chem. Soc.* **1937**, *59*, 524.

13. Rabe, P.; Huntenburg, W.; Schultze, A.; Volger, G. *Ber.* **1931**, *64*, 2487.

14. Campbell, K. N.; Tipson, R. S.; Elderfield, R. C.; Campbell, B. K.; Clapp, M. A.; Gensler, W. J.; Morrison, D.; Moran, W. J. *J. Org. Chem.* **1946**, *11*, 803.

15. Langlois, M.; Bremont, B.; Shen, S.; Poncet, A.; Andrieux, J.; Sicsic, S.; Serraz, I.; Mathe-Allainmat, M.; Renard, P.; Delagrange, P. *J. Med. Chem.* **1995**, *38*, 2050.

16. Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425.

17. Selected ^{1}H NMR data for **7b**: mp: 176-178 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.0 (t, 3H, J = 7.5 Hz, CH_3), 1.09 (t, 3H, J = 7.5 Hz, CH_3), 2.10 (q, 2H, J = 7.5 Hz, CH_2CO), 2.51 (q, 2H, J = 7.5 Hz, CH_2CO), 3.22 (m, 1H, Ha of CH_2N), 3.75 (m, 1H, Hb of CH_2N), 4.01 (s, 3H, OCH_3), 6.47 (d of d, 1H, ArCH-), 7.45 (m, 2H, ArH), 7.81 (d, 1H, J = 2.7 Hz, ArH), 7.97 (d, 1H, J = 9.0 Hz, ArH), 8.30 (t, 1H, J = 5.7 Hz, NH), 8.72 (d, 1H, J = 4.5 Hz, ArH).

18. Selected ^{1}H NMR data for **2b**: mp: 98-100 °C;

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.11 (t, 3H, J = 7.5 Hz, CH_3), 2.16 (q, 2H, J = 7.5 Hz, CH_2CO), 3.23 (t, 2H, J = 7.2 Hz, $ArCH_2$), 3.61 (m, 2H, CH_2N), 3.96 (s, 3H, OCH_3), 5.76 (brS, 1H, NH), 7.14 (d, 1H, J = 4.5 Hz, ArH), 7.34 (d of d, 1H, J = 2.7, 9.0 Hz, ArH), 7.40 (d, 1H, J = 2.7 Hz, ArH), 7.96 (d, 1H, J = 9.0 Hz, ArH), 8.59 (d, 1H, J = 4.5 Hz, ArH).

19. Witt-Enderby, P. A.; Dubocovich, M. L. *Mol. Pharmacol.* **1996**, *50*, 166.

20. Garrett, P.; Vonhoff, S.; Rowe, S. J.; Sugden, D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1559.

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