Novel Conformationally Restrained Melatononergic Compounds: Synthesis and Biological Activity

A.Tsotinis[1], M. Panoussopoulou[1], P. J. Garratt[2], R. Jones[2], L-K. Yeh[2]
T. Calogeropoulou[3], D. Sugden[4]

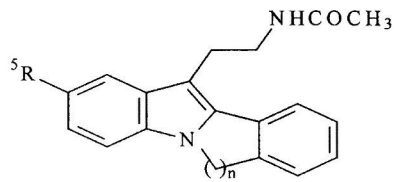
[1]*School of Pharmacy, Division of Pharmaceutical Chemistry, University of Athens, Panepistimiopoli-Zografou, Athens 157 71, Greece.*

[2]*Department of Chemistry, University College London 20 Gordon Street, London WC1H 0AJ, United Kingdom.*

[3]*Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 48 Vas. Constantinou Ave., Athens 116 35, Greece.*

[4]*Physiology Group, Biomedical Sciences Division, King's College London Campden Hill Road, London W8 7AH, United Kingdom.*

Melatonin (*N*-acetyl-5-methoxytryptamine), is the principal hormone of the pineal gland, and is produced mainly at night [1]. Melatonin plays a major role in the control of circadian rhythms and the regulation of seasonal cycles[1]. These effects are achieved through the binding of the hormone to its high affinity G-protein coupled Mel_1 receptor. Analogs of melatonin may be useful in restoring disorganized circadian rhythms following jet-lag, shift-work, boosting the immune system and preventing cancer [2]. In this project, a series of novel *N*-acetyl 2-phenyltryptamine-derived analogs have been synthesized with a 2-phenyl ring attached to the indole nitrogen by a carbon chain of 1, 2 or 3 methylene groups (Fig. 1). The binding affinities of these analogs at the Mel_{1a} and Mel_{1b} receptor subtypes as well as their biological activity on *Xenopus laevis* melanophores were examined in pharmacological assays, revealing information about the stereoelectronic requirements of the Mel_1 receptor and its subtypes[3].



2, n = 1, ^{5}R = H
3, n = 1, ^{5}R = OMe
4, n = 2, ^{5}R = H
5, n = 2, ^{5}R = OMe
6, n = 3, ^{5}R = H
7, n = 3, ^{5}R = OMe

Figure 1

References

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[2] Mahle, C.D. et al, *Ann. Rev. Med. Chem.* **1997**, 32, 31.
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