Department of Pharmaceutical Chemistry[1], Department of Biochemistry[2], Faculty of Pharmacy (ECZACILIK), University of Ankara, Turkey

Synthesis and antioxidant properties of some indole ethylamine derivatives as melatonin analogs

Z. Ates-Alagoz[1], Z. Buyukbingol[2], E. Buyukbingol[1]

Received August 3, 2004, accepted October 28, 2004

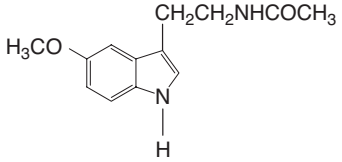
Erdem Buyukbingol, PhD, Department of Pharmaceutical Chemistry, Faculty of Pharmacy (ECZACILIK), University of Ankara, Tandogan 06100, Ankara, Turkey
erdem@pharmacy.ankara.edu.tr

Pharmazie 60: 643–647 (2005)

The synthesis and lipid peroxidation (LP) inhibition activity of several novel indole melatonin analogues are reported. Compounds have shown variable antioxidant features depending on the substitution pattern. Melatonin and the antioxidant reference compound butyl hydroxy toluen (BHT) were used to compare the antioxidant capability of the compounds synthesized.

1. Introduction

Melatonin (*N*-acetyl 5-methoxytryptamine), a neurohormone, first isolated in 1958 from bovine pineal tissue, has a central role in the regulation of daily rhythms and seasonal cycles in vertebrates (Lerner et al. 1958). Its potential therapeutic use in diseases related to the desynchronization of biological rhythms, such as jet-lag, disturbed sleep-wake cycles (Arendt et al. 1984), seasonal disorders and depression (Guardiola-Lemaitre 1991) are known. Melatonin may also play a role in the cardiovascular system (Seltzer et al. 1992). This is supported by recent findings which show that 2-[^{125}I] iodomelatonin-binding sites are localized in both the caudal and cerebral arteries of the rat. In addition, melatonin binding has been reported at many other sites including the retina (probably related to resynchronization role) and peripheral tissues such as the spleen (related to a role immune system), gastrointestinal tract, blood platelets and the harderian gland (Depreux et al. 1994). Furthermore antioxidant properties of melatonin have recently been proposed (Poeggler et al. 1993). Although the effects of melatonin in oncogenesis are unclear; the majority of studies conclude that the hormone has a protective role in the modulation of cancer or cancerous cells (Jones et al. 2000; Li and Witt-Enderby 2000). Melatonin may also play a role in brain function (Avery et al. 1998) but the mechanisms underlying such functions are not known (Witt-Enderby and Li 2000).



Melatonin

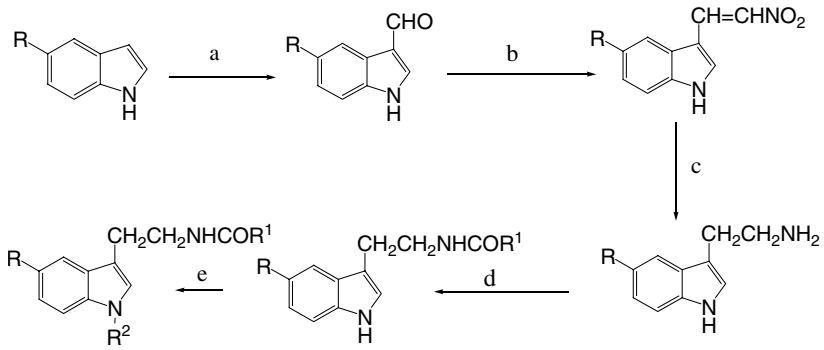
Despite its potential involvement in the regulation of many physiological processes, two problems limit its therapeutic use at present. The first is its very short biological half-life (15–30 min), due to its rapid metabolism to 6-hydroxymelatonin and *N*-acetylkynurenamines, and the second is the lack of selectivity of melatonin at target sites (Depreux et al. 1994). It is thought that the development of novel analogues may provide a strategic approach to overcome both of these limitations. Therefore, the aim of our work was the synthesis of new indole derivatives related to melatonin and the investigation of the synthesized compounds for their antioxidant capacity.

2. Investigations, results and discussion

2.1. Synthesis of the compounds

The synthesis of the compounds was carried out as shown in the Scheme. The indole-3-aldehyde was obtained by direct formylation of indole with dimethylformamide, using phosphorous oxychloride as a catalyst (Buyukbingol et al. 1994; James and Synder 1930; Shabica et al. 1946). 5-Methoxy-indole-3-carboxaldehyde was refluxed in nitromethane and ammonium acetate to produce 5-methoxy-3-(2-nitroethenyl)-1*H*-indoles in 52% yield (Spadoni et al. 1997) followed by synthesizing 3-indole-ethylamine achieved by $LiAlH_4$ as described Faust et al. (2000). The crude oil amine was then used for acylation with Ac_2O or propionic anhydride without purification (Mor et al. 1998). Melatonin and melatonin analogs were substitued by alkyl halides in the position-1 as described by Mor et al. (1998).
The structural and pharmacological data for the synthesized compounds shown in Table 1.
In this study, 18 novel and 5 previously reported (**1a**, **1b**, **2a**, **2c**, and **2e**) melatonin derivatives were synthesized and investigated on the inhibition of NADPH-bounded lipid peroxidation activity on rat liver microsomal mixed-

Scheme



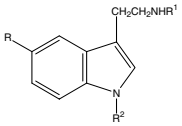
a) $POCl_3$, DMF b) CH_3NO_2, $AcONH_4$ c) $LiAlH_4$ d) Ac_2O or $(EtCO)_2O$ e) R^2X, DMF, NaH

function oxidase system. The compounds were considered in two series in where the 5th position has been remained intact (non-substituted) (compounds **1a**–**l**) and substituted with methoxy (compounds **2a**–**k**).

2.2. Pharmacological studies

It was found that compounds **1c**–**f**, and **1k** (first series), **2g** and **2i** (second series) show significant lipid peroxidation (LP) inhibitory activity when compared with melatonin. When the first position was substituted with ethyl or propyl groups the LP inhibitory activity was found to be changeable due to the substitution pattern at the 5-position of the indole ring. The alkyl substitution at the 1-position of the indole ring showed no inhibitory activity when the 5-position was reserved with methoxy group. The exception is compound **2g** which has an ethyl inclusion instead of methyl at the chain terminal of 3-position. However, the compounds having similar alkyl substitution, possess a remarkable higher activity pattern while the methoxy group was removed (compounds **1c, 1d** and **1e** with LP inhibition of 50%, 48%, and 51%, respectively). This might be a special effect of the substitution feature at the 5-position whereas the electron-donor groups might be involved in the interaction with those located at the 1-position. The manner of the substitution at 1-position might become significance in relation to the cross-over effect obtained from the 5-substitution, while alkyl groups at 1-position migh initiate the contrary collision of the electron density which might decrease the overall effect of the compounds at the target site. However, more clues are needed to prove this approach with several substitution patterns at both positions.

Table 1: Structural and pharmacological data for indole derivatives



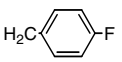
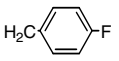
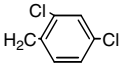
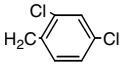
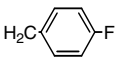
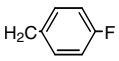
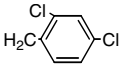
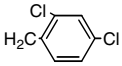
Compd.	R	R^1	R^2	LP inh. (%)	Compd.	R	R^1	R^2	LP inh. (%)
1a	H	CH_3	H	30	**2a**	OCH_3	C_2H_5	H	2
1b	H	C_2H_5	H	4	**2b**	OCH_3	CH_3	C_2H_5	5
1c	H	CH_3	C_2H_5	50	**2c**	OCH_3	CH_3	n-C_3H_7	20
1d	H	CH_3	n-C_3H_7	48	**2d**	OCH_3	CH_3	i-C_3H_7	33
1e	H	CH_3	i-C_3H_7	51	**2e**	OCH_3	CH_3		30
1f	H	CH_3		51	**2f**	OCH_3	CH_3		9
1g	H	CH_3		32	**2g**	OCH_3	C_2H_5	C_2H_5	60
1h	H	C_2H_5	C_2H_5	40	**2h**	OCH_3	C_2H_5	n-C_3H_7	33
1i	H	C_2H_5	n-C_3H_7	4	**2i**	OCH_3	C_2H_5	i-C_3H_7	71
1j	H	C_2H_5	i-C_3H_7	34	**2j**	OCH_3	C_2H_5		42
1k	H	C_2H_5		53	**2k**	OCH_3	C_2H_5		37
1l	H	C_2H_5		35	BHT: 64% LP inhibition Melatonin: 54% LP inhibition				

Table 2: Structural and physical data for indole derivatives

Compd.	M.P (°C)	Yield (%)	^{1}H NMR	MASS (m/z)	IR (cm^{-1})
1a	75	39	1.84 (s, 3 H, CO−C*H*$_3$), 2.90 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.52 (q, 2 H, C*H*$_2$−NH, J = 6.7), 5.33 (s, 3 H, O−C*H*$_3$), 7.52–8.32 (m, 6 H, Ar−H)	203 (M + 1), 202 (M^+), 143 (M−NH−COCH$_3$ + 1), 117 (indole ring)	Amid I, 1633 Amid II, 1564
1b	84	37	1.04 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 2.07 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.90 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.53 (q, 2 H, C*H*$_2$NH, J = 6.7), 5.36 (s, H, N*H*−CO), 6.94–8.16 (m, 6 H, Ar−H)	217 (M + 1), 216 (M^+), 158 (M−COCH$_2$CH$_3$ + 1), 143 (158-NH), 117 (indole ring)	Amid I, 1637 Amid II, 1563
1c	87	51	1.38 (t, 3 H, CH$_2$C*H*$_3$, J = 7.3), 1.85 (s, 3 H, CO−C*H*$_3$), 2.90 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.52 (q, 2 H, C*H*$_2$−NH, J = 6.7), 4.07 (q, 2 H, N−C*H*$_2$, J = 7.3), 5.72 (s, H, N*H*−CO), 6.89–7.52 (m, 5 H, Ar−H)	231 (M + 1), 230 (M^+), 172 (M−NHCOCH$_3$), 142 (171-CH$_2$CH$_3$), 127 (142-CH$_3$)	Amid I, 1638 Amid II, 1567
1d	79	82	0.95 (t, 3 H, CH$_2$C*H*$_3$, J = 7.4), 1.90 (m, 2 H, C*H*$_2$CH$_3$), 1.94 (s, 3 H, CO−C*H*$_3$), 2.98 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.60 (q, 2 H, C*H*$_2$−NH, J = 6.7), 4.07 (t, 2 H, N−C*H*$_2$, J = 7.1), 5.60 (s, H, N*H*−CO), 6.96–7.61 (m, 5 H, Ar−H)	244 (M^+), 186 (M−NHCOCH$_3$), 171 (186-CH$_3$), 156 (171-CH$_3$), 155 (184-CH$_2$CH$_3$), 141 (184-CH$_2$CH$_2$CH$_3$)	Amid I, 1638 Amid II, 1557
1e	106	33	1.44 (d, 6 H, CH(C*H*$_3$)$_2$, J = 6.7), 1.86 (s, 3 H, CO−C*H*$_3$), 2.90 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.8), 3.51 (q, 2 H, C*H*$_2$−NH, J = 6.7), 4.68 (m, H, N−C*H*), 5.52 (s, H, N*H*−CO), 6.99–7.52 (m, 5 H, Ar−H)	245 (M + 1), 244 (M^+), 185 (M−NHCOCH$_3$ + 1), 170 (185-CH$_3$), 156 (170-CH$_2$), 143 (156-CH), 129 (143-CH$_3$)	Amid I, 1640 Amid II, 1561
1f	104	20	1.84 (s, 3 H, CO−C*H*$_3$), 2.90 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.52 (q, 2 H, C*H*$_2$−NH), 5.17 (s, 2 H, N−C*H*$_2$), 5.51 (s, H, N*H*−CO), 6.87–7.55 (m, 9 H, Ar−H).	310 (M^+), 251 (M−NHCOCH$_3$ + 1), 223 (251-CH$_2$−CH$_2$), 109 (p-flouro-benzyl ring)	Amid I, 1637 Amid II, 1558
1g	96	37	1.85 (s, 3 H, CO−C*H*$_3$), 2.92 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.8), 3.53 (q, 2 H, C*H*$_2$−NH, J = 6.7), 5.25 (s, 2 H, 1.85 (s, 3 H, CO, N−C*H*$_2$), 5.70 (s, H, N*H*−CO), 6.49–7.57 (m, 8 H, Ar−H)	360.5 (M^+), 303 (M−NHCOCH$_3$), 288 (303-CH$_3$), 264 (288-CH$_2$), 252 (264-CH$_2$), 159 (o,p-dichloro-benzyl ring)	Amid I, 1639 Amid II, 1561
1h	69	53	1.47 (t, 3 H, CH$_2$C*H*$_3$, J = 7.6), 1.13 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.3), 2.16 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.99 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.61 (q, 2 H, C*H*$_2$NH, J = 6.7), 4.16 (q, 2 H, N−C*H*$_2$, J = 7.3) 5.29 (s, H, N*H*−CO), 6.97–7.62 (m, 5 H, Ar−H)	245 (M + 1), 244 (M^+), 171 (M−NHCOCH$_2$CH$_3$ + 1), 158 (172-CH$_2$), 144 (158-CH$_2$), 142 (171-CH$_2$CH$_3$), 130 (144-CH$_2$)	Amid I, 1632 Amid II, 1544
1i	48	64	0.95 (t, 3 H, CH$_2$C*H*$_3$, J = 7.4), 1.13, (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 1.87 (m, 2 H, C*H*$_2$CH$_3$), 2.16 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.99 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.61 (q, 2 H, C*H*$_2$NH, J = 6.7), 4.07 (t, 2 H, N−C*H*$_2$, J = 7.1) 5.57 (s, H, N*H*−CO), 6.96–7.62 (m, 5 H, Ar−H)	258 (M^+), 185 (M−NHCOCH$_2$CH$_3$ + 1), 156 (185-CH$_2$CH$_3$), 130 (158-CH$_2$CH$_2$), 141 (156-CH$_3$)	Amid I, 1633 Amid II, 1561
1j	84	35	1.13 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 1.53 (d, 6 H, CHC*(H*$_3$)$_2$, J = 6.7), 2.16 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.99 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.61 (q, 2 H, C*H*$_2$NH, J = 6.6), 4.67 (m, 1 H, N−C*H*), 5.53 (s, H, N*H*−CO), 7.02–7.62 (m, 5 H, Ar−H)	259 (M + 1), 258 (M^+), 185 (M−NHCOCH$_2$CH$_3$ + 1), 156 (185-CH$_2$CH$_3$), 130 (158-CH$_2$CH$_2$)	Amid I, 1636 Amid II, 1561
1k	82	33	1.11 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 2.15 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.98 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.61 (q, 2 H, C*H*$_2$NH, J = 6.7), 5.26 (s, 2 H, N−C*H*$_2$), 5.54 (s, H, N*H*−CO), 6.96–7.65 (m, 9 H, Ar−H)	325 (M + 1), 324 (M^+), 252 (M−NHCOCH$_2$CH$_3$), 238 (252-CH$_2$), 127 (142-CH$_3$), 109 (p-flouro-benzyl ring)	Amid I, 1637 Amid II, 1556
1l	102	57	1.12 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 2.15 (q, 2 H, CO−C*H*$_2$, J = 7.6), 3.01 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.62 (q, 2 H, C*H*$_2$NH, J = 6.7), 5.34 (s, 2 H, N−C*H*$_2$), 5.58 (s, H, N*H*−CO), 6.55–7.67 (m, 8 H, Ar−H)	374.5 (M^+), 301 (M−NHCOCH$_2$CH$_3$ + 1), 288 (303-CH$_3$), 266 (251-CH$_3$), 266 (252-CH$_2$), 158.9 (o,p-dichloro-benzyl ring)	Amid I, 1642 Amid II, 1546
2a	91	31	1.04 (t, 3 H, CO−CH$_2$C*H*$_3$, J = 7.6), 2.07 (q, 2 H, CO−C*H*$_2$, J = 7.6), 2.87 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.6), 3.52 (q, 2 H, C*H*$_2$NH, J = 6.6), 3.78 (s, 3 H, O−C*H*$_3$), 5.55 (s, H, N*H*−CO), 6.78–8.13 (m, 5 H, Ar−H)	247 (M + 1), 246 (M^+), 189 (M−COCH$_2$CH$_3$), 173 (189-NH), 158 (173-CH$_3$), 130 (158-CH$_2$CH$_3$), 117 (indole ring)	Amid I, 1625 Amid II, 1551
2b	84	52	1.45 (t, 3 H, CH$_2$C*H*$_3$, J = 7.3), 1.95 (s, 3 H, CO−C*H*$_3$), 2.95 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.60 (q, 2 H, C*H*$_2$−NH, J = 6.7), 3.88 (s, 3 H, O−C*H*$_3$), 4.12 (q, 2 H, N−C*H*$_2$, J = 7.3), 5.36 (s, H, N*H*−CO), 6.91–7.25 (m, 4 H, Ar−H)	260 (M^+), 202 (M−NHCOCH$_3$), 174 (202-CH$_2$CH$_2$), 173 (202-CH$_2$CH$_3$), 159 (174-CH$_3$), 130 (159-CH$_2$CH$_3$), 116 (130-CH$_2$), 116 (indole ring)	Amid I, 1631 Amid II, 1577
2c	58	62	0.93 (t, 3 H, CH$_2$C*H*$_3$, J = 7.4), 1.85 (m, 2 H, C*H*$_2$CH$_3$), 1.95 (s, 3 H, CO−C*H*$_3$), 2.94 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.6), 3.60 (q, 2 H, C*H*$_2$−NH, J = 6.6), 3.88 (s, 3 H, O−C*H*$_3$), 4.03 (t, 2 H, N−C*H*$_2$, J = 7), 5.43 (s, H, N*H*−CO), 6.9–7.24 (m, 4 H, Ar−H)	274 (M^+), 216 (M−NHCOCH$_3$), 201 (216-CH$_3$), 185 (214-CH$_2$CH$_3$), 185 (216-OCH$_3$), 144 (158-CH$_2$), 130 (158-CH$_2$CH$_2$), 117 (indole ring)	Amid I, 1632 Amid II, 1577
2d	92	25	1.51 (d, 6 H, CH(C*H*$_3$)$_2$, J = 6.7), 1.95 (s, 3 H, CO−C*H*$_3$), 2.95 (t, 2 H, C*H*$_2$CH$_2$NH, J = 6.7), 3.60 (q, 2 H, C*H*$_2$−NH, J = 6.7), 3.88 (s, 3 H, O−C*H*$_3$), 4.60 (m, 1 H, N−C*H*), 5.76 (s, H, N*H*−CO), 6.90–7.27 (m, 4 H, Ar−H)	274 (M^+), 231 (M−COCH$_3$), 216 (231-NH), 200 (231-OCH$_3$), 172 (200-CH$_2$CH$_2$), 145 (160-CH$_3$), 130 (145-CH$_3$), 117 (indole ring)	Amid I, 1639 Amid II, 1577

Table 2: (Continued)

Compd.	M.P (°C)	Yield (%)	^{1}H NMR	MASS (m/z)	IR (cm^{-1})
2e	121	50	1.94 (s, 3 H, CO−CH_3), 2.95 (t, 2 H, CH_2CH$_2$NH, J = 6.8), 3.60 (q, 2 H, CH_2−NH, J = 6.8), 3.87 (s, 3 H, O−CH_3), 5.22 (s, 2 H, N−CH_2), 5.72 (s, H, NH−CO), 6.88–7.28 (m, 8 H, Ar−H)	340 (M^+), 281 (M−NHCOCH$_3$ + 1), 266 (281-CH$_3$), 144 (158-CH$_2$), 115 (144-CH$_2$CH$_3$), 108.93 (p-flouro-benzyl ring)	Amid I, 1637 Amid II, 1562
2f	149	59	1.95 (s, 3 H, CO−CH_3), 2.97 (t, 2 H, CH_2CH$_2$NH, J = 6.7), 3.60 (q, 2 H, CH_2−NH, J = 6.6), 3.88 (s, 3 H, O−CH_3), 5.31 (s, 2 H, N−CH_2), 5.76 (s, H, NH−CO), 6.54–7.45 (m, 7 H, Ar−H)	393 (M + 2), 392 (M + 1), 391 (M^+), 334 (M−NHCOCH$_3$), 318 (333-CH$_3$), 282 (296-CH$_2$), 159 (o,p-dichloro-benzyl ring)	Amid I, 1640 Amid II, 1563
2g	77	60	1.45 (t, 3 H, CH$_2$CH_3, J = 7.6), 1.13 (t, 3 H, CO−CH$_2$CH_3, J = 7.4), 2.17 (q, 2 H, CO−CH_2, J = 7.6), 2.95 (t, 2 H, CH_2CH$_2$NH, J = 6.7), 3.60 (q, 2 H, CH_2NH, J = 6.6), 3.88 (s, 3 H, O−CH_3), 4.12 (q, 2 H, N−CH_2, J = 7.3) 5.39 (s, H, NH−CO), 6.92–7.26 (m, 4 H, Ar−H)	275 (M + 1), 274 (M^+), 217 (M−COCH$_2$CH$_3$), 202 (217-NH), 173 (201-CH$_2$CH$_2$), 144 (173-CH$_2$CH$_3$), 116 (indole ring)	Amid I, 1632 Amid II, 1575
2h	65	61	0.93 (t, 3 H, CH$_2$CH_3, J = 7.4), 1.13 (t, 3 H, CO−CH$_2$CH_3, J = 7.6), 1.85 (m, 2 H, CH_2CH$_3$), 2.16 (q, 2 H, CO−CH_2, J = 7.6), 2.94 (t, 2 H, CH_2CH$_2$NH, J = 6.7), 3.60 (q, 2 H, CH_2NH, J = 6.7), 3.88 (s, 3 H, O−CH_3), 4.02 (t, 2 H, N−CH_2, J = 7) 5.39 (s, H, CO−NH), 6.9–7.23 (m, 4 H, Ar−H)	288 (M^+), 216 (M−NHCOCH$_2$CH$_3$), 185 (216-OCH$_3$), 173 (216-C$_3$H$_7$), 173 (201-CH$_2$CH$_2$)	Amid I, 1644 Amid II, 1560
2i	75	34	1.14 (t, 3 H, CO−CH$_2$CH_3, J = 7.6), 1.51 (d, 6 H, CH(CH_3)$_2$, J = 6.7), 2.17 (q, 2 H, CO−CH_2, J = 7.6), 2.95 (t, 2 H, CH_2CH$_2$NH, J = 6.7), 3.60 (q, 2 H, CH_2NH, J = 6.7), 3.88 (s, 3 H, O−CH_3), 4.60 (m, H, N−CH), 5.71 (s, H, NH−CO), 6.9–7.27 (m, 4 H, Ar−H)	289 (M + 1), 288 (M^+), 215 (M−NHCOCH$_2$CH$_3$ + 1), 187 (215-CH$_2$CH$_2$), 173 (216-C$_3$H$_7$), 117 (indole ring)	Amid I, 1634 Amid II, 1576
2j	112	58	1.13 (t, 3 H, CO−CH$_2$CH_3, J = 7.6), 2.15 (q, 2 H, CO−CH_2, J = 7.6), 2.95 (t, 2 H, CH_2CH$_2$NH, J = 6.8), 3.60 (q, 2 H, CH_2NH, J = 6.7), 3.87 (s, 3 H, O−CH_3), 5.21 (s, 2 H, N−CH_2), 5.21 (s, H, NH−CO), 6.85–7.28 (m, 8 H, Ar−H)	355 (M + 1), 354 (M^+), 281 (M−NHCOCH$_2$CH$_3$ + 1), 116 (144-CH$_2$CH$_2$), 173 (216-C$_3$H$_7$), 116 (indole ring), 108.96 (p-flouro-benzyl ring)	Amid I, 1642 Amid II, 1552
2k	114	52	1.12 (t, 3 H, CO−CH$_2$CH_3, J = 7.6), 2.16 (q, 2 H, CO−CH_2, J = 7.6), 2.97 (t, 2 H, CH_2CH$_2$NH, J = 6.8), 3.61 (q, 2 H, CH_2NH, J = 6.7), 3.88 (s, 3 H, O−CH_3), 5.30 (s, 2 H, N−CH_2), 5.72 (s, H, NH−CO), 6.53–7.44 (m, 7 H, Ar−H)	404.78 (M^+), 331 (M−NHCOCH$_2$CH$_3$ + 1), 267 (295-CH$_2$CH$_2$), 173 (204-OCH$_3$), 116 (indole ring), 159 (o,p-dichoro-benzyl ring)	Amid I, 1643 Amid II, 1544

The benzyl substitutions for both series showed also controversial results regarding LP inhibitory activity. The *p*-fluoro benzyl derivatives in both groups showed slightly good activity behavior (**1f**, **1k**, and **2j**, 51%, 53%, and 42%, respectively) whereas the *o*,*p*-chloro benzyl derivatives failed to express activity (compounds **1g**, 32%, **1l**, 35%, **2f**, 9%, and **2k**, 37%, respectively). We found it very difficult to explain the influence of the alkyl substitution pattern in this case. However, the higher activity of *p*-fluoro compounds in both series indicated the obvious influence of the fluoro group which cannot be explained in the same way as found in di-chloro derivatives, i.e. electron releasing/withdrawal effects. A similar activity pattern can also be seen with the compounds having an ethyl group in the side chain (**1k**, **1l**, **2j**, and **2k**). The removal of the methoxy group in the 5-position of the indole ring seemed to exert not much influence on the overall inhibitory activity.

3. Experimental

3.1. Apparatus

Melting points were determined with a Büchi SMP-20 and Büchi 9100 apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with a Bruker DPX-400 (400 MHz) spectrophotometer, in $CDCl_3$ unless otherwise stated, δ scale (ppm) from internal standard TMS, coupling constants (J) were reported in Hertz. The IR spectra were recorded on a Jasco FT/IR-420 spectrophotometer as potassium bromide pellets. The Mass spectra (İN El mode at 70 eV) were recorded with a Nicromass UK. Platform II LC-Ms. The spectral analyses are given in Table 2.

3.2. Synthesis of tryptamine derivatives

The suitable 3-(2-nitroethenyl)-1*H*-indole (10.66 mmol) in tetrahydrofuran (15 mL) was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (0.25 g, 6.59 mmol) in THF (6 mL). After completion of addition, the mixture was refluxed overnight and then allowed to reach ambient temperature. After cooling to 0 °C, water (17 mL) was added. The mixture was filtered and the filtrate was taken up in ethyl acetate (50 mL), washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give an oily crude amine which was then used without further purification (Faust et al. 2000).

3.3. Acylation of tryptamine derivatives

Triethylamine (TEA) (1.1 equiv), Ac_2O or propionic anhydride (1.1 equiv) were added to a cold solution of the suitable primary tryptamine (1 mmol) in THF (5 mL), and the resulting reaction mixture was left under stirring at room temperature for 6 h. The solvent was evaporated under reduced pressure and the residue was taken up in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$ and then with brine. After drying over Na_2SO_4, the solvent was evaporated under reduced pressure to give a crude product, which was purified by column chromatography (Mor et al. 1998).

3.4. Synthesis of 1-alkyl substituted melatonin analogs

A solution of melatonin or melatonin analogs (1 mmol) in dry DMF (5 mL) was added dropwise to a stirred ice-cooled suspension of sodium hydride (0.042 g of a 80% dispersion in mineral oil, 1.4 mmol) in dry DMF (5 mL) under a N_2 atmosphere. After the addition, the mixture was stirred at 0 °C for 30 min, and then alkyl halide (1.3 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 16 h and then poured into ice-water (25 g) and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give a residue which was purified by column chromatography (Mor et al. 1998).

3.5. In vitro lipid peroxidation inhibition

Reagents for biochemical assays were purchased from Sigma (Chemical Company, Saint Louis, Missouri, A.B.D.) and BDH (BDH Chemicals, Ltd., Poole, England) and were of analytical grade. White male rats weighing 200–225 g were used for the pharmacological studies.

For *in vitro* lipid peroxidation inhibition, heat inactivated hepatic microsomal fractions from untreated male white rats, corresponding to 0.1 g liver/ml was used. Lipid peroxidation was induced by the Fe^{2+} system. The tested compounds were dissolved in dimethyl sulphoxide (DMSO) and added to the incubation mixture 10^{-4} M concentrations. All compounds and dimethyl sulfoxide (DMSO) were tested and found not to interfere with the assay. Butyl hydroxy toluen (BHT) and melatonin were used as reference compounds (Bishayee and Balasubramanian 1971; Iscan et al. 1984; Lowry et al. 1951; Wills 1966; Wills 1969).

Acknowledgement: This work is supported by Ankara University Research Fund (2001-08-03-029)

References

Arendt J, Boberly AA, Franey C, Wright J (1984) The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man. Neurosci Lett 45: 317.

Avery D, Lenz M, Landis C (1998) Guidelines for prescribing melatonin. Ann Med 30: 122.

Bishayee S, Balasubramanian AS (1971) Lipid peroxide formation in rat brain. J Neurochem 18: 909–920.

Buyukbingol E, Suzen S, Klopman G (1994) Studies on the synthesis and structure-activity relationships of 5-(3′-indolal)-2-thio-hydantoin derivatives as aldose reductase enzyme inhibitors. Farmaco 49: 443–447.

Depreux P, Lesieur D, Mansour HA, Morgan P, Howell HE, Renard P, Caignard D-H, Pfeiffer B, Delagrange P, Guardiola B, Yous S, Demarque A, Adam G, Andrieux J (1994) Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands. J Med Chem 37: 3231–3239.

Faust R, Garratt P, Jones R, Yeh Li-K (2000) Mapping the melatonin receptor. 6. Melatonin agonist and antagonists derived from 6*H*-isoindolo[2,1-*a*]indoles, 5,6-dihydroindolo[2,1-*a*]isoquinolines and 6,7-dihydro-5*H*-benzo[*c*]azepino [2,1-*a*]indoles. J Med Chem 43: 1050–1061.

Guardiola-Lemaitre B (1991) Development of melatonin analogues. Adv Pineal Res 351–353.

Iscan M, Arinc E, Vural N, Iscan MY (1984) *In vivo* effects of 3-methylcholanthrene, phenobarbital, pyrethrum and 2.4.5-T isooctylester on liver, lung and kidney microsomal mixed-function oxidase system of guinea-pig; a comparative study. Comp Biochem Physiol 77C: 177–190.

James PN, Synder HR (1930) Indole-3-aldehyde. Org Synthesis 539–541.

Jones MP, Melan MA, Witt-Enderby PA (2000) Melatonin decreases cell proliferation and transformation in a melatonin receptor-dependent manner. Cancer Lett 151: 133.

Lerner AB, Case JD, Takahaski Y, Lee TH, Mori W (1958) Isolation of melatonin the pineal gland factor that lightens melanocytes. J Am Chem Soc 80: 2587.

Li PK, Witt-Enderby PA (2000) Melatonin receptors as potential targets for drug discovery. Drugs Future 25: 945.

Lowry OH, Rosebrough NJ, Farr AL, Randall RT (1951) Protein measurement with the folin phenol reagent. J Biol Chem, 193: 265–275.

Mor M, Rivara S, Silva C, Bordi F, Plazzi PV, Spadoni G, Diamantini G, Balsamini C, Tarzia G (1998) Melatonin receptor ligands: synthesis of new melatonin derivatives and comprehensive comparative molecular field analysis (CoMFA) study. J Med Chem 41: 3831–3844.

Poeggler B, Reiter RJ, Tan DX, Chen LD, Manchester LG (1993) Melatonin hydroxy radical-mediated oxidative damage and aging: a hypothesis. J Pineal Res 14: 151.

Seltzer A, Viswanathan M, Sazwedra JM (1992) Melatonin-binding sites in brain and caudal arteries of the female rat during the estrous cycle and after estrogen administration. Endocrinology 30: 1890.

Shabica AC, Howe EE, Zeigler JB, Tishler M (1946) Improved synthesis of indole-3-aldehyde. J Am Chem Soc 68: 1156–1157.

Spadoni G, Balsamini C, Diamantini G, Di-Giacoma B, Tarzia G, Mor M, Plazzi PV, Rivara S, Lucini V, Nonno R, Pannacci M, Franschini F, Stankov BM (1997) Conformationally restrained melatonin analogues: synthesis, binding affinity for the melatonin receptor, evaluation of the biological activity and molecular modeling study. J Med Chem 40: 1990–2002.

Wills ED (1966) Mechanism of lipid peroxide formation in animal tissues. Biochem J 99: 667–676.

Wills ED (1969) Lipid peroxide formation in microsomes. Relationship of hidroxylation to lipid peroxide formation. Biochem J 113: 333–341.

Witt-Enderby PA, Li PK (2000) Melatonin receptors and ligands. Vitam Horm 58: 321.