Department of Pharmaceutical Chemistry[1], Department of Toxicology[2], Ankara University, Faculty of Pharmacy, Tandogan, Ankara, Turkey

Synthesis and antioxidative properties of novel thiazolidinedione/imidazolidinedione compounds as retinoids

B. Dundar[1], O. Bozdag-Dundar[1], B. Can-Eke[2], T. Coban[2], M. Iscan[2] and E. Buyukbingol[1]

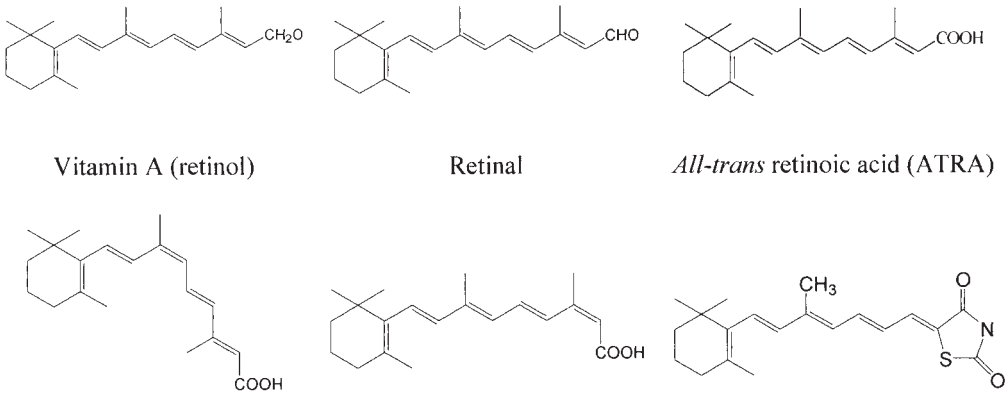
The general term "retinoids" refers to both naturally occurring as well as synthetic compounds which exhibit biological activity similar to vitamin A (retinol). Vitamin A and its two metabolites, retinaldehyde and retinoic acid, are fat-soluble unsaturated isoprenoids necessary for the growth, differentiation and maintenance of epithelial tissues. In this study, we have synthesized thiazolidinedione/imidazolidinedione compounds as retinoids. Their *in vitro* effects on rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels and superoxide anion formation were determined.

1. Introduction

Retinoids consist of a family of naturally occurring compounds including vitamin A (retinol), retinal, *all-trans* retinoic acid (ATRA), 9-*cis* retinoic acid (9-*cis* RA) and 13-*cis* retinoic acid (13-*cis* RA) as well as a large number of synthetic analogs [1]. Both natural and synthetic retinoids elicit beneficial pharmacological responses in a variety of disorders [2]. Activities of retinoids are well-known in cancer therapy, although all have some toxic properties in varying degrees depending on their structures [3]. Subsequently, novel retinoid molecules are designed to diminish toxicity, however, some unwanted side effects remain, such as hypervitaminosis A, skin irradiation, headache, lipid and bone toxicity and teratogenicity [4]. These compounds modulate cell differentiation and proliferation and exert anti-tumoral activities through the interaction with specific receptors: nuclear receptors (RAR α, β, γ, and RXR α, β, γ), and cytoplasmatic receptors (CRABP I and II, CRBP I and II) [5]. Additionally, retinoids inhibit microsomal lipid peroxidation, being effective antioxidants [6–8].
Several polyenylidene thiazolidinedione derivatives (e.g. thiazolidinedione retinoid) elucidate retinoidal type of activities [9] when examined towards various nuclear receptors including RARs, and RXRs. This shows that the retinoidal carboxylic acid moiety can be replaced with a thiazolidine ring with retention of retinoidal activity [9]. Recently several thiazolidines were reported to bind at some nuclear receptors such as peroxisome proliferative activated receptors (PPARs) [10, 11] and retinoid Z receptor (RZR) [12]. Therefore, as a part of a program directed toward the development of new drugs acting on the retinoidal pathway, we are interested in the synthesis of new compounds comprising tetrahydronaphthalene and thiazolidinedione/imidazolidinedione moieties, and the present work initially was performed to evaluate the antioxidant capacity of these compounds.

2. Investigations, results and discussion

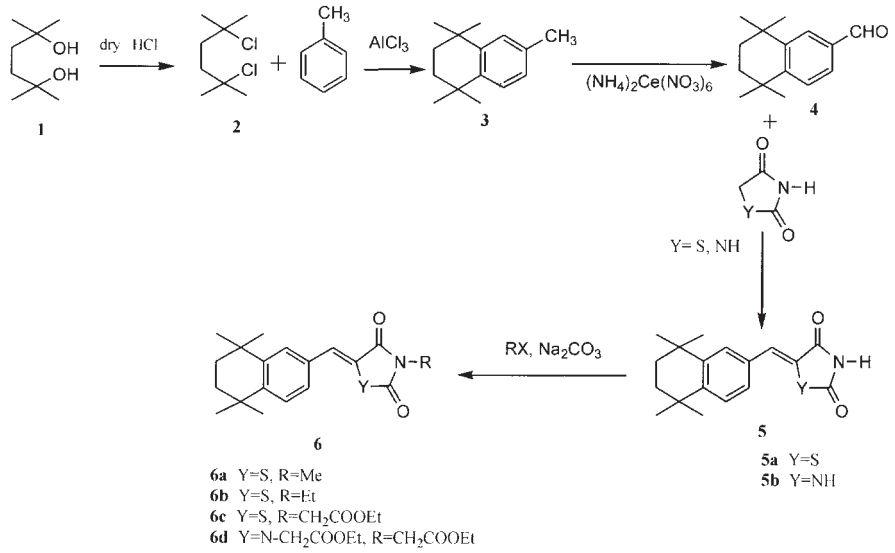
The synthetic routes to the thiazolidinedione/imidazolidinedione derivatives **5a–b**, **6a–d** are shown in the Scheme. This scheme shows two parts of synthesis. First, the tetramethyltetrahydronaphthalene part is synthesized, the thiazolidinedione/imidazolidinedione ring closure is performed followed by condensation with the tetramethyltetrahydronapthalene aldehyde. In the second part, the thiazolidinedione ring is obtained according to Lima et al. by refluxing chloroacetic acid with thiourea [13]. Imidazolidinedione was purchased from Merck Inc.
For the first part of synthesis, the starting material, 2.5-dichloro-2.5-dimethylhexane (**2**) was prepared by passing HCl gas through 2,5-dimethyl-2,5-hexandiole (**1**) [14]. Toluene was alkylated by **2** to produce 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene, (**3**), [14] followed by synthesizing 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxaldehyde (**4**) which was achieved by



Vitamin A (retinol) Retinal *All-trans* retinoic acid (ATRA)

9-cis Retinoic acid (*9-cis* RA) *13-cis* Retinoic acid (13-*cis* RA) Thiazolidinedione retinoid

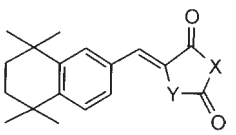
Scheme 1



($(NH_4)_2Ce(NO_3)_6$) as described [15]. Condensation of **4** with thiazolidinedione/imidazolidinedione resulted the 5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-thiazolidine-2,4-dione or 5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-imidazolidine-2,4-dione derivatives **5**, which were reacted with alkyl halides in alkali to obtain the substituted thiazolidinedione/imidazolidinediones (Table 1). In the ^{1}H NMR spectra typical singlets for 4 methyl groups of the tetralene can be seen at approximate δ 1.24–1.33 values. The compounds showed ($M^{+\bullet}$) peak along with the peaks (M + 1; M + 2) except compounds **6b** and **6d** which have shown the additional M + 3 peak. We failed to obtain free carboxylic acid moieties in compounds **6c** and **6d**. Even under mild conditions the hydrolysis of the esters resulted in several degradation products which were not elucidated spectroscopically.

We have studied the antioxidative capacity of the synthesized compounds in rat liver microsomes with two different assays, the effects of compounds on lipid peroxidation (Table 2) and the effects of the compounds on superoxide anion ($O_2^{\bullet -}$) inhibition (Table 3). Their intrinsic reactivity of $O_2^{\bullet -}$ and its ability to generate other reactive entities constitute a threat to cellular integrity. Superoxide dismutase (SOD) enzyme catalytically scavenges these radicals. Therefore, we used the SOD enzyme for an evaluation of the compounds synthesized.

Table 1: Some data of the synthesized compounds



Compd.	X	Y	M.p. (°C)	Yield (%)
5a	NH	S	192	68.57
5b	NH	NH	235	29
6a	N–CH_3	S	252	76.59
6b	N–C_2H_5	S	243	64.28
6c	N–$CH_2COOC_2H_5$	S	258	70.7
6d	N–$CH_2COOC_2H_5$	N–$CH_2COOC_2H_5$	105	53.26

Studies on new retinoids which have less toxic effects led to various compounds with characteristic properties including receptor-selective or antagonist compounds. Retinoids structurally consist of three parts which are a hydrophobic head, a terminal polar group and a linking group of appropriate conformation. In this study, the tetramethyltetrahydronaphthalene moiety is thought to be the hydrophobic head. There is a wide variety of hydrophobic head "and linking group" in which both moieties are replaced with bioisosteric groups, which the terminal polar moiety still is a carboxyl and/or its related alcohol group. Aromatization and/or cyclic replacement of the polyene chain in retinoic acid was shown to be a successful approach for obtaining new retinoids. This approach provides compounds in which one or two olefinic bonds (and single bonds between them) are more or less conformationally restricted. In this study, we substituted the polyene chain with a thiazolidinedione/imidazolidinedione ring system,

Table 2: Effects of the compounds on liver LP levels[a]

Compd.	Concentration in incubation medium (M)	LP (nmol MDA/mg protein)	Percent of Control
Control[b] DMSO		67.1 ± 1.5	100
5a	10^{-5}	71.6 ± 1.1	107
	10^{-4}	88.1 ± 1.0	132
5b	10^{-5}	73.3 ± 5.1	110
	10^{-4}	63.5 ± 6.9	95
6a[c]	10^{-5}	–	–
	10^{-4}	–	–
6b	10^{-5}	63.1 ± 2.9	93
	10^{-4}	63.7 ± 2.3	95
6c	10^{-5}	51.8 ± 7.3	77
	10^{-4}	58.5 ± 4.0	87
6d	10^{-5}	60.2 ± 3.4	90
	10^{-4}	64.8 ± 5.7	96
ATRA	10^{-5}	49.6 ± 0.3	74
	10^{-4}	44.4 ± 0.6	66

[a] Each value represents the mean ±S.D. of 2–4 independent experiments
[b] Dimethylsulfoxide only, control for compounds
[c] No results obtained for LP with compound **6a**

Table 3: Effects of the compounds on liver superoxide anion production[a]

Compd.	Concentration in incubation medium (M)	Superoxide anion ($O_2^{\bullet -}$) production percent of control
Control[b] DMSO		100 ± 6
5a	10^{-5}	130 ± 5
	10^{-4}	127 ± 16
5b	10^{-5}	150 ± 7
	10^{-4}	52 ± 12
6a[c]	10^{-5}	–
	10^{-4}	–
6b[c]	10^{-5}	–
	10^{-4}	–
6c	10^{-5}	73 ± 1
	10^{-4}	78 ± 9
6d	10^{-5}	145 ± 7
	10^{-4}	22 ± 1
Control[d]	Water	100 ± 2
SOD	30 IU	24 ± 2
	45 IU	11 ± 1

[a] Each value represents the mean ± S. D. of 2–4 independent experiments
[b] Dimethylsulfoxide only, control for compounds
[c] No results obtained for superoxide anion with compounds 6a and 6b.
[d] Distilled water, control for SOD

bearing the polar moieties attached to mentioned rings. As can be seen from Table 2, *all-trans* retinoic acid (ATRA), decreased the LP level by about 34% and 26% at 10^{-4} M and 10^{-5} M concentrations, respectively. However, the synthesized compounds have no significant effect on lipid peroxidation. Compounds **6b–d** show rather limited inhibition on the lipid peroxidation at 10^{-5} M and 10^{-4} M concentrations, whereas compound **5b** (an imidazolidinedione) slightly inhibited LP (5%) at 10^{-4} M but induced LP 10% at 10^{-5} M. Compound **5a** (a thiazolidinedione) induced LP by 7% and 31% at 10^{-5} M and 10^{-4} M, respectively. These compounds lack of substituents on the thiazolidinedione/imidazolidinedione rings. The most active compound is **6c** which caused 23% inhibition of LP at 10^{-5} M concentration. This inhibition is quite similar to that obtained from ATRA. It is noteworthy to indicate that higher concentrations of **6b–d** and also of ATRA show decreasing inhibition.

The activity pattern of the compounds on superoxide anion formation are similar to those obtained in LP. Superoxide anion formation normally plays significant roles in a number of pathophysiologic states including oxygen toxicity, radiation damage, phagocyte-mediated inflammation, and postischemic injury. In this manner, **6d** is the most active at 10^{-5} M concentration when compared with the others. Moreover, this compound showed activity similar to 30 IU superoxide dismutase. Therefore, inhibition of $O_2^{\bullet -}$ by **6d** is likely to render this compound as promising antioxidant. However, as can be seen from Table 2, compounds **5b** and **6d** showed biphasic effects at both concentrations in which **5b** had an inductive effect (50% induction) on superoxide anion formation at 10^{-5} M. At 10^{-4} M, however, this compound caused an inhibition. **6d** showed a similar effect. Induction of superoxide anion formation (45% induction) occurred at 10^{-4} M, and inhibition (78% inhibition) was found at 10^{-4} M concentration. This different pattern of effects can be seen in biological assays when inductions may occur at lower concentrations whereas inhibition results at higher concentrations [16, 17]. Biphasic effects of several other oxidants such as hydroxychalcones on the formation of superoxide radical anion have been well established in various *in vitro* systems [18–22]. Distinct effects of hydroxychalcone derivatives have been noted in two different assay systems [18]. The hydroxychalcones elicited severe depression on lipid peroxidation whereas slight elevation on the formation of superoxide radical anion in the hypoxanthine-xanthine oxidase system at the same concentration (10^{-5} M) [18].

Thus, herein, the observation of biphasic effects of some compounds on LP and formation of superoxide radical anion is not surprising since the mechanisms of production of oxidative stress (or reactive oxygen species) in these assays are different [19–22].

3. Experimental

3.1. Apparatus

Melting points were determined with Büchi SMP-20 and Buchi 9100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker GmbH DPX-400 (400 MHz) spectrometer in $CDCl_3$. IR spectra were recorded on a Jasco FT/IR-420 spectrophotometer as KBr pellets. Mass spectra (El mode, 70 eV) were recorded on a Micromass UK. Platform II LC-MS and peaks are shown with their intensities in parenthesis. Elemental analyses were performed on LECO 932 CHNSO. All the results were in an acceptable range.

3.2. Synthesis

3.2.1. 5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylmethylene)-thiazolidine-2,4-dione **(5a)**

Compound **4** (1.60 g, 7.407 mmol), 2,4-thiazolidinedione (0.85 g, 7.256 mmol) and CH_3COONa (1.00 g, 7.348 mmol) were dissolved in 8 ml of acetic acid and heated to 140–150 °C for 16 h. The mixture was poured into ice water and extracted with ether. After evaporation the oily crude product crystallized from ethanol. Light yellowish crystals obtained, m.p. 192 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3), 1.72 (s, 4 H, $(CH_2)_2$), 7.26 (d, 1 H, 3-H), 7.41 (d, 1-H, $J_{4,3} = 8.24$ Hz, 4-H), 7.45 (d, 1 H, $J_{1,3} = 1.90$ Hz, 1-H), 7.83 (s, 1 H, =CH), 8.68 (s, 1 H, N–H). MS [m/z (%)]: 315 (56.63) (M^+), 316 (14.86) (M + 1), 317 (4.97) (M+2), 244 (27.81), 229 (40.05), 185 (32.65), 141 (32.14), 128 (38.78), 115 (41.58), 83 (100.00). IR (KBr) cm^{-1} 1736, 1692 (C=O stretching), 1601 (C=C stretching), 3151 (NH stretching), 1556 (NH bending).
$C_{18}H_{21}NO_2S$

3.2.2. 5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)-imidazolidine-2,4-dione **(5b)**

Compound **5b** was prepared similarly to **5a** as described above. Compound **4** (1.40 g, 6.481 mmol) and 2,4-imidazolidinedione (0.65 g, 6.481 mmol) were used. The oily product was obtained after 32 h at 140–150 °C, purified by column chromatography (silica gel 60, 0.040–0.063 mm (230–400 mesh ASTM), hexane-chloroform (1 : 1), m.p. 235 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 6 H, CH_3), 1.33 (s, 6 H, CH_3), 1.73 (s, 4 H, $(CH_2)_2$), 6.73 (s, 1 H, =CH), 7.19 (dd, 1 H, $J_{3,4} = 8.18$ Hz, $J_{3,1} = 1.86$ Hz, 3-H), 7.33 (d, 1 H, $J_{1,3} = 1.75$ Hz, 1-H), 7.41 (d, 1 H, $J_{4,3} = 8.19$ Hz, 4-H), 7.47 (broad s, 1 H, N–H), 7.76 (broad s, 1 H, N–H). MS [m/z (%)]: 298 (14.53) (M^+), 299 (4.82) (M + 1), 300 (1.25) (M + 2), 283 (26.20), 153 (14.61), 141 (20.18), 128 (21.99), 115 (24.10), 70 (77.11), 55 (100.00). IR (KBr) cm^{-1} 1723, 1658 (C=O stretching), 1604 (C=C stretching), 3448, 3251 (NH stretching), 1496 (NH bending).
$C_{18}H_{22}N_2O_2$

3.2.3. 3-Methyl-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-methylene)-thiazolidine-2,4-dione **(6a)**

To a solution of compound **5a** (0.20 g, 0.635 mmol), and anh. Na_2CO_3 (0.067 g, 0.635 mmol) in 5 ml dimethylformamide, methyl iodide (0.08 ml, 1.27 mmol) was added and the mixture vigorously stirred at 40 °C for 1 h, poured into ice water, and the precipitate was dissolved in EtOH and filtrated. Leaving overnight at 4 °C resulted in white crystals, recrystallized from EtOH, m.p. 252 °C. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3), 1.71 (s, 4 H, $(CH_2)_2$), 3.24 (s, 3 H, N–CH_3), 7.27 (d, 1 H, 3-H), 7.40 (d, 1 H, $J_{4,3} = 8.24$ Hz, 4-H), 7.46 (d, 1 H, $J_{1,3} = 1.80$ Hz, 1-H), 7.88 (s, 1 H, =CH). MS [m/z (%)]: 329 (41.40) (M^+), 330 (10.62) (M + 1), 331 (3.49) (M + 2), 314 (65.86), 272 (17.74), 186 (25.27), 171 (19.09), 128 (24.19), 115 (22.58), 83 (100.00). IR (KBr) cm^{-1} 1753, 1697 (C=O stretching), 1496 (C=C stretching).
$C_{19}H_{23}NO_2S$

3.2.4. 3-Ethyl-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-methylene)-thiazolidine-2,4-dione **(6b)**

6b was prepared similarly to **6a**. Ethyl iodide (1.27 mmol, 0.10 ml) was used instead of methyl iodide. White crystals obtained from EtOH left overnight at 4 °C, m.p. 243 °C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3 H, J = 7.02 Hz, CH_2-CH_3), 1.28 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 1.72 (s, 4 H, $(CH_2)_2$), 3.85 (q, 2 H, J = 7.17 Hz, $N-CH_2$), 7.25–7.45 (m, 3 H, Ar-H), 7.85 (s, 1 H, 0CH). MS [m/z (%)]: 343 (95.28) (M^+), 344 (57.08) (M + 1), 345 (16.16) (M + 2), 346 (3.95) (M + 3), 328 (100.00), 286 (13.92), 229 (65.57), 186 (45.28), 141 (32.55), 115 (37.74). IR (KBr) cm^{-1} 1749, 1687 (C=O stretching), 1610 (C=C stretching).
$C_{20}H_{25}NO_4S$

3.2.5. Ethyl-[2,4-dioxo-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)-thiazolidine-3-yl]-acetate **(6c)**

6c Was prepared similarly to **6a**. Ethyl bromoacetate (1.587 mmol, 0.18 ml) was used instead of methyl iodide. White crystals obtained from EtOH, left overnight at 4 °C, recrystallized with EtOH, m.p. 258 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3 H, J = 7.19 Hz, CH_2-CH_3), 1.30 (s, 6 H, CH_3), 1.32 (s, 6 H, CH_3), 1.71 (s, 4 H, $(CH_2)_2$), 4.24 (q, 2 H, J = 7.19 Hz, CH_2), 4.25 (s, 2 H, $N-CH_2$), 7.28 (d, 1 H, $J_{3,4}$ = 8.27 Hz, 3-H), 7.41 (d, 1 H, $J_{4,3}$ = 8.27 Hz, 4-H), 7.47 (d, 1 H, $J_{1,3}$ = 1.81 Hz, 1-H), 7.91 (s, 1 H, =CH). MS [m/z (%)]: 401 (49.17) (M^+), 402 (13.96) (M + 1), 403 (4.53) (M+2), 386 (47.50), 270 (23.13), 244 (26.56), 229 (100.00), 200 (24.06), 185 (32.08), 83 (14.17). IR (KBr) cm^{-1} 1748, 1692 (C=O stretching), 1613 (C=C stretching).
$C_{22}H_{27}NO_4S$

3.2.6. Ethyl-{4-[4-(1,1-Dimethyl-pentyl)-3-methyl-benzylidene]-3-ethoxycarbonylmethyl-2,5-dioxo-imidazolidine-1-yl}-acetate **(6d)**

To a vigorously stirred solution of **5b** (0.50 g, 1.678 mmol) and anh. Na_2CO_3 (0.356 g, 3.356 mmol) in 5 ml DMF were added ethyl bromoacetate (0.37 ml, 3.356 mmol) at 40 °C for 1 h. The mixture was poured into ice water and purified by column chromatography as described for **5b**, m.p. 105 °C. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 3 H, OCH_2CH_3, ethyl acetate methyl on N_1 in the imidazolidinedione ring), 1.30 (t, 3 H, OCH_2CH_3, ethyl acetate methyl on N_2 in the imidazolidinedione ring), 1.31 (s, 6 H, CH_3), 1.33 (s, 6 H, CH_3), 1.73 (s, 4 H, $(CH_2)_2$), 4.00 (q, 2 H, OCH_2CH_3, ethyl acetate on the N_1 of imidazolidinedione ring), 4.28 (q, 2 H, OCH_2CH_3, ethyl acetate on the N_2 of imidazolidinedione ring), 4.34 (s, 2 H, N_1-CH_2), 4.41 (s, 2 H, N_2-CH_2), 7.02–7.32 (m, 3 H, Ar-H). MS [m/z (%)]: 470 (64.08) (M^+), 471 (18.45) (M + 1), 472 (3.12) (M + 2), 473 (3.06) (M + 3), 455 (36.41), 342 (4.22), 240 (1.87), 182 (4.67), 119 (4.37), 91 (17.48), 83 (100.00). IR (KBr) cm^{-1} 1749, 1687 (C=O stretching), 1610 (C=C stretching).
$C_{26}H_{34}N_2O_6$

3.3. Antioxidant activity studies

3.3.1. Assay of lipid peroxidation

NADPH-dependent LP was determined under the optimum conditions described previously [23]. Mal albino (local strain) rats (200–225 g) were fed with standard laboratory rat chow and tab water *ad libitum*. The animals were starved for 24 h prior to sacrifice and then killed by decapitation under anaesthesia. The livers were removed immediately and washed in ice-cold distilled water, and microsomes were prepared as described [19]. NADPH-dependent LP was measured spectrophotometrically by estimation of thiobarbituric acid reactant substances (TBARS). Amounts of TBARS were expressed in terms of nmol malondialdehyde (MDA)/mg protein. A typical optimized assay mixture contained 0.2 mM Fe^{++}, 90 mM KCl, 62.5 mM potassium phosphate buffer, pH 7.4, a NADPH generating system consisting of 0.25 mM $NADP^+$, 2.5 mM $MgCl_2$, 2.5 mM glucose-6-phosphate buffer pH 7.8 and 0.2 mg microsomal protein in a final volume of 1.0 ml.

3.3.2. Inhibition of superoxide anion formation

The inhibition of superoxide anion formation was determined spectrophotometrically on the basis of inhibition of cytochrome C reduction according to the modified method of McCord et al. [24]. The absorbance was measured spectrophotometrically at 550 nm for cytochrome C reduction. Each experiment was performed in triplicate, and the results are expressed related to the percent of the control.

Acknowledgements: This work is supported by Ankara University Research Fund (97–03-00–08) and TUBITAK (SBAG-1864).

References

1 Nadzan, A. M.: Ann. Rep. Med. Chem. **30**, 119 (1995)
2 Sporn, M. B.; Roberts, A. B.: Cancer Res. **43**, 3034 (1993)
3 Tzimas, G.; Nau, H.: Curr. Pharm. Des. **7**, 803 (2001)
4 Armstrong, R. B.; Ashenfelter, K. O.; Eckhoff, C.; Levin, A. A.; Shapiro, S. S; in: Sporn, M. B.: Roberts, A. B.: Goodman, D. S. (Eds.): Retinoids, Biology, Chemistry and Medicine, 2nd Ed. P. 545, Raven Press, New York, N.Y. 1994
5 Charpentier, B.; Bernardon, J.-M.; Eustache, J.; Millois, C.; Martin, B.; Michel, S.; Shroot, B.: J. Med. Chem. **38**, 4993 (1995)
6 Samokyszyn, V. M.; Marnett, L. J.: Methods in Enzymol. **190**, 281 (1990)
7 Levin, G.; Mokady, S.: Free Rad. Biol. Med. **17**, 77 (1994)
8 Takahashi, N.: Biol. Pharm. Bull. **23**, 222 (2000)
9 Tashima, T.; Kagechika, H.; Tsuji, M.; Fukasawa, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K.: Chem.Pharm. Bull. **45**, 1805 (1997)
10 Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliwer, S. A.: J. Biol. Chem. **270**, 12953 (1995)
11 Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M.: Cell **83**, 803 (1995)
12 Wiesenberg, I.; Missbach, M.; Kahlen, J.-P.; Schrader, M.; Carlberg, C.: Nucleic Acids Res. **23**, 327 (1995)
13 Lima, M. C. A.; Costa, D. L. B.; Goes, A. J. S.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C.: Pharmazie **47**, 182 (1992)
14 Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Merger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A.: J. Med. Chem. **37**, 2930 (1994)
15 Dawson, M. I.; Hobbs, P. D.; Derdzinski, K. A.; Chao, W. –W.; Frenking, G.; Loew, G. H.; Jetten, A. M.; Napoli, J. L.; Williams, J. B.; Sani, B. P.; Wille, Jr. J. J.; Schiff, L. J.: J. Med. Chem. **32**, 1504 (1989)
16 Iscan, M.: Comp. Biochem. Physiol. **79C**, 429 (1984)
17 Al-Assadi, H. M.; Rodgers, E. H; Grant, M. H.: Biochem. Soc. Trans. 68S (1992)
18 Sogawa, S.; Nihro, Y.; Ueda, H.; Tokutar, M.; Matsumoto, H.; Satoh, T.: Biol. Pharm. Bull. **17**, 251 (1994)
19 McCord, J. M.; Fridowich, I.: J. Biol. Chem. **243** 6049 (1969)
20 Kornbrust, D. J.; Maris, R. D.: Mol. Pharmacol. **17**, 400 (1980)
21 Parke, D. V.; Ionnides, C.; Lewis, D. F.: Can. J. Physiol. Pharmacol. **69**, 537 (1991)
22 Dix, T. A.; Aikens, J.: Chem. Res. Toxicol. **6**, 2 (1993)
23 Tuncbilek, M.; Ayhan-Kilcigil, G.; Ertan, R., Can-Eke, B.; Iscan, M.: Pharmazie **55**, 359 (2000)
24 Iscan, M.; Arinc, E.; Vural, N.; Iscan, M. Y.: Comp. Biochem. Physiol. **77C**, 177 (1984)

Received August 21, 2001
Accepted December 4, 2001

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