Antipsoriatic Anthrones with Modulated Redox Properties. 4. Synthesis and Biological Activity of Novel 9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracenecarboxylic and -hydroxamic Acids[1,†]

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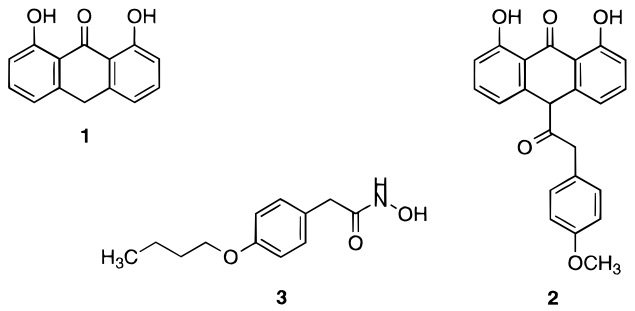
A novel series of carboxylic and hydroxamic acids based on 1,8-dihydroxy-9(10*H*)-anthracenone were synthesized from 8-hydroxy-1-methoxy-9,10-anthracenedione as the key intermediate and evaluated both in the bovine polymorphonuclear leukocyte 5-lipoxygenase (5-LO) assay and in the HaCaT keratinocyte proliferation assay for their enzyme inhibitory and antiproliferative activity, respectively. The most potent inhibitors in both assays were the *N*-methylated hydroxamic acids **5d**−**8d** with straight chain alkyl spacers. Incorporation of these structural features on the anthracenone pharmacophore resulted in increased inhibitory activity against 5-LO while the antiproliferative activity was retained. In addition, prooxidant properties as measured by deoxyribose degradation and cytotoxicity as assessed by LDH release were largely reduced as compared with the antipsoriatic anthralin. Contrary to anthralin, antioxidant properties were observed as documented by the reactivity of the novel compounds against free radicals and inhibition of lipid peroxidation in model membranes.

Anthracenones such as anthralin (**1**) are among the major topical remedies for the treatment of psoriasis.[2] While these drugs are considered generally safe, like most forms of therapy unpleasant effects do accompany their topical administration. The most notable and prevalent are the staining and irritation of the non-affected skin.[2] An encouraging trend has been to elucidate the molecular origin of the proinflammatory action of the anthrone class and, by appropriate chemical modification, to improve the therapeutic index.[3] Thus, irritation of the nonaffected psoriatic skin caused by anthracenones may be interpreted in terms of their efficacy to produce oxygen radicals.[4,5] As part of our project aimed at providing improved antipsoriatic anthrones, we have synthesized analogs in which one or both active methylene protons at C-10 were replaced by suitable substituents (e.g., **2**) which permit control over the release of active oxygen species.[6] As a result, **2** is currently undergoing clinical evaluation as a topical treatment for psoriasis.

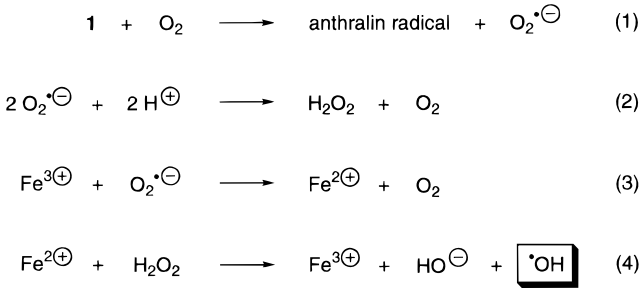
An alternative approach to the control of oxygen-radical formation would be to chelate the transition metal that facilitates the autoxidation of the anthracenone molecule with the concomitant production of oxygen radicals. In this context, several factors regarding oxygen-radical generation by anthrones and the role of iron have to be considered in the design of novel derivatives.

The evidence is convincing that iron plays a role in radical production by antipsoriatic anthrones *in vivo* (Scheme 1). First, one-electron reduction of oxygen by anthralin produces superoxide radical (eq 1).[7] As the direct reaction of oxygen with biomolecules is spin forbidden, significant production of superoxide radical

Chart 1



Scheme 1. Iron-Dependent Production of Active Oxygen Species by Anthralin



requires the presence of transition metals, such as iron.[8] Second, superoxide radical readily undergoes dismutation to form hydrogen peroxide and oxygen (eq 2), which have only moderate reactivity and, therefore, cannot account for the biological damage observed in systems in which they are generated.[9,10] It has been suggested, therefore, that the observed damage to a target is due to their conversion into the highly reactive hydroxyl radical.[9,10] Third, iron is an important catalyst of hydroxyl-radical production, *via* the Haber−Weiss cycle (eqs 3 and 4, a superoxide-driven Fenton reaction).[11] Moreover, iron is the most likely candidate for stimulating hydroxyl-radical generation *in vivo*[12] and has been demonstrated to play a key role in the formation of these

† Dedicated to Prof. Dr. G. Wurm, Berlin, on the occasion of his 60th birthday.

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species by anthralin.[13,14] In support of this, the catalytic function of iron in the enhancement of anthralin-induced lipid peroxidation (LPO) has been documented.[14] Finally, the importance of iron in mediating oxidative damage by antipsoriatic anthrones is of particular interest because the skin is a significant site of iron excretion which is increased in psoriasis.[15] On the basis of the above information, we have designed synthetic analogs combining an anthracenone chromophore and a hydroxamic acid moiety, which has a high affinity for iron,[16] to suppress iron-dependent generation of oxygen radicals. In addition to and independently of their iron-chelating properties, hydroxamates act as free radical scavengers.[17]

A second aspect of 1,8-dihydroxy-9(10*H*)-anthracenones containing an iron-chelating functionality, such as hydroxamic acid, results from the known role of iron in the mechanism of 5-lipoxygenase (LO).[18] Indeed, since Corey's disclosure[19] that hydroxamic acid analogs of arachidonic acid are effective inhibitors of the enzyme, numerous attempts have been made to develop hydroxamic acid-based 5-LO inhibitors as therapeutic agents.[20−25] An example of a hydroxamate-based topical antiinflammatory agent is bufexamac (**3**). Furthermore, inhibitors of 5-LO could have therapeutic utility in a number of inflammatory disease states including psoriasis.[18,26]

Although hydroxamic acid derivatives exhibit potent 5-LO inhibitory activity, this structural pattern *per se* may not be sufficient for attaining antiproliferative activity. With psoriasis as target for therapy, both the inflammatory and hyperproliferative aspects of the disease have to be resolved. Nevertheless, with the 1,8-dihydroxy-9(10*H*)-anthracenone pharmacophore attached to the hydroxamic acid moiety by proper side chains, it is believed that compounds having desired biological activity could be obtained.

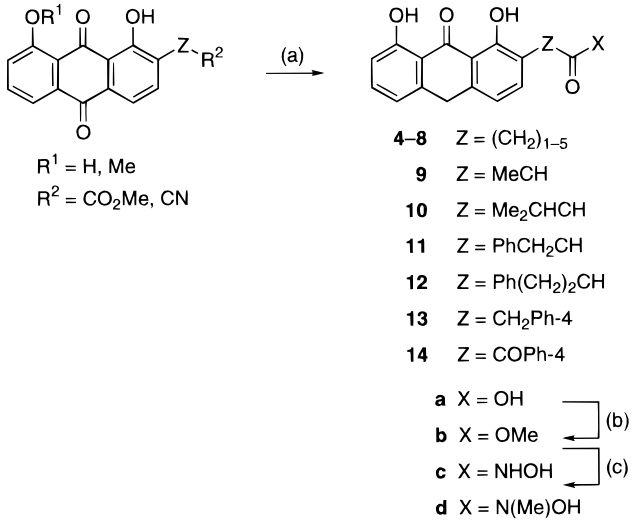
In this paper we describe the synthesis and biological activity of 1,8-dihydroxy-9(10*H*)-anthracenones (**4**−**14**, **a**−**d**), bearing various linked carboxylic and hydroxamic acids in the 2-position. The *N*-methyl-substituted hydroxamates show reduced hydroxyl-radical generation as compared to anthralin and are potent inhibitors of enzymatic (5-LO-mediated) and nonenzymatic (free radical-induced) lipid peroxidation (LPO). Furthermore, these compounds exhibit high antiproliferative activity against the keratinocyte cell line HaCaT.

Chemistry

Introduction of the appropriate side chains onto the 2-position of the anthralin nucleus was achieved at the anthracenedione stage, and reduction of the appropriately 2-substituted 9,10-anthracenediones in glacial acetic acid with $SnCl_2$/HCl was envisioned as the last step in the preparation of the desired 1,8-dihydroxy-9(10*H*)-anthracenone carboxylic acids **4a**−**14a**. Esterification of the acids with methanol gave the 2-substituted 1,8-dihydroxy-9(10*H*)-anthracenone methyl carboxylates **4b**−**14b**. These were reacted with hydroxylamine hydrochloride or *N*-methylhydroxylamine hydrochloride according to conventional methods to yield the desired 2-substituted 1,8-dihydroxy-9(10*H*)-anthracenone hydroxamic acids **4c**−**14c** or *N*-methylhydroxamic acids **4d**−**14d**, respectively (Scheme 2).

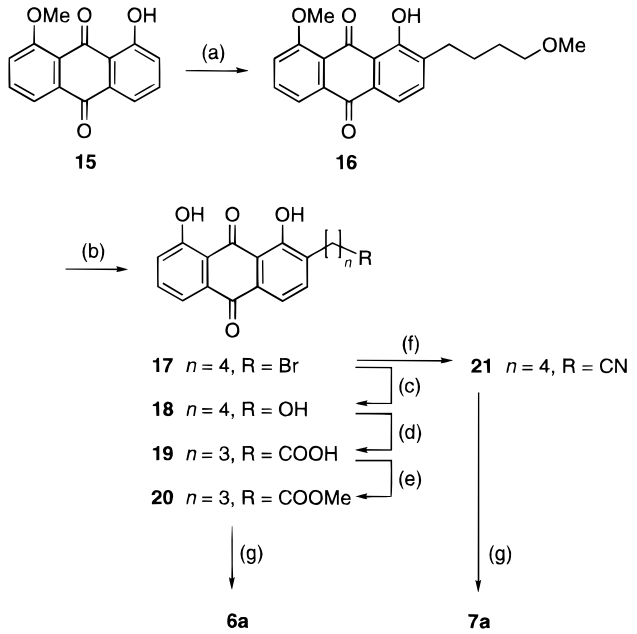
The requisite 2-substituted anthracenedione precursors were obtained by Marschalk reaction[27] from 1-hydroxy-8-methoxy-9,10-anthracenedione[28] (**15**) as the key intermediate (Scheme 3). Alkylation of **15** with methyl 4-oxobutanoate gave only poor yields of the desired anthracenedione **22**, (Scheme 4). Therefore, an alternative method was developed. As outlined in Scheme 3, alkylation of **15** with 4-methoxybutyraldehyde afforded **16**, which was directly converted to bromide **17** with hydrobromic acid. Replacement of the bromo with a hydroxy function using sodium hydroxide was troublesome and resulted in intramolecular ether formation at the 1-hydroxy group. However, an aqueous solution of hexamethylphosphorous triamide provided a potent source of nucleophilic oxygen[29] for the conversion of **17** to the alcohol **18**. Oxidation of **18** with pyridinium dichromate gave the butyric acid **19** which was then esterified to **20** and reduced to **6a**. The homologous **7a**

Scheme 2[a]



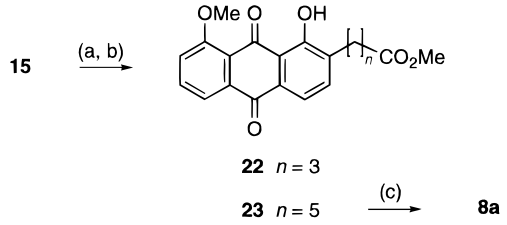
[a] Reagents: (a) $SnCl_2$, HCl, glacial acetic acid, 118 °C; (b) MeOH, concentrated H_2SO_4; (c) NH(R)OH·HCl (R = H, Me), Na/MeOH, N_2, 0−5 °C.

Scheme 3[a]



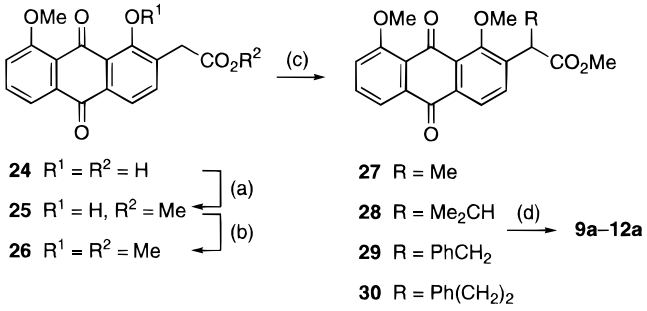
[a] Reagents: (a) $Na_2S_2O_4$, NaOH, $MeO(CH_2)_3CHO$, N_2, 90 °C; (b) HBr (62%), glacial acetic acid, 118 °C; (c) HMPA/H_2O, 128 °C; (d) PDC, DMF, room temperature; (e) MeOH, concentrated H_2SO_4; (f) NaCN, DMSO; (g) $SnCl_2$, HCl, glacial acetic acid, 118 °C.

Scheme 4[a]



[a] Reagents: (a) $Na_2S_2O_4$, NaOH, $MeO_2C(CH_2)_2CHO$ or $MeO_2C(CH_2)_4CHO$, N_2, 90 °C; (b) MeOH, concentrated H_2SO_4; (c) $SnCl_2$, HCl, glacial acetic acid, 118 °C.

Scheme 5[a]



[a] Reagents: (a) MeOH, concentrated H_2SO_4; (b) Me_2SO_4, K_2CO_3, acetone, 55 °C; (c) methyl, isopropyl, benzyl, or phenylethyl bromide, NaH, DMSO; (d) $SnCl_2$, HCl, HOAc, 118 °C.

was also obtained from **17** by displacement of bromide with sodium cyanide in DMSO to give valeronitrile **21**, followed by direct reduction to the anthracenone stage. In contrast to the synthesis of **22**, alkylation of **15** with methyl 6-oxohexanoate followed by esterification of the corresponding acid afforded ester **23** in good yields, which was then reduced to the hexanoic acid **8a** (Scheme 4).

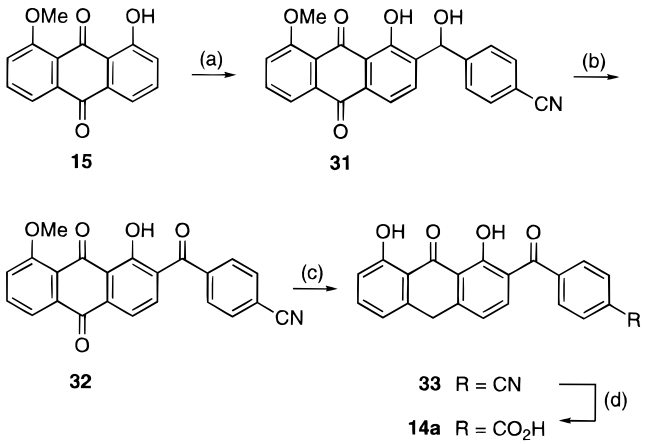
Anthracenone acetic and propionic acids **4a** and **5a** were prepared as previously described.[30] 2-Propionic acids **9a**−**11a** were prepared from **24**,[30] which was esterified (**25**) and protected as the methyl ether **26**, alkylated with the appropriate bromides (**27**−**30**), and then reduced (Scheme 5).[28]

The benzyl-linked acid **13a** was recently described,[31] and the benzoyl-linked acid **14a** was prepared as illustrated in Scheme 6. Our recently reported synthesis of an analogous compound involved a multistep procedure from a benzyl precursor.[31] However, conducting the Marschalk reaction of **15** with 4-cyanobenzaldehyde at low temperature, to avoid thermal elimination of the hydroxyl group, directly afforded the secondary alcohol **31**. Oxidation of **31** with pyridinium dichromate gave the ketone **32**, which was selectively reduced to the anthracenone **33** and hydrolyzed to yield **14a**.

Biological Evaluation

The procedures used were exactly as those described in our previous studies.[1,6,31] Thus, inhibition of the 5-LO pathway by the novel compounds was evaluated as a measure of their potency to resolve the inflammatory aspect of psoriasis, whereas antiproliferative action in cell cultures may be critical in the management of the proliferative nature of the disease. HaCaT keratinocytes were used as a model for highly proliferative epidermis of psoriasis.

Scheme 6[a]



[a] Reagents: (a) $Na_2S_2O_4$, NaOH, NCC_6H_5CHO, N_2, 0−5 °C; (b) PDC, DMF, room temperature; (c) $SnCl_2$, HCl, HOAc, 118 °C; (d) H_2SO_4/H_2O, glacial acetic acid, 118 °C.

Since the mode of action and induction of side effects of anthralin are related to its redox activity leading to the production of oxygen radicals,[4,5] the novel compounds were further evaluated by the use of three test systems specifically addressed to three aspects of redox properties: reactivity against the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), inhibition of lipid peroxidation in model membranes,[14] and hydroxyl-radical generation (prooxidant potential).

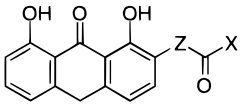
Inhibition of 5-Lipoxygenase. 5-LO inhibitory activity was determined by measuring production of 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B_4 (LTB_4) in bovine polymorphonuclear leukocytes (PMNL), since potential antipsoriatic drugs are evaluated for their ability to inhibit the production of LTB_4.[25,32−34]

Among the hydroxamate analogs, there was a clear pattern of greater inhibitory activity for those with *N*-methyl substitution (type **d**) than those with *N*-unsubstituted hydroxamic acid groups (type **c**), as already seen in other studies.[21] Corresponding carboxylic acids (type **a**) were generally less active, and compounds bearing ester functions were inactive (type **b**). Within each class of analogs, the potency roughly correlated with the overall lipophilicity, as already described for hydroxamic acids and other compounds (log *P* values are given in Table 2).[21,35]

The introduction of methylene units between the anthracenone nucleus and the hydroxamate moiety (**4c**−**7c** and **4d**−**8d**) slightly improved potency, and this was also observed for the carboxylic acids **4a**−**8a**. Although the activity of carboxylic acid analogs with branched chain alkyl spacers (**10a**−**12a**) increased as compared to straight chain spacers (**4a**−**8a**), inverse results were obtained with the *N*-methyl-substituted hydroxamates (**10d**, **11d** vs **4d**−**8d**).

Antioxidant Determination. Aside from eicosanoids, free radicals and end products derived from lipid peroxidation are important components in inflammatory diseases.[36] As a measure of their potential to scavenge free radicals, we determined the reactivities of the compounds with the stable free radical DPPH.[6] Carboxylic acid analogs and their corresponding esters gave values (k_{DPPH} = 19−24 M^{-1} s^{-1}) similar to that of anthralin (24 ± 4.2 M^{-1} s^{-1}),[6] except for the 2-benzoyl

Table 1. Deoxyribose Degradation, 5-LO Inhibition in Bovine PMNL, Antiproliferative Activity, and Cytotoxicity against HaCaT Cells by 9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracenecarboxylic and -hydroxamic Acids



				IC$_{50}$ (μM)		
compd[a]	Z	X	DD (•OH)[b]	5-LO[c]	AA	LDH (mU)[e]
4a	CH_2	OH	3.74 ± 0.23	22	>5	ND
5a	$(CH_2)_2$	OH	2.67 ± 0.23	19	>5	ND
6a	$(CH_2)_3$	OH	2.61 ± 0.38	18	>5	ND
7a	$(CH_2)_4$	OH	2.62 ± 0.41	13	>5	ND
8a	$(CH_2)_5$	OH	2.29 ± 0.03	10	>5	ND
9a	CH_3CH	OH	ND	17	>5	ND
10a	$(CH_3)_2CHCH$	OH	3.58 ± 0.30	2	>5	128[f]
11a	$PhCH_2CH$	OH	3.25 ± 0.45	1	>5	ND
12a	$Ph(CH_2)_2CH$	OH	2.47 ± 0.16	2	>5	142[f]
13a	CH_2Ph-4	OH	<0.15	2	2.6	ND
14a	COPh-4	OH	1.34 ± 0.10	2	>5	ND
4b	CH_2	OCH_3	ND	>30	0.5	ND
5b	$(CH_2)_2$	OCH_3	ND	>30	0.8	ND
6b	$(CH_2)_3$	OCH_3	0.33 ± 0.03	>30	1.1	ND
7b	$(CH_2)_4$	OCH_3	0.62 ± 0.03	>30	1.8	146[f]
8b	$(CH_2)_5$	OCH_3	ND	>30	1.6	142[f]
9b	CH_3CH	OCH_3	ND	>30	0.8	ND
10b	$(CH_3)_2CHCH$	OCH_3	0.54 ± 0.01	>30	1.5	ND
11b	$PhCH_2CH$	OCH_3	<0.15	>30	1.8	ND
12b	$Ph(CH_2)_2CH$	OCH_3	0.28 ± 0.03	>30	1.3	142[f]
13b	CH_2Ph-4	OCH_3	<0.15	>30	ND	ND
14b	COPh-4	OCH_3	ND	>30	1.8	ND
4c	CH_2	NHOH	1.89 ± 0.14	6	1.8	ND
5c	$(CH_2)_2$	NHOH	1.67 ± 0.31	4	1.3	ND
6c	$(CH_2)_3$	NHOH	1.46 ± 0.02	3	1.5	ND
7c	$(CH_2)_4$	NHOH	1.38 ± 0.09	2	2.0	135[f]
9c	CH_3CH	NHOH	1.30 ± 0.11	6	2.0	ND
10c	$(CH_3)_2CHCH$	NHOH	1.66 ± 0.08	6	1.5	192
11c	$PhCH_2CH$	NHOH	1.04 ± 0.00	4	1.5	ND
13c	CH_2Ph-4	NHOH	ND	5	1.1	ND
4d	CH_2	$N(CH_3)OH$	1.67 ± 0.08	1	0.8	150[f]
5d	$(CH_2)_2$	$N(CH_3)OH$	0.92 ± 0.03	0.6	0.6	135[f]
6d	$(CH_2)_3$	$N(CH_3)OH$	1.50 ± 0.02	0.6	0.6	181
7d	$(CH_2)_4$	$N(CH_3)OH$	1.36 ± 0.05	0.5	0.8	124[f]
8d	$(CH_2)_5$	$N(CH_3)OH$	ND	0.4	0.7	ND
9d	CH_3CH	$N(CH_3)OH$	1.57 ± 0.16	6	1.5	142[f]
10d	$(CH_3)_2CHCH$	$N(CH_3)OH$	0.86 ± 0.01	5	1.5	135[f]
11d	$PhCH_2CH$	$N(CH_3)OH$	1.68 ± 0.13	5	0.9	ND
13d	CH_2Ph-4	$N(CH_3)OH$	ND	0.7	0.9	ND
14d	COPh-4	$N(CH_3)OH$	0.92 ± 0.08	4	1.8	ND
bufexamac				35	>5	135[f]
anthralin			2.89 ± 0.14	37	0.6	294

[a] Compounds with the structural pattern **8c** and **12c**,**d** have not been prepared. [b] Deoxyribose degradation as a measure of hydroxyl-radical formation. Indicated values are μmol of malondialdehyde/mmol of deoxyribose released by 75 μM test compound (controls < 0.1, values are significantly different with respect to control; $P < 0.01$). [c] Inhibition of 5-HETE and LTB_4 biosynthesis in bovine PMNL. Inhibition was significantly different with respect to that of the control; $N = 3$ or more, $P < 0.01$. Standard errors average 10% of the indicated values. Nordihydroguaiaretic acid (NDGA) was used as the standard inhibitor for 5-LO (IC$_{50}$ = 0.4 μM). [d] Antiproliferative activity against HaCaT cells. Inhibition of cell growth was significantly different with respect to that of the control; $N = 3$, $P < 0.01$. [e] Activity of LDH release in HaCaT cells after treatment with 2 μM test compound ($N = 3$, SD < 10%). [f] Values are not significantly different with respect to vehicle control. ND = not determined.

derivatives **13a**,**b** (k_{DPPH} > 100 M^{-1} s^{-1}, data not shown), which showed increased reactivity as a result of their resonance-stabilized C-10 radicals. The reactivity of *N*-unsubstituted hydroxamic acid groups (type **c**) was up to 3-fold enhanced (k_{DPPH} = 34−66 M^{-1} s^{-1}, data not shown). However, *N*-methyl-substituted analogs (type **d**) were throughout highly reactive (k_{DPPH} > 100 M^{-1} s^{-1}, data not shown), reflecting potent antioxidant capability of the *N*-methyl hydroxamate group. These observations confirm the action of hydroxamates as radical scavengers,[17] probably by acting as reducing agents through their ability to donate hydrogen atoms or electrons.

Moreover, these compounds also protected against 2,2′-azobis(2-amidinopropane) hydrochloride (AAPH)-induced LPO in bovine brain phospholipid liposomes[6] and may thus be helpful in preventing tissue injury. In good agreement with the results of the DPPH test, *N*-methyl-substituted hydroxamates were the most active representatives of this series. For example, compound **6d** had an IC$_{50}$ of 11 μM in this model, whereas anthralin itself was not protective but rather stimulated LPO both in vivo and in model membranes.[7,14] Although much attention has been focused on the iron-catalyzed hydroxyl-radical generation as the important step for induction of LPO,[37] iron-catalyzed decomposition of lipid hydroperoxides may also be a driving force. In either case, a central role for iron in LPO cannot be questioned.[38] As LPO was induced by an azo initiator rather than by iron in our model, the inhibitory effect

of **6d** may be the result of its action as a hydrogen atom donor, consistent with its reactivity against DPPH.

Hydroxyl-Radical Generation. Further studies on the redox behavior of the novel series were performed using the deoxyribose assay.[6] The release of malondialdehyde (MDA) is indicative of hydroxyl-radical generation. Table 1 shows that with the exception of the carboxylic acid derivatives (type **a**), generation of hydroxyl radicals was substantially reduced with respect to anthralin. In most cases, the release of MDA decreased to about 50% of that induced by anthralin.

Antiproliferative Activity. The antiproliferative potential of this series was studied by evaluating the ability of the compounds to inhibit the proliferation of HaCaT cells, a rapidly multiplying human keratinocyte cell line. Proliferation of the keratinocytes was determined directly by counting the dispersed cells under a phase-contrast microscope after 48 h of treatment.

It is interesting to note that while the ester derivatives (type **b**) were not active as 5-LO inhibitors, they were active as inhibitors of cell growth. As both assays use intact cell systems, the lack of activity could not result from the inability of the compounds to cross the cellular membrane. By contrast, the corresponding acids showed activity in the 5-LO assay but did not exhibit antiproliferative activity.

The structure−activity relationship trend for the antiproliferative activity of hydroxamate analogs followed that seen with the 5-LO assay. Potency was significantly improved by methyl substitution on the hydroxamate nitrogen (type **d**). Inserting methylene groups between the anthracenone nucleus and the hydroxamate function (**4d**−**8d**) did not affect the potency to any great extent. On the other hand, branched chain alkyl spacers (**10d**, **11d**) were somewhat detrimental to potency.

LTB_4 can effect keratinocyte proliferation,[39,40] and cultured HaCaT keratinocytes express the 5-LO gene.[41] The keratinocyte 5-LO pathway may therefore play a primary role in skin biology. However, the negative results obtained with the ester analogs in the 5-LO assay suggest a different mode of action for the strong antiproliferative activity of compounds **4b** and **5b**.

Furthermore, the antiproliferative activity of 1,8-dihydroxy-9(10*H*)-anthracenones is clearly independent of their potency to generate hydroxyl radicals. Keratinocytes were also tested for their susceptibility for the action of the compounds on plasma membrane integrity. Cytotoxicity of the cell cultures was assessed by the activity of lactate dehydrogenase (LDH) released into the culture medium.[42] In contrast to anthralin, which showed a 2-fold increase in LDH activity as compared to controls, LDH release after treatment of HaCaT cells with the most potent inhibitors of cell growth did not exceed the control values. This further confirms that appropriate structural modification of anthralin leads to control of the release of oxygen radicals resulting in reduced oxidative damage to membrane without sacrifice of biological activity.

Conclusions

Being rich in polyunsaturated fatty acids, the skin is uniquely vulnerable to oxidative attack by oxygen radicals, and a central role of these species and iron in the pathogenesis of inflammatory skin disease has been reported.[43] Novel therapeutic strategies are based on their removal by chelation of iron before formation of the highly reactive hydroxyl radicals can occur.[43]

On the basis of this concept, a novel series of anthracenone derivatives with modulated redox properties has been synthesized, and a number were potent inhibitors of 5-LO and the growth of keratinocytes in cellular assays. Replacement of the carboxylic acid function with the iron-chelating hydroxamic acid provided compounds that had increased inhibitory activity against 5-LO and retained activity against the growth of keratinocytes. *N*-Methylation appeared important for both 5-LO inhibition and antiproliferative activity and also supplied antioxidant potential.

Compounds **5d**−**8d** demonstrate that an antiproliferative anthracenone pharmacophore can be modified such that it contains both antiproliferative activity and potency against the 5-LO enzyme combined with reduced toxicity.

Table 2. Chemical Data of 9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracenecarboxylic and -hydroxamic Acids

compd	log *P*[a]	formula[b]	mp (°C)	yield (%)	solvent[c]
4a	3.10 (3.51)	$C_{16}H_{12}O_5$	220[d,e]	82	MC/M (9/1)
5a	3.78 (3.97)	$C_{17}H_{14}O_5$	220[d,e]	71	MC/M (9/1)
6a	3.91 (4.51)	$C_{18}H_{16}O_5$	201[f]	84	A
7a	4.22 (5.05)	$C_{19}H_{18}O_5$	181	81	A
8a	4.60 (5.59)	$C_{20}H_{20}O_5$	169	79	A
9a	3.40 (3.92)	$C_{17}H_{14}O_5$	231[g]	81	A
10a	3.90 (4.87)	$C_{19}H_{18}O_5$	224[g]	79	A
11a	4.11 (5.34)	$C_{23}H_{18}O_5$	218[g]	72	A
12a	4.33 (5.88)	$C_{24}H_{20}O_5$	134[g]	80	A
13a	4.10	$C_{22}H_{16}O_5$	245[d,h]	69	MC/E (7/3)
14a	(5.10)	$C_{22}H_{14}O_6$	240[d]	83	A
4b	3.93 (3.93)	$C_{17}H_{14}O_5$	119	79	MC/M (9/1)
5b	4.55 (4.36)	$C_{18}H_{16}O_5$	101	76	MC/M (9/1)
6b	4.63 (4.90)	$C_{19}H_{18}O_5$	123	89	MC
7b	4.97 (5.44)	$C_{20}H_{20}O_5$	90	86	MC
8b	5.34 (5.98)	$C_{21}H_{22}O_5$	102	81	MC
9b	4.16 (4.34)	$C_{18}H_{16}O_5$	143	71	MC
10b	4.77 (5.29)	$C_{20}H_{20}O_5$	173	72	MC
11b	4.86 (5.89)	$C_{24}H_{20}O_5$	178	80	MC
12b	5.17 (6.43)	$C_{25}H_{22}O_5$	112	71	MC
13b	5.34	$C_{23}H_{18}O_5$	181−182[h]	78	MC/H (4/1)
14b	5.22 (5.35)	$C_{23}H_{16}O_6$	199	76	MC
4c	(2.40)	$C_{16}H_{13}NO_5$	200[d]	29	MC/M (9/1)
5c	(2.75)	$C_{17}H_{15}NO_5$	164[d]	21	MC/M (9/1)
6c	(3.29)	$C_{18}H_{17}NO_5$	156[d]	29	MC/M (9/1)
7c	(3.83)	$C_{19}H_{19}NO_5$	149[d]	21	MC/M (9/1)
9c	(2.81)	$C_{17}H_{15}NO_5$[i]	190[d]	19	MC/M (9/1)
10c	(3.76)	$C_{19}H_{19}NO_5$	176[d]	17	MC/M (9/1)
11c	(4.23)	$C_{23}H_{19}NO_5$	168[d]	23	MC/M (9/1)
13c	(4.57)	$C_{22}H_{17}NO_5$[j]	180[d]	28	MC/M (9/1)
4d	(2.64)	$C_{17}H_{15}NO_5$	174[d]	39	MC/M (95/5)
5d	(2.99)	$C_{18}H_{17}NO_5$	188[d]	31	MC/M (95/5)
6d	(3.53)	$C_{19}H_{19}NO_5$	165[d]	36	MC/M (95/5)
7d	(4.07)	$C_{20}H_{21}NO_5$	132[d]	30	MC/M (95/5)
8d	(4.61)	$C_{21}H_{23}NO_5$	142[d]	43	MC/M (95/5)
9d	(3.05)	$C_{18}H_{17}NO_5$	179[d]	34	MC/M (95/5)
10d	(4.00)	$C_{20}H_{21}NO_5$	156[d]	34	MC/M (95/5)
11d	(4.47)	$C_{24}H_{21}NO_5$	153[d]	15	MC/M (95/5)
13d	(4.81)	$C_{23}H_{19}NO_5$	136[d]	39	MC/M (95/5)
14d	(3.73)	$C_{23}H_{17}NO_6$	138[d]	36	MC/M (95/5)

[a] Experimentally determined partition coefficients; values in parentheses are calculated.[48] [b] All new compounds displayed ^1H NMR, FTIR, UV, and MS spectra consistent with the assigned structure. Elemental analyses were within ±0.4% of calculated values. [c] A = acetic acid; E = ether; H = hexane; M = methanol; MC = methylene chloride. [d] Decomposition. [e] Literature[30] value. [f] Literature[49] mp 187−192 °C. [g] Literature[28] value. [h] Literature[31] value. [i] C: calcd, 65.17; found, 64.53. [j] C: calcd, 70.39; found, 68.84.

Experimental Section

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Chromatography refers to column chromatography on silica gel (E. Merck, 70−230 mesh); eluants are given in Table 2. ^{1}H NMR spectra were recorded with a Varian EM 390 (90 MHz) or a Bruker Spectrospin WM 250 (250 MHz) spectrometer, using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on a Nicolet 510M FTIR spectrometer. UV spectra were recorded on a Kontron 810 spectrometer. Mass spectra (EI, unless otherwise stated) were obtained on a Varian MAT CH5 spectrometer (70 eV). HPLC (Kontron 420, 735 LC UV detector) was performed on a 250- × 4-mm column (4- × 4-mm precolumn) packed with LiChrospher 100 RP18 (5-μm particles; Merck, Darmstadt, Germany). Data were recorded on a MacLab data acquisition system (WissTech, Germany), and analysis was performed with the software Peaks on an Apple Macintosh computer.

Compounds **4a** and **5a**,[30] **9a**−**12a**,[28] and **13a**[31] were prepared as described.

General Procedure for the Reduction of 9,10-Anthracenediones to 9(10*H*)-Anthracenones.[44] 4-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)butanoic Acid (6a). To a suspension of **20** (0.30 g, 0.88 mmol) in HOAc (15 mL) heated to reflux was added, dropwise over 30 min, a solution of $SnCl_2$ (2.0 g, 8.86 mmol) in 37% HCl (10 mL). The solution was refluxed for 6 h and then cooled, and the resulting crystals were collected by filtration. Recrystallization from HOAc provided a pale yellow powder (Table 2): FTIR 1694 (COOH), 1623 cm^{-1} (CO); ^{1}H NMR (90 MHz, DMSO-d_6) δ 12.38 (s, 1H), 12.00 (s, 1H), 7.63−6.77 (m, 5H), 4.32 (s, 2H), 2.70−2.42 (m, 2H), 2.33−2.12 (m, 2H), 2.02−1.67 (m, 2H). Anal. ($C_{18}H_{16}O_5$) C, H.

Analogously, compounds **7a** and **8a** were prepared by reduction of the anthracenones **21** and **23**, respectively (Table 2).

4-[(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracenyl)-carbonyl]benzoic Acid (14a). A suspension of **33** (0.20 g, 0.52 mmol) in water (15 mL), 96% H_2SO_4 (10 mL), and HOAc (10 mL) was refluxed for 3 days (TLC control). Then the mixture was cooled to room temperature, treated with water (10 mL), and allowed to stand overnight. The violet precipitate was filtered by suction, washed with water, and dried (Table 2): FTIR 1694 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.62 (s, 1H), 11.89 (s, 1H), 8.11−6.89 (m, 9H), 4.59 (s, 2H). Anal. ($C_{22}H_{14}O_6$) C, H.

General Procedure for the Preparation of 2-Substituted 1,8-Dihydroxy-9(10*H*)-anthracenone Methyl Carboxylates. Methyl 4-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)butanoate (6b). A solution of **6a** (0.5 g, 1.60 mmol) in absolute methanol (50 mL) and 96% H_2SO_4 (0.2 mL) was refluxed for 6 h (TLC control). The solution was then cooled to room temperature, treated with water (50 mL), and extracted with CH_2Cl_2. The organic phase was washed with water and dried over Na_2SO_4, and the solution was evaporated. The residue was purified by chromatography, and the product was treated with a small amount of hexane or petroleum ether (40−60) to induce precipitation of a pale yellow powder (Table 2): FTIR 1725 (CO_2Me), 1631 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$) δ 12.60 (s, 1H), 12.32 (s, 1H), 7.57−6.73 (m, 5H), 4.27 (s, 2H), 3.65 (s, 3H), 2.80−2.60 (m, 2H), 2.48−2.27 (m, 2H), 2.15−1.85 (m, 2H). Anal. ($C_{19}H_{18}O_5$) C, H.

Analogously, compounds **4b**, **5b**, and **7b**−**14b** were prepared from **4a**, **5a**, and **7a**−**14a**, respectively (Table 2).

General Procedure for the Preparation of 2-Substituted 1,8-Dihydroxy-9(10*H*)-anthracenone Hydroxamic Acids. *N*-Hydroxy-4-(9,10-dihydro-1,8-dihydroxy-9-oxo-2-anthracene)butanamide (6c). To a solution of Na (2.07 g, 90 mmol) in absolute methanol (40 mL) was added a solution of hydroxylamine-HCl (4.17 g, 60 mmol) in methanol (40 mL) at 0−5 °C, after which the mixture was suction filtered. The filtrate was added dropwise to a suspension of **6b** (0.30 g, 0.92 mmol) in absolute methanol (15 mL) at 0−5 °C under N_2. The clear, yellow-orange solution was stirred until the reaction was completed (TLC control). The solution was then neutralized with 2 N HCl (pH control), and the resulting precipitate was suction filtered, washed with water, and dried. The crude product was purified by flash chromatography to afford a yellow powder (Table 2): FTIR 1623 cm^{-1} (CO); ^{1}H NMR (90 MHz, DMSO-d_6) δ 12.47 (s, 1H), 12.10 (s, 1H), 10.47 (s, 1H), 8.73 (s, 1H), 7.70−6.80 (m, 5H), 4.37 (s, 2H), 2.70−2.43 (m, 4H), 2.17−1.67 (m, 2H). Anal. ($C_{18}H_{17}NO_5$) C, H, N.

Analogously, compounds **4c**, **5c**, **7c**, **9c**−**11c**, **13c**, and **14c** were prepared from **4b**, **5b**, **7b**, **9b**−**11b**, **13b**, and **14b**, respectively (Table 2).

***N*-Hydroxy-*N*-methyl-4-(9,10-dihydro-1,8-dihydroxy-9-oxo-2-anthracene)butanamide (6d).** According to the method described above, **6b** (0.30 g, 0.92 mmol) was treated with *N*-methylhydroxylamine-HCl (5.01 g, 60 mmol). The mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the organic phase was washed with cold water (3 × 50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography, and the product was treated with a small amount of petroleum ether (40−60) at 0 °C to induce precipitation of yellow crystals (Table 2): FTIR 1619 cm^{-1} (CO); ^{1}H NMR (90 MHz, DMSO-d_6) δ 12.50 (s, 1H), 12.13 (s, 1H), 9.77 (s, 1H), 7.70−6.80 (m, 5H), 4.37 (s, 2H), 3.10 (s, 3H), 2.73−2.30 (m, 4H), 2.00−1.70 (m, 2H). Anal. ($C_{19}H_{19}NO_5$) C, H, N.

Analogously, compounds **4d**, **5d**, **7d**−**11d**, **13d**, and **14d** were prepared from **4b**, **5b**, **7b**−**11b**, **13b**, and **14b**, respectively (Table 2).

1-Hydroxy-8-methoxy-4-[1-(4-methoxybutyl)]-9,10-anthracenedione (16). To a solution of NaOH (12.0 g, 0.30 mol) in water (600 mL) was added **15**[28] (10 g, 39.5 mmol), and the solution was stirred for 15 min at 40 °C. A solution of $Na_2S_2O_4$ (12 g, 68.9 mmol) in water (50 mL) was added under N_2. The solution was stirred and heated to 70 °C for 15 min. 4-Methoxybutyraldehyde[45] (10 g, 98.0 mmol) was added dropwise, and the temperature was raised to 90 °C. The reaction mixture was stirred for 12 h under N_2, then cooled to room temperature, and aerated for 45 min. Water was added (500 mL); the mixture was acidified by 2 N HCl until it turned orange and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phase was washed with water (4 × 400 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue purified by chromatography using CH_2Cl_2/methanol (99−1) to provide orange crystals (5.3 g, 40%): mp 139 °C; FTIR 1671 (CO), 1634 cm^{-1} (CO···HO); ^{1}H NMR (90 MHz, $CDCl_3$) δ 13.43 (s, 1H), 8.07−7.27 (m, 5H), 4.08 (s, 3H), 3.53−3.25 (m, 2H), 3.32 (s, 3H), 2.88−2.65 (m, 2H), 1.85−1.57 (m, 4H). Anal. ($C_{20}H_{20}O_5$) C, H.

2-[1-(4-Bromobutyl)]-1,8-dihydroxy-9,10-anthracenedione (17). A suspension of **16** (5.00 g, 14.69 mmol) in glacial acetic acid (100 mL) was heated to reflux. To the resulting solution was added dropwise 62% HBr (50 mL), and the solution was refluxed for 3 h. The solution was then cooled to room temperature, and water (50 mL) was added. After 30 min the precipitate was filtered by suction and washed with water (4 × 50 mL). The residue was dried under vacuum at 50 °C and purified by chromatography to afford orange-yellow crystals (4.7 g, 85%): mp 125 °C dec; FTIR 1669, 1621 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 12.40 (s, 1H), 12.02 (s, 1H), 7.85−7.17 (m, 5H), 3.28 (t, J = 6 Hz, 2H), 2.73 (t, J = 6 Hz, 2H), 2.05−1.75 (m, 4H). Anal. ($C_{18}H_{15}BrO_4$) C, H.

4-(9,10-Dihydro-1,8-dihydroxy-9,10-dioxo-2-anthracene)-butan-1-ol (18). 17 (4.50 g, 11.99 mmol) was suspended in a solution of 15% water in HMPA (50 mL), and the temperature was slowly raised to 130 °C. The mixture was stirred at 130 °C for 6 h (TLC control), then cooled to room temperature, poured into water (1 L), and extracted with ether (3 × 200 mL). The combined organic phase was washed with water (3 × 400 mL), dried over Na_2SO_4, evaporated, and purified by chromatography using ether to give orange crystals (3.0 g, 81%): mp 149 °C; FTIR 3330, 1669, 1619 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 11.57 (s, 2H), 7.80−7.17 (m, 5H), 4.40 (s, 1H), 3.57−3.35 (m, 2H), 2.70−2.42 (m, 2H), 1.77−1.32 (m, 4H). Anal. ($C_{18}H_{16}O_5$) C, H.

4-(9,10-Dihydro-1,8-dihydroxy-9,10-dioxo-2-anthracene)-butanoic Acid (19). A solution of **18** (2.0 g, 6.40 mmol) in dry DMF (25 mL) and PDC (9.64 g, 25.61 mmol) was stirred at room temperature for 6 h. The solution was poured into

water (500 mL), and the product was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phase was washed with water (4 × 200 mL), dried over Na_2SO_4, and evaporated. The resulting residue (60 mL) was treated with a small amount of petroleum ether (40−60), shaken thoroughly, and allowed to stand at 0 °C. The precipitate was filtered by suction, and the crude product was used in the subsequent esterification step.

Methyl 4-(9,10-Dihydro-1,8-dihydroxy-9,10-dioxo-2-anthracene)butanoate (20). A suspension of **19** in methanol (500 mL) and 96% H_2SO_4 (5 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature, kept at 0 °C for 2 h, then filtered by suction, washed with precooled methanol (100 mL), and dried under vacuum. The residue was purified by chromatography to give orange crystals (1.3 g, overall 59%): mp 139 °C; FTIR 1742, 1661, 1619 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 12.38 (s, 1H), 12.00 (s, 1H), 7.85−7.17 (m, 5H), 3.68 (s, 3H), 2.75 (m, 2H), 2.13−1.85 (m, 2H), 1.73−1.47 (m, 2H). Anal. ($C_{19}H_{16}O_6$) C, H.

5-(9,10-Dihydro-1,8-dihydroxy-9,10-dioxo-2-anthracene)-valeronitrile (21). NaCN (1.10 g, 22.5 mmol) was suspended in dry DMSO (40 mL) and heated to 90 °C (oil bath). The oil bath was removed, and to the resulting solution was added slowly a solution of **17** (1.69 g, 4.50 mmol) in DMSO (15 mL). The solution was stirred until the reaction was completed (TLC control). The solution was poured into water (500 mL), and the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, and evaporated. The resulting residue was purified by chromatography to give orange crystals (0.9 g, 62%): mp 175 °C; FTIR 2244 (CN), 1667 (CO), 1621 cm^{-1} (CO···OH); ^1H NMR (90 MHz, $CDCl_3$) δ 12.43 (s, 1H), 12.02 (s, 1H), 7.87−7.18 (m, 5H), 2.78 (m, 2H), 2.42 (m, 2H), 1.93−1.70 (m, 4H). Anal. ($C_{19}H_{15}NO_4$) C, H, N.

Methyl 4-Oxobutanoate. To a suspension of PCC (30.0 g, 139.2 mmol) in dry CH_2Cl_2 (200 mL) was added in one portion methyl 4-hydroxybutanoate[46] (11.8 g, 100 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 3 h. Then the product was extracted with ether (4 × 200 mL), thoroughly shaken, and filtered through a short column (SiO_2, ether), and the solvent was removed *in vacuo*. The crude product was used in the subsequent step: ^1H NMR (90 MHz, $CDCl_3$) δ 9.92 (s, 1H), 3.67 (s, 3H), 2.90−2.03 (m, 4H).

Methyl 6-Oxohexanoate.[47] ϵ-Caprolactone (11.4 g, 100 mmol) in absolute methanol (200 mL) and concentrated H_2SO_4 (0.5 mL) was heated to reflux for 12 h. The mixture was then cooled in an ice bath, and anhydrous $NaHCO_3$ (1.5) was added. The mixture was stirred for 20 min, and the solvent was removed *in vacuo*. The product was oxidized directly with PCC (30.0 g, 139.2 mmol) as described above without purification.

Methyl 4-(9,10-Dihydro-9,10-dioxo-1-hydroxy-8-methoxy-2-anthracene)butanoate (22). This compound was prepared from **15**[28] and methyl 4-oxobutanoate according to the method described for **16**. The crude acid was used in the subsequent esterification step, which was performed as described for **6b** to afford orange crystals (0.67 g, overall 12%): mp 144 °C; FTIR 1733, 1671, 1634 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 13.32 (s, 1H), 8.05−7.23 (m, 5H), 4.05 (s, 3H), 3.67 (s, 3H), 2.77 (m, 2H), 2.38 (m, 2H), 2.18−1.87 (m, 2H). Anal. ($C_{20}H_{18}O_6$) C, H.

Methyl 6-(9,10-Dihydro-9,10-dioxo-1-hydroxy-8-methoxy-2-anthracene)hexanoate (23). This compound was prepared from **15**[28] and methyl 6-oxohexanoate according to the method described for **16**. The crude acid was used in the subsequent esterification step, which was performed as described for **6b** to afford orange crystals (2.3 g, overall 31%): mp 104 °C; FTIR 1731, 1665, 1631 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 13.43 (s, 1H), 8.17−7.28 (m, 5H), 4.12 (s, 3H), 4.03 (s, 3H), 2.91−2.65 (m, 2H), 2.52−2.23 (m, 2H), 1.90−1.40 (m, 6H). Anal. ($C_{22}H_{22}O_6$) C, H.

Anthracenedione precursors **24**−**30** were prepared as described.[28]

4-[(9,10-Dihydro-9,10-dioxo-1-hydroxy-8-methoxy-2-anthracenyl)hydroxymethyl]benzonitrile (31). To a solution of NaOH (12 g, 0.30 mol) in methanol (600 mL) was added **15**[28] (10 g, 39.5 mmol), and the solution was stirred at room temperature for 10 min. A solution of $Na_2S_2O_4$ (12 g, 68.9 mmol) in water (50 mL) was added under N_2, and the solution turned yellow-brown. The solution was then cooled to 0−5 °C and stirred for 30 min. 4-Cyanobenzaldehyde (12 g, 91.51 mmol) in THF (50 mL) was added dropwise, and the reaction mixture was allowed to stir at 0−5 °C for 12 h under nitrogen. The mixture was aerated for 45 min, poured into water (500 mL), and acidified by 2 N HCl until it turned orange. The product was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phase was washed with water (3 × 500 mL), dried over Na_2SO_4, and evaporated. The resulting residue was purified by chromatography using CH_2Cl_2/methanol (99−1) to give orange crystals (5.6 g, 37%): mp 223 °C; FTIR 3489, 2229, 1669, 1623 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.03−7.43 (m, 9H), 6.33 (m, 1H), 6.17 (m, 1H), 3.92 (s, 3H). Anal. ($C_{23}H_{15}NO_5$) C, H, N.

4-[(9,10-Dihydro-9,10-dioxo-1-hydroxy-8-methoxy-2-anthracenyl)carbonyl]benzonitrile (32). A solution of **31** (2.00 g, 5.19 mmol) in dry DMF (25 mL) and PDC (7.81 g, 20.76 mmol) was stirred at room temperature for 1 h. The mixture was poured into water (500 mL), and the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with water (4 × 200 mL), dried over Na_2SO_4, and evaporated. The resulting residue was purified by chromatography using CH_2Cl_2/methanol (99−1) to give orange crystals (1.7 g, 86%): mp 218 °C dec; FTIR 2232, 1671, 1631 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 13.38 (s, 1H), 8.02−7.26 (m, 9H), 4.08 (s, 3H). Anal. ($C_{23}H_{13}NO_5$) C, H, N.

4-[(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracenyl)-carbonyl]benzonitrile (33). According to the method described for **6a**, **32** (0.30 g, 0.78 mmol) was reduced to yield a violet powder (0.26 g, 83%): mp 230 °C dec; FTIR 2231, 1665, 1615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 12.91 (s, 1H), 11.98 (s, 1H), 7.95−6.93 (m, 9H), 4.45 (s, 2H). Anal. ($C_{22}H_{13}NO_4$) C, H, N.

Biological Assay Methods. Determination of the reducing activity against 2,2-diphenyl-1-picrylhydrazyl,[6] degradation of 2-deoxy-*d*-ribose,[6] inhibition of lipid peroxidation,[31] bovine PMNL 5-LO assay,[6] HaCaT keratinocyte proliferation assay,[31] and LDH release[1] were described previously in full detail.

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