Anthralin Derivatives - Inhibition of 5-Lipoxygenase - Antipsoriatic Efficacy

Helene Tanzer, Christine Braun, Matthias Seidel, and Wolfgang Wiegrebe*, **, ***

Institute of Pharmacy, University, P.O.Box 397, D-8400 Regensburg, Germany

Received August 10, 1990

Inhibition of 5-lipoxygenase by anthralin (**1**) and 41 derivatives is determined: the acids **38** and **39**, the lactones **40-42** and 9-anthrone (**8**) are the most potent inhibitors, the lactone **41** reaching the efficacy of nordihydroguaiaretic acid (NDGA). The results were correlated with the hydrophilic/lipophilic balance of the test compounds and their clinical efficacy as far as known. There is no correlation between the "minimum structure" of *Krebs* and *Schaltegger*[7] concerning antipsoriatic activity and the inhibitory effects against 5-lipoxygenase.

Dithranol-Derivate: Hemmung der 5-Lipoxygenase und antipsoriatische Wirksamkeit

Die Hemmung der 5-Lipoxygenase durch Dithranol (**1**) und 41 Derivate wird bestimmt: die Säuren **38** und **39**, die Laktone **40-42** und 9-Anthron (**8**) sind die stärksten Inhibitoren, das Lakton **41** erreicht die Wirksamkeit der Nordihydroguajaretsäure. Die Ergebnisse werden mit den hydrophilen/lipophilen Eigenschaften der Verbindungen und - soweit bekannt - mit deren klinischer Wirksamkeit in Beziehung gesetzt: es besteht keine Korrelation zwischen der sog. "antipsoriatischen Minimalstruktur" nach *Krebs* und *Schaltegger*[7] und der Hemmwirkung auf die 5-Lipoxygenase.

Psoriasis is a common chronic inflammatory and proliferative skin disease with unknown aetiology. An important feature is the abnormal metabolism of arachidonic acid, particularly by the lipoxygenase pathways. Lesional skin contains increased concentrations of arachidonic acid, 12-HETE and LTB_4, whereas the cyclooxygenase-products $PGF_{2\alpha}$ and PGE_2 are only modestly elevated[1]. LTB_4 and 12-HETE are potent chemoattractans for human polymorphonuclear leukocytes (PMNs)[2], which are part of a characteristic inflammatory infiltrate and were suggested to play an important physiologic role in cutaneous lesion of psoriasis[3].

Anthralin (dithranol), an effective topical antipsoriatic remedy, inhibits the 5- and 12-lipoxygenase pathways of arachidonic acid metabolism *in vitro* and various functional responses of human neutrophils[4,5,6]. Whether these properties are relevant to the clinical efficacy of the drug has not yet been established.

In the present study structure-activity relationships concerning the *in vitro* 5-lipoxygenase inhibitory activity of various anthrone derivatives and related compounds were investigated. The results were compared with the antipsoriatic properties of the compounds according to the "minimum structure" concept by *Krebs* and *Schaltegger*[7].

Materials and Methods

Calcium ionophore A 23187, arachidonic acid (99% pure), nordihydroguaiaretic acid and Histo Paque 1077: Sigma Chemie, München; Standard LTB_4, 5-HETE, 5S, 12S-diHETE, and PGB_2: Paesel GmbH, Frankfurt.

The test compounds were purchased or synthesized by described procedures (*vide infra*) or by reduction of the corresponding anthraquinones according to *Auterhoff*[8], purification by column chromatography on silica gel or crystallization. Analytical data are in accord with those described.

Anthralin[8] (**1**); 1-acetoxy-9-anthrone[9] (**2**); 1,8-diacetoxy-9-anthrone[10] (**3**); 1-hydroxy-8-methoxy-9-anthrone[11] (**4**); 1,8-dimethoxy-9-anthrone[11] (**5**); 1-amino-9-anthrone[12] (**6**) from 1-amino-anthraquinone (Aldrich); 1-hydroxy-9-anthrone[13] (**7**); 9-anthrone (**8**) (Janssen); 1,8-dichloro-9-anthrone[14] (**9**); benzophenone (**10**) (Merck); 2,2'-dihydroxybenzophenone (**11**) (EGA-Chemie); (9,10-dihydro-1,8-dihydroxy-9-oxo-anthracen-2-yl)-acetic acid[15] (**12**); 3-(9,10-dihydro-1,8-dihydroxy-9-oxo-anthracen-2-yl)-propionic acid[15] (**13**); 2,7-bis-(carboxymethyl)-1,8-dihydroxy-9(10*H*)-anthracenone[15] (**14**); 1,8-dihydroxy-2-methoxycarbonylmethyl-9(10*H*)-anthracenone[16] (**15**); 1,8-dihydroxy-2-methoxycarbonylethyl-9(10*H*)-anthracenone[16] (**16**); aloeemodin-anthrone[17] (**17**); crysarobin[18] (**18**) from crysophanic acid (Aldrich); danthrone (**19**) (Aldrich); 1,8-dimethoxy-anthraquinone[19] (**20**); 9,10-anthraquinone (**21**) (Aldrich); 1,5-dihydroxy-9-anthraquinone (**22**) (Aldrich); 1,8,9-triacetoxyanthracene[9] (**23**); 1,8,9-trimethoxyanthracene[10] (**24**); 1,5-dihydroxy-9-anthrone[20] (**25**) from **22**; bianthrone[8] (1,8,1',8'-tetrahydroxybianthron) (**26**); 1,8,10-trihydroxy-9-anthrone[21] (**27**); 9,10-dihydroanthracene (**28**) (Aldrich); 10-bromo-1,8-dihydroxy-9(10*H*)-anthracenone[9] (**29**); 1,8-dihydroxy-10-ethyl-9(10*H*)-anthracenone[22] (**30**); 1,8-dihydroxy-10,10-dipropyl-9(10*H*)-anthracenone[10] (**31**); 10-acetyl-1,8-dihydroxy-9(10*H*)-anthracenone[21] (**32**); 1,8-dihydroxy-10-(1'-oxobutyl)-9(10*H*)-anthracenone[23] (**33**); 1,8-dihydroxy-10-(3'-methoxycarbonyl-1'-oxopropyl)-9(10*H*)-anthracenone[15] (**34**); 1,8-dihydroxy-10-(4'-methoxycarbonyl-1'-oxobutyl)-9(10*H*)-anthracenone[15] (**35**); 1,8-dihydroxy-10-(3'-benzyloxycarbonyl-1'-oxopropyl)-9(10*H*)-anthracenone[24] (**36**); 4-(9,10-dihydro-1,8-dihydroxy-9-oxo-anthracen-10-yl)-4-oxobutyric acid[24] (**37**); 5-(9,10-dihydro-1,8-dihydroxy-9-oxo-anthracen-10-yl)-5-oxopentylic acid[24] (**38**); 6-(9,10-dihydro-1,8-dihydroxy-9-oxo-anthracen-10-yl)-6-oxohexylic acid[24] (**39**); 1,8-dihydroxy-10-(dihydro-5'-oxo-2'(3'*H*)-furanyliden)-9(10*H*)-anthracenone[15] (**40**); 1,8-dihydroxy-10-(tetrahydro-6'-oxo-2'*H*-pyran-2'-yliden)-9(10*H*)-anthracenone, analogously to[24] (**41**); 1,8-dihydroxy-10-(7'-oxo-oxepan-2'-yliden)-9(10*H*)-anthracenone[24] (**42**). Test compounds were dissolved in DMSO (p.a.) immediately before use.

Partition coefficients were determined by a HPLC method[25,26,27]. Stationary phase: Nucleosil 100 C18 7-µM; mobile phase: methanol/water/acetic acid (77:23:0.1 by vol., pH 5.5); flow rate: 1 ml/min; standards: benzoic acid, benzophenone, naphthalene, anthracene, 1,8-diacetoxy-9-anthrone. Results were calculated by means of 3 independent experiments.

** Dedicated with warm regards to Prof. Dr. *J. Knabe*, Saarbrücken, on the occasion of his 70th birthday.

*** Part of a lecture, Pharmazeutische Gesellschaft Brandenburg, DDR, Berlin, July 13, 1989; Pharmazie *45*, 298 (1990).

  0365-6233/91/1111-0841 $ 3.50 + .25/0

Cell Preparation

Bovine polymorphonuclear leukocytes were isolated as described by *Walstra* et al.[28a]. Na_2-EDTA (0.077 M, 0.1 l per l blood) was used instead of trisodium citrate as anticoagulating agent and at the end of the procedure contaminating platelets were removed by repeated centrifugations at 100 x g for 20 min[28b].

Incubation procedures

Polymorphonuclear leukocytes were suspended in phosphate-buffered saline, pH 7.4, at a final concentration of 1 x 10^7 cells/ml. 2.4 ml of this suspension were preincubated with the anthracene-derivatives by adding 10 µl of a DMSO stock solution and shaking in a water bath at 37°C for15 min. Control samples contained DMSO alone. Thereafter $CaCl_2$ (2 mM) as well as Ca^{2+} ionophore A 23187 (20 µM) were added. Incubation was carried out for 5 min at 37°C and stopped by addition of a mixture of acetonitril and methanol (1:1) containing 60 ng prostaglandin B_2 (PGB_2) (internal standard) and NDGA (24 µM) as radical scavenger. The samples were cooled in an ice bath for 20 min and centrifuged at 4000 x g for 15 min. After centrifugation the supernatants were collected and stored at -20°C until they were analyzed by reversed-phase-HPLC.

Reversed-Phase High-Performance Liquid Chromatography[28]

The cell supernatant was applied to an octadecyl (C_{18}) (250 x 4 mm) reversed-phase extraction column, which had previously been washed with methanol and water according to the manufacturer's instructions. After applying the supernatant to the column and washing with water (10 ml) the adsorbed leukotrienes were eluted with 3 ml methanol. Recovery for all leukotrienes was found to be better than 80%. After addition of 3 ml water to the methanolic solutions of leukotrienes aliquots of 2 ml were directly subjected to reversed-phase-HPLC.

High-performance liquid chromatography was performed with a 250 x 4 mm Nucleosil 100 C_{18} 7-µM column, attached to a Kontron 420 pump and a Kontron Uvikon 735 LC UV detector.

Isocratic elution was carried out with tetrahydrofuran/methanol/water/acetic acid (25:30:45:0.1 by vol.) which had been brought to pH 5.5 with ammonia[28]. A flow rate of 0.9 ml/min was used and the detection was at 270 nm. 5-HETE was detected at 232 nm with methanol/water/acetic acid (77:23:0.1 by vol., pH 5.5) and a flow rate of 1 ml/min.

Peak areas were integrated with a Merck-Hitachi D-2000 integrator by relation to external standards of authentic samples. The recovery of the internal standard PGB_2 was used to correct for losses during sample preparation. Molar absorption coefficients (M^{-1} cm^{-1}) of 28,650 for PGB_2 and 50,000 for LTB_4 at 270 nm and 29,500 for 5-HETE at 232 nm were used[6].

Statistics

The test compounds were studied for their influence on the LTB_4- or 5-HETE production of bovine polymorphonuclear leukocytes. Product formation in the treatment groups (N = 2, range < 10%) was compared to the mean level in the control group (N = 6-8; SD < 5%). Results are expressed as percent inhibition.

Results

In Fig. 1 a typical reversed-phase HPLC-chromatogram of the leukotrienes formed by bovine polymorphonuclear leukocytes is shown.

The LTB_4-peak is well separated from the two all-*trans*-leukotriene B_4 isomers 6-*trans*-leukotriene B_4 and 12-*epi*-6-*trans*-leukotriene B_4 and the interaction product 5(*S*),12(*S*)-diHETE. The small concentration of 5(*S*),12(*S*)-diHETE demonstrates a negligible platelet contamination of the PMN preparations. In contrast to the human polymorphonu-

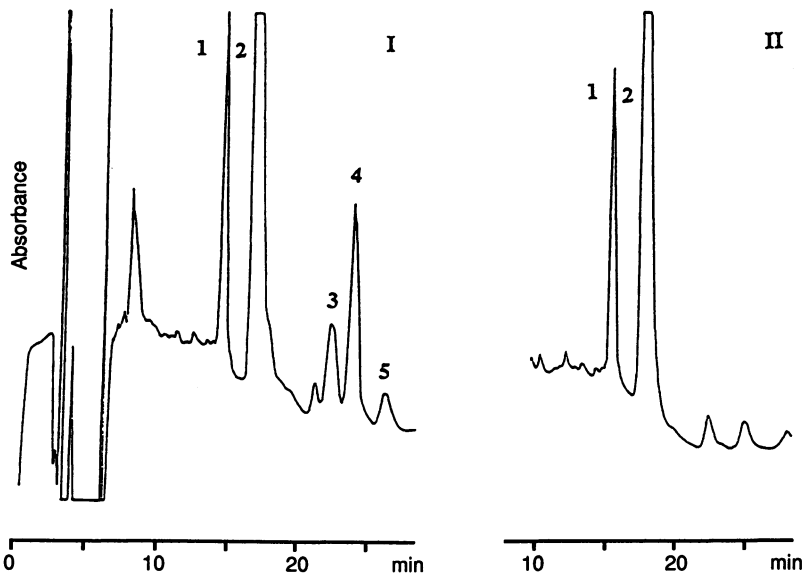


Figure 1: Reversed phase HPLC chromatograms of arachidonic acidmetabolites produced by calcium ionophore A 23187 (20 µM)-stimulated bovine neutrophils (10^7 cells/ml) in the absence (I) and presence (II) of 100 µM anthralin. Solvent system: tetrahydrofuran/methanol/water/acetic acid (25:30:45:0.1 by vol.). pH 5.5. Flow rate 0.9 ml/min with detection at 270 nm. Peak identification: 1: PGB_2 (internal standard); 2: NDGA (radical scavenger); 3: 6-trans-leukotriene B_4 and 12-epi-6-trans-leukotriene B_4; 4: LTB_4; 5: 12-epi-6-trans-8-cis-leukotriene B_4 (5(s),12(s)-diHETE).

clear leukocytes bovine leukocytes are unable to metabolize LTB_4 into 20-hydroxy-LTB_4[28].

Pretreatment of neutrophils with anthralin (100 µM) and subsequent activation of PMN-5-LO by Ca-ionophore results in nearly complete absence of the 5-LO products LTB_4 (Fig. 1) and 5-HETE (not shown).

A dose response study for anthralin (**1**) (Fig. 2) revealed an inhibition within a narrow concentration range of 20-40 µM and a similar IC_{50} for LTB_4 as well as for 5-HETE was obtained.

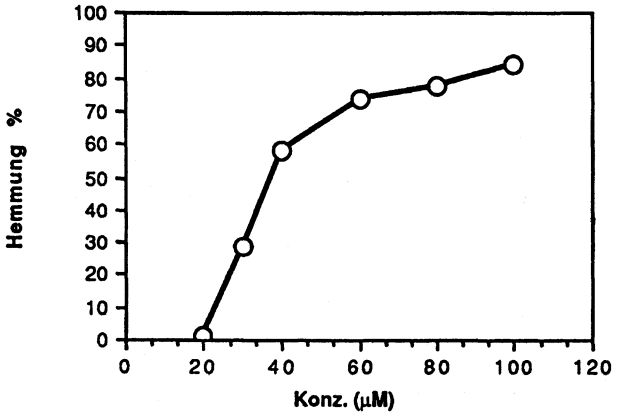
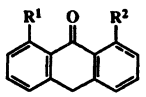
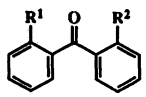


Figure 2: Dose-dependent inhibition of ionophore-stimulated LT production of bovine PMN leukozytes by anthralin. The values represent the average of two determinations (range < 10%).

Table 1: Inhibition of 5-LO by anthrones and benzophenones

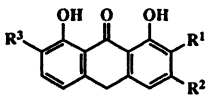
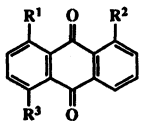
compound	R^1	R^2	inhibition % conc. (µM) 10	30	log P
					
1	OH	OH	0	29	4.23
1*	OH	OH	0	33	
2	OH	$OCOCH_3$	0	83	3.25
3	$OCOCH_3$	$OCOCH_3$	30	100	2.40
4	OH	OCH_3	0	20	3.44
5	OCH_3	OCH_3	91	100	3.12
6	H	NH_2	-	41	2.45
7	H	OH	39	100	3.99
8	H	H	100	100	3.46
9	Cl	Cl	100	100	3.51
					
10	H	H	-	29	3.18
11	OH	OH	-	0	3.00

Inhibition of LTB_4 - resp. 5-HETE*-synthesis. The values represent the average of two determinations (range < 10%). - "-": not tested

Tables 1-4 show the effects of several anthralin derivatives and related compounds on the production of 5-LO-products.

Table 1 summarizes the inhibitory potencies of several analogues of anthrone (**8**) as well as of benzophenone (**10**). Derivatization and substitution of the phenol groups improved the inhibitory efficacy nearly 10-fold as compared with anthralin. A net lipophilicity range from log P = 3-3.5 seems to be favorable for optimal activity. The activity of benzophenone is comparable to that of anthralin (**1**).

Table 2: Inhibition of 5-LO by anthralin derivatives and anthraquinones

compound	R^1	R^2	R^3	inhibition % conc. (µM) 10	30	log P
						
12	CH_2COOH	H	H	27	100	3.10
13	$(CH_2)_2COOH$	H	H	0	65	3.78
14	CH_2COOH	H	CH_2COOH	-	0	-
15*	CH_2COOCH_3	H	H	0	40	3.93
16	$(CH_2)_2COOCH_3$	H	H	13	48	4.55
17*	H	CH_2OH	H	0	53	3.25
18	H	CH_3	H	-	0	4.69
						
19	OH	OH	H	-	0	4.16
20	OCH_3	OCH_3	H	-	0	3.04
21	H	H	H	-	0	3.70
22	H	OH	OH	-	0	4.10

Inhibition of LTB_4 - resp. 5-HETE*-synthesis. The values represent the average of two determinations (range < 10%). - "-": not tested

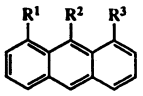
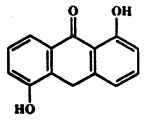
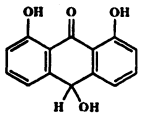
As seen in Table 2 an overall trend of lower activity for dithranol derivatives with side chains at C-2 (C-7) is evident, despite a favorable log P for some compounds. Anthraquinones are generally not effective. This holds true also for the antipsoriatically active chrysarobin (**18**).

The data from Table 3 reveal a modest inhibitory activity also for trimethoxyanthracene (**24**) and 1,5-dihydroxy-9-anthrone (**25**), whereas the dithranol metabolite bianthrone is inactive.

As seen in Table 4 the 10-(ω-carboxyacyl)dithranol derivatives **38** and **39** show an inhibitory efficacy comparable to that of the anthrones **5**, **8**, and **9**. In contrast acid **37** is only a weak inhibitor possibly due to the low log P value of the compound. C-10-substituted derivatives without an acyl-side chain (**29-31**) possess only marginal activity as well as the antipsoriatic active butantrone (**33**). Esterification of the ω-carboxyl groups results in a decrease of activity. Derivatives bearing lacton ring structures at C-10 (**40-42**) show an inhibitory potential, which surmounts that of all other compounds tested so far (Tables 4 and 5. This holds true also for their inhibitory potential against the 12-lipoxygenase from bovine thrombocytes[29].

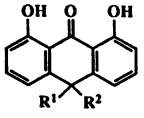
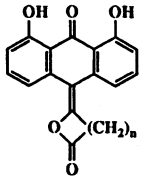
Table 5 summarizes the inhibitory potencies of some selected compounds at lower concentrations.

Table 3: Inhibition of 5-LO by anthrone and anthracene derivatives

compound	R^1	R^2	R^3	inhibition % conc.(μM) 10	30	log P
						
23	$OCOCH_3$	$OCOCH_3$	$OCOCH_3$	-	15	2.02
24*	OCH_3	OCH_3	OCH_3	51	78	4.10
						
25	1,5-Dihydroxy-9-anthrone			46	100	3.51
26	Bianthrone			-	0	5.01
						
27	1,8,10-Trihydroxy-9-anthrone			-	0	2.91
28	9,10-Dihydro-anthracene			-	17	4.06

Inhibition of LTB_4 - resp. 5-HETE*-synthesis. The values represent the average of two determinations (range < 10%). - "-": not tested

Table 4: Influence of C-10-substituted anthralin derivatives on the LTB_4 production by PMN leukozytes

compound	R^1	R^2	inhibition % conc. (μM) 10	30	log P
					
29	H	Br	-	0	3.94
30	H	C_2H_5	-	31	4.37
31	C_3H_7	C_3H_7	-	17	5.19
32*	H	$COCH_3$	0	100	3.49
33	H	COC_3H_7	-	38	4.12
34	H	$CO(CH_2)_2COOCH_3$	0	100	3.34
35	H	$CO(CH_2)_3COOCH_3$	10	100	3.59
36	H	$CO(CH_2)_2COOBz$	31	100	4.23
37	H	$CO(CH_2)_2COOH$	0	52	2.74
38	H	$CO(CH_2)_3COOH$	97	100	2.94
39	H	$CO(CH_2)_4COOH$	100	100	3.14
					
40	n = 2		100	100	3.71
41	n = 3		100	100	3.85
42	n = 4		100	100	3.93

Inhibition of LTB_4 - resp. 5-HETE*-synthesis. The values represent the average of two determinations (range < 10%). - "-": not tested

Table 5: Inhibition of 5-LO by anthrones

compound	inhibition % 5 μM	3 μM	1 μM
38	25	-	0
39	36	-	0
40	83	47	-
41	100	91	42
42	98	95	15
8	-	84	-
9	-	40	-

Inhibition of LTB_4 - resp. 5-HETE*-synthesis. The values represent the average of two determinations (range < 10%). - "-": not tested

The stronger efficacy of the 10-acyldithranol derivatives as compared to anthralin (**1**) indicates that these substances can not be prodrugs of **1** but are effective by themselves (cf. also its inhibitory effects against glucose-6-phosphate-dehydrogenase[24]). These results are supported by experiments concerning the metabolism of these substances by mouse skin homogenates. Skin homogenates of NMRI-mice (approx. 35 g) were prepared as described[30], but instead of barbital buffer tris buffer (0.1 M, pH 7.4) was used. Aliquots taken from the incubation mixture of mouse skin homogenate and test compounds were HPLC-analyzed as described[24]. Anthralin (**1**) was never detected as a metabolite indicating that the 10-acyl linkage was not split enzymatically. In the ester derivatives **34** and **35** the ester group was hydrolyzed affording the corresponding acids **37** and **38**[29], but the phenylogous β-dicarbonyl system remained unaffected.

Table 6: Effect of substrate concentration on the inhibition of 5-HETE production by neutrophils (10^7/ml)[a]

	Percent inhibition of 5-HETE production exogenic arachidonic acid (μM) 0	1	3	10	40	80
anthralin (1) (50 μM)	92	-	-	88	74	80
anthrone (8) (10 μM)	100	-	-	89	76	76
Acid 12 (20 μM)	100	82	51	0	23	33
Ester 34 (30 μM)	100	-	100	98	94	88
Lacton 40 (8 μM)	100	-	100	98	84	50
Acid 39 (8 μM)	100	-	95	82	28	0

[a] Results represent the average of two determinations, range < 10%. - "-": not tested

Effect of different substrate concentrations on the inhibition of leukotriene production

For several anthrone derivatives the effect of increasing arachidonic acid concentrations on the inhibition of 5-HETE production is shown in Table 6.

For anthralin (**1**), anthrone (**8**), ester **34**, and lacton **40** 5-HETE production increases only slightly at high arachidonic acid concentrations. In contrast, inhibition by acids **12** and **39** depends strongly on exogenic substrate concentration and in the case of **39** is totally absent at higher arachidonic acid concentrations.

Discussion

In our study we investigated the inhibition of 5-LO from bovine polymorphonuclear leukocytes, because they constitute an easily available and inexpensive cellular source for this enzyme[28]. Anthralin (**1**) showed 50% inhibition at 37 µM which is comparable to the IC_{50} found by *Schröder* with human PMN and was shown to depend strongly upon cell density (7-74 µM!)[6]. 12-HETE production by mouse epidermal homogenates and human platelets is also inhibited by anthralin[4] and it was suggested that the drug exerts its action by modulation of arachidonic acid metabolism.

In 1969 *Krebs* and *Schaltegger*[7] claimed 1-hydroxy-9-anthrone (**7**) as the minimum basic structure for *clinical* antipsoriatic activity. Our results show remarkable differences between this "minimum structure" concept and the *in vitro* activity of the anthrones in the 5-lipoxygenase test.

Nonphenolic anthrones with no antipsoriatic activity proved to be up to 10-fold more active than anthralin; lipophilic parameters may be responsible for this fact, since the 5-lipoxygenase associates with leukocyte membranes in the active state[31]. However, the results are in contrast to general findings with other substance classes, where replacement of the phenolic functions leads to a decrease of inhibitory efficacy[32,33]. The inhibition is only slightly influenced by increasing substrate concentrations, which indicate a mainly "non-competitive"*) way of action. For anthralin derivatives with side chains at C-2 (C-7) there might exist a steric hindrance for binding at the active site of the enzyme according to the binding hypothesis of *Summers*[34]. This fact may explain their general low activity (Table 2) as well as the strong influence of exogenic substrate concentrations on the inhibition of 5-HETE production by **12** (Table 6).

The inhibitory efficacy of non-phenolic anthrones is partly exceeded by that of some 10-ω-carboxyacyl-anthralin derivatives as well as derivatives bearing lactone ring structures at the C-10-position. Comparable to compound **12**, their activity seems to depend on the exogenic substrate concentration and suggests a "competitive"*) binding to the active site of the 5-lipoxygenase. Interestingly this is not the case for ester **34** (Table 6). Recently we have found the lactones **40-42** to be able to inhibit several cell growth parameters in cultured human keratinocytes comparable with the effects of anthralin[35]. Their clinical efficacy has not yet been established on account of legal restrictions.

Some clinical inactive benzophenone and anthracene derivatives are also capable of inhibiting the 5-lipoxygenase enzyme, the efficacy of benzophenone (**10**) might be due to radical scavenging properties.

Known antipsoriatic agents on the other hand like anthralin (**1**) and butantrone (**33**) were only weak inhibitors of the leukotriene production and chrysarobin (**18**) was not effective at all at the concentrations tested.

Our data suggest that anthralin (**1**) does not exert its antipsoriatic activity through inhibition of leukotriene production from polymorphonuclear leukocytes. This view is corroborated by the fact that during treatment with dithranol neither 12-HETE nor LTB_4 concentrations were significantly affected in lesional psoriatic skin[36]. Consequently the suitability of the lipoxygenase assay as an antipsoriatic screening system is disputable.

It should, however, be kept in mind that anthralin (**1**) also influences other functional parameters in human neutrophils[5].

In cultured human keratinocytes the manifestation of the biologic responses under treatment with anthralin (**1**) occurred after a latency phase of some h, which preceded an intracellular distribution process with accumulation in the mitochondria[37].

Thus the exposure time to the cells may be crucial for the detection of biologic effects. Nevertheless, our finding that nonphenolic anthrones and some C-10-acyl derivatives possess a strong lipoxygenase inhibiting potential, is an unexpected result. Their antiphlogistic potential needs further evaluation.

References

1 S. Hammarström, M. Hamberg, B. Samuelsson, E.A. Duell, M. Stawiski, and J.J. Voorhees, Proc. Natl. Acad. Sci. USA *72*, 5130 (1975).
2 F.M. Cunningham, M.W. Graeves, and P.M. Woollard, Br. J. Dermatol. *87*, 107 (1986).
3 P.R. Bergstresser in: Psoriasis, (H.H. Roenigk and H.I. Maibach, eds.), p. 203, Marcel Dekker, New York 1985.
4 C.J. Bedord, J.M. Young, and B.M. Wagner, J. Invest. Dermatol. *81*, 566 (1983).
5 J.M. Schröder, U. Kosfeld, and E. Christophers, J. Invest. Dermatol. *85*, 30 (1985).
6 J.M. Schröder, J. Invest. Dermatol. *86*, 331 (1986).
7 A. Krebs and H. Schaltegger, Hautarzt *20*, 204 (1969).
8 H. Auterhoff and F.C. Scherff, Arch. Pharm. (Weinheim) *293*, 918 (1960).
9 O.E. Schultz and H.H. Schultze-Mosgau, Arch. Pharm. (Weinheim) *298*, 273 (1965).
10 W. Wiegrebe, A. Gerber, J. Kappler, and C. Bayerl, Arzneim. Forsch. *29*, 1083 (1979).
11 G.F. Attree and A.G. Perkin, J. Chem. Soc. (London) *1931*, 144.
12 W. Bradley and R.F. Maisey, J. Chem. Soc. *1954*, 274.
13 A. Steyermark and J.H. Gardiner, J. Am. Chem. Soc. *52*, 4887 (1930).
14 H.O. House, J.L. Haack, N.J. Ghali, and D. VanDerveer, J. Org. Chem. *45*, 1812 (1980).
15 H. Tanzer, M. Seidel, and W. Wiegrebe, Arch. Pharm. (Weinheim) *321*, 447 (1988).
16 M. Seidel, PhD-thesis, Regensburg 1990.
17 H. Böhme and J. Bertram, Arch. Pharm. (Weinheim) *288*, 510 (1955).
18 R. Eder, Arch. Pharm. *253*, 1 (1915).
19 H. Brockmann, R. Neef, and E. Mühlmann, Chem. Ber. *83*, 467 (1950).
20 B. Pleus, Ber. Dtsch. Chem. Ges. *35*, 2923 (1902).
21 B.L. Van Duuren, A. Segal, S.S. Tseng, G.M. Rusch, G. Loewengart, U. Maté, D. Roth, S. Melchionne, and I. Seidman, J. Med. Chem. *21*, 26 (1978).
22 A. Schaltegger and W. Steiger, Arch. Pharm. (Weinheim) *319*, 575 (1986).
23 K.K. Mustakallio, A.K. Pippuri, and E.J. Honkanen, Patent Nr. 57743, Int. Cl C 07 C 49/747. Finnish Patent Office 1980; C.A. *93*, P 204348z (1980).
24 H. Tanzer, M. Seidel, and W. Wiegrebe, Arch. Pharm. (Weinheim) *322*, 441 (1989).

*) Here the term "(non)-competitive" is not used in the strict meaning of *Michaelis-Menten* kinetics.

25 H. Terada, Quant. Struct.-Act. Relat. *5*, 81 (1986).
26 S.H. Unger, J.R. Cook, and J.S. Hollenberg, J. Pharm. Sci. *67*, 1364 (1964).
27 A.C. De Kock and D.A. Lord, Chemosphere *16*, 133 (1987).
28a P. Walstra, J. Verhagen, G.A. Veldink, and J.F.G. Vliegenthart, Biochimica Biophysica Acta *795*, 499 (1984).
28b M. Lehr and G. Dannhardt, J. Pharm. Pharmacol., in press.
29 H. Tanzer, PhD-thesis, Regensburg 1990.
20 W. Wiegrebe, A. Retzow, E. Plumier, N. Ersoy, A. Garbe, H.-P. Faro, and R. Kunert, Arzneim. Forsch. *34*, 48 (1984).
31 B. Samuelsson, C.A. Rouzer, and T. Matsumoto, Adv. Prostaglandin, Thromboxane, Leukotriene Res. *17*, 1 (1987).
32 T. Yoshimoto, M. Furukawa, S. Yamamoto, T. Horie, and S. Watanabe-Kohno, Biochem. Biophys. Res. Comm. *116*, 612 (1983).
33 D.G. Batt, G.D. Maynard, J.J. Petraitis, J.E. Shaw, W. Galbraith, and R.R. Harris, J. Med. Chem. *33*, 360 (1990).
34 J.B. Summers, H. Mazdiyasni, J.H. Holms, J.D. Ratajczyk, R.D. Dyer, and G.W. Carter, J. Med. Chem. *30*, 574 (1987).
35 B. Bonnekoh, H. Tanzer, M. Seidel, J. Geisel, H.F. Merk, G. Mahrle, and W. Wiegrebe, Arch. Pharm. (Weinheim) *324*, 899 (1991).
36 R.M. Barr, E. Wong, F.M. Cunningham, A.I. Mallet, and M.W. Graeves, Arch. Dermatol. Res. *280*, 474 (1989).
37 U. Reichert, Y. Jacques, M. Grangeret, and R. Schmidt, J. Invest. Dermatol. *84*, 130 (1985). [Ph859]