(6,7-Diaryldihydropyrrolizin-5-yl)acetic Acids, a Novel Class of Potent Dual Inhibitors of Both Cyclooxygenase and 5-Lipoxygenase

Stefan A. Laufer,*,† Jan Augustin,† Gerd Dannhardt,‡ and Werner Kiefer‡

Merckle GmbH, P.O. 1161, 89135 Blaubeuren, Germany, and Institute of Pharmacy, University of Mainz, 55099 Mainz, Germany

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A novel class of nonantioxidant dual inhibitors of both CO and 5-LO is described. The balance between the activity against CO and 5-LO can be shifted by modifying the substitution pattern of the phenyl moiety at the 6-position of the pyrrolizine ring. Structure–activity relationships are discussed. Compound **3e** with a 4-Cl substituent (IC_{50} = 0.21 μM (CO); 0.18 μM (5-LO)) and **3n** with a 4-OCH_3 substituent (IC_{50} = 0.1 μM (CO); 0.24 μM (5-LO)) are the most potent and well-balanced dual inhibitors of both enzymes. The inhibition of CO was determined in a bovine thrombocyte intact cell assay and that of 5-LO using intact bovine PMNL. Compound **3e** was also investigated in human cells.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are the main therapeutic agents for the treatment of the symptoms of arthritis. The common mechanism of action of this broad class of drugs is believed to be the inhibition of the enzyme cyclooxygenase and consecutively the conversion of the arachidonic acid into prostaglandins.[1] The clinical signs are reduction of pain and swelling associated with arthritis. The major drawbacks of these NSAIDs are severe mechanism-based side effects including gastrointestinal ulceration and bronchospasm.[2]

Prostaglandins have been proved to be cytoprotective and antisecretory;[3] thus a decrease of these mediators by inhibition of cyclooxygenase disturbs this cytoprotective mechanism. Another hypothesis focuses on the so-called shunt to the leucotrienes, metabolites of arachidonic acid formed by the 5-lipoxygenase enzyme. Inhibiting cyclooxygenase may increase the metabolism of arachidonic acid via the leucotriene pathway.[4]

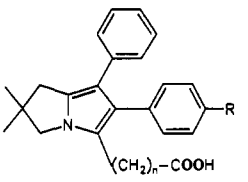
The peptidoleucotrienes LTC_4, $-D_4$, and $-E_4$ are potent bronchoconstrictors,[5] and LTB_4 has been reported to possibly play an important pathophysiological role in the development of gastrointestinal ulceration.[6] By inhibiting both cyclooxygenase and 5-lipoxygenase it should be possible to develop compounds with improved efficacy and reduced side effects when compared to selective cyclooxygenase inhibitors.[7] In recent times effort has been made to clarify this hypothesis.

One approach is to incorporate 5-lipoxygenase-inhibiting activity into the pharmacophore by conversion of various nonsteroidal antiinflammatory drugs to their corresponding hydroxamic acid.[8] Other approaches focus on di-*tert*-butylphenol derivatives[9] as dual inhibitors of both cyclooxygenase and 5-lipoxygenase.

This report concerns pyrrolizine derivatives with inhibitory activity against cyclooxygenase and 5-lipoxygenase with no antioxidant as with the di-*tert*-butylphenols and no iron-chelating properties as in hydroxamic acids.

The pyrrolizine derivatives **3a** and **4** (Scheme 1) selectively inhibit the enzymes cyclooxygenase and 5-lipoxygenase.[10] Starting with these compounds, the aim was to develop a potent and well-balanced dual inhibitor. As **3a** and **4** differ only in the chain length of the carboxylic acid residue at the 5-position of the pyrrolizine ring system and the para substituent of the 6-phenyl moiety, it seemed logical to exchange these substituents.

Scheme 1



	n	R	IC_{50} [μM] CO	5-LO
3a	1	H	0.1	4
4	2	O-Ph	5.5	1
3b	1	O-Ph	2	1.6
5	2	H	0.3	4.2

The first results were discouraging: **5** remained a selective cyclooxygenase-inhibitor and **3b** became only a weak dual inhibitor.

Quantitative structure–activity relationship studies are reported for a different series of 5-lipoxygenase inhibitors, and from these it is evident that there is a strong positive correlation between lipophilicity and activity.[11] Summers et al.[12] have reported similar correlations for other classes of 5-lipoxygenase inhibitors in a cell-free assay, so they cannot be explained by the enrichment in the cell membrane alone, but also by lipophilic interactions at the binding position of the enzyme. This correlates with the finding that one of the key structural features of the active site of the 5-lipoxygenase is a hydrophobic domain (beneath a non-heme ferric ion and a carboxylic acid binding site).[13]

QSAR data are also available for cyclooxygenase inhibitors that demonstrate some relationship between lipophilicity and activity.[14] In contrast to 5-lipoxygenase, however, an optimum of lipophilicity was observed (compounds with lipophilicity values below or above this optimum lead to decreased activity). On the basis of these results, lead **3a** was modified to improve the inhibition of 5-lipoxygenase and to preserve the cyclooxygenase-inhibiting activity.

Chemistry

To ensure easy synthetic access, the substituent R^1 of the pyrrolizine ring was modified. The synthetic route is analogous to that of **3a**[10] and is outlined in Scheme 2. The Δ^1-pyrrolines were cyclized with the corresponding bro-

† Merckle GmbH.
‡ University of Mainz.
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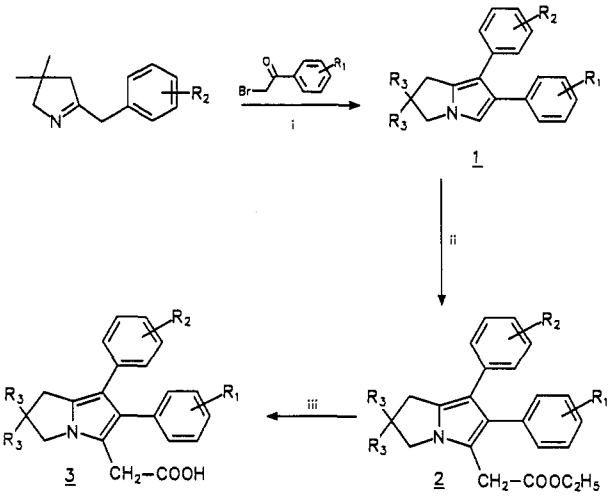
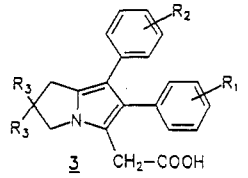
Scheme 2[a]



[a] Reagents: (i) EtOH/aqueous $NaHCO_3$, 36 h, room temperature 12–65%; (ii) $N_2CHCOOC_2H_5$, Cu^0, toluene, 110 °C, 1 h, 12–61%; (iii) EtOH, aqueous NaOH, 78 °C, 15 min, 5–84%.

Table 1. Inhibition of Cyclooxygenase and 5-Lipoxygenase by **3a–r**



				IC_{50}[a] (μM)	
no.	R_1	R_2	R_3	CO	5-LO
3a[10]	H	H	CH_3	0.1	4.0
3b	4-OC_6H_5	H	CH_3	2.0	1.6
3c	2-Cl	H	CH_3	61.0	4.4
3d	3-Cl	H	CH_3	3.6	1.7
3e[b]	4-Cl	H	CH_3	0.21	0.18
3f	2,4-Cl_2	H	CH_3	18.0	2.1
3g	3,4-Cl_2	H	CH_3	4.5	1.7
3h	2,5-Cl_2	H	CH_3	12.0	4.3
3i	2,3,4-Cl_3	H	CH_3	12	1.8
3j	4-t-C_4H_9	H	CH_3	20	0.18
3k	4-NO_2	H	CH_3	0.03	1.5
3l	4-NH_2	H	CH_3	1.0	6.0
3m	4-F	H	CH_3	3.2	>10.0
3n	4-OCH_3	H	CH_3	0.1	0.24
3o	H	4-Cl	CH_3	3.4	5.2
3p	4-Cl	H	H	2.0	1.6
3q	4-OH	H	CH_3	1.6	7.7
3r	4-NHCO-CH_3	H	CH_3	0.8	10.0

[a] CO: bovine thrombocyte intact cell assay. 5-LO: bovine PMNL cell assay. Experimental method, see ref 16; average of at least two determinations. [b] **3e** was tested in human cells, too: IC_{50} = 0.16 μM (CO); 0.23 μM (5-LO).

moacetophenones in ethanol/aqueous $NaHCO_3$ solution at room temperature for 36 h with moderate yields of the dihydropyrrolizines (**1**). Refluxing **1** with ethyl diazoacetate/Cu^0 in toluene led to acetic acid esters (**2**) which were cleaved with aqueous sodium hydroxide/ethanol to the corresponding free acids (**3**).

Results and Discussion

Table 1 summarizes the results. The aim to develop potent and well-balanced dual inhibitors of both 5-lipoxygenase and cyclooxygenase was achieved with two compounds (**3e**, **3n**). By substituting the 6-phenyl group of the dihydropyrrolizine, it is possible to direct the specificity for cyclooxygenase or 5-lipoxygenase, respectively.

Substituents with positive hydrophobicity constants (π values)[17] increase the inhibition of 5-lipoxygenase, but only if they are located at the para position of the 6-phenyl group. It is evident that the postulated hydrophobic domain[13] allows interactions only at this position. Sterical factors at the binding site of the enzyme may also be an explanation for these observations. 4-Cl (**3e**), 4-OCH_3 (**3n**), and 4-*tert*-butyl (**3j**) strongly increase the inhibition of 5-lipoxygenase; substituents with negative π values like 4-NH_2 (**3l**) modestly decrease it. The 4-F substituent (**3m**) does not fit into this explanation, possibly due to electronic parameters, e.g., high electron density.

Looking at the inhibition of cyclooxygenase, it is striking that the substituent position at the 6-phenyl residue is of marked importance. 4-Cl (**3e**) only weakly affects the activity compared to 4-H (**3a**). 3-Cl (**3d**) greatly reduces and 2-Cl (**3c**) leads to an almost complete loss of inhibition of cyclooxygenase. 4-OCH_3 (**3n**) is equipotent to the unsubstituted compound (**3a**). The improved activity of the 4-NO_2 substituent (**3k**) may be explained by its positive σ value and by its ability to form a complex bond to the iron at the active site of the enzyme. Bulky and hydrophobic substituents like 4-*tert*-butyl (**3j**) or 4-phenoxy (**3b**) greatly reduce the activity. As observed at the 5-lipoxygenase site, the 4-F substituent (**3m**) again forms an exception. By substituting the para position of the phenyl residue at C-7 with a chloro atom, the inhibition of cyclooxygenase and 5-lipoxygenase is reduced (**3o**).

Summarizing these data, it can be stated that less bulky hydrophobic substituents at para position of the 6-phenyl moiety increase the 5-lipoxygenase-inhibiting potency while retaining of the cyclooxygenase inhibition. The C-2 unsubstituted compound **3p** is very much less active than **3e** with a dimethyl substitution pattern.

Since iron chelating and antioxidant properties are missing, it is assumed that the compounds may be substrate analogues in a broad sense. On the basis of the hypothetical conformation of arachidonic acid at the active site of the 5-LO,[17] an alignment of **3e** and arachidonic acid was made. As the double bonds of the arachidonic acid were believed to be planar and to form a w-conformation, no attempt was made to define the conformation of the saturated parts. **3e** was superimposed as well as possible on the hypothetical enzyme bond conformation of arachidonic acid in the model of Summers,[18] whereby the following assumptions were made: (a) the carboxylic acid residue should be in the same area and (b) the two phenyl residues at **3e** should match the C=C double bonds of the arachidonic acid.

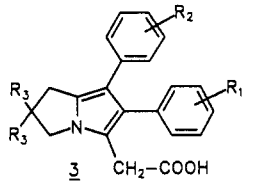
The best fit was obtained by superimposing the $\Delta^{5,6}$-bonds of the arachidonic acid and the 6-phenyl group of **3e** and $\Delta^{11,12}$ on the 7-phenyl group.

Only minor changes in geometries of arachidonic acid, described by Summers as "less certain geometries", were necessary to achieve this fit.

For cyclooxygenase, Gund and Shen[19] postulated a hypothetical enzyme bond conformation of arachidonic acid, which was slightly modified by Lopez[20] and Salvetti.[21] Fixing the carboxylic groups together, the 6-phenyl group of **3e** roughly matches the $\Delta^{8,9}$-bond and the 7-phenyl group matches the $\Delta^{14,15}$ of arachidonic acid.

It should be noted that these simple graphical alignments are not intended to be a sophisticated representation of the conformation at the active site, but make their mode of action as substrate analogues likely. For the cyclooxygenase/peroxidase enzyme, Jahnke et al.[22] reported a

Table 2



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no.	yield (%)	mp (°C)	formula	IR (cm^{-1})	^1H NMR δ (ppm)
a[10]	44.0	162.0	$C_{23}H_{23}NO_2$	3420, 1705, 1598	7.25–6.95 (m, 10H, ArH), 3.75 (s, 2H, H-3), 3.48 (s, 2H, CH_2-C-5), 2.83 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
b	42.0	159.4	$C_{29}H_{27}NO_3$	3435, 1711, 1483	7.34–6.91 (m, 14H, ArH), 3.75 (s, 2H, H-3), 3.62 (s, 2H, CH_2-C-5), 2.87 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
c	36.6	155.6	$C_{23}H_{22}ClNO_2$	3425, 1706, 1426	7.43–6.97 (m, 9H, ArH), 3.76 (d, J = 1.2, 2H, H-3), 3.49 (d, J = 1.2, CH_2-C-5), 2.91 (s, 2H, H-1), 1.31 (s, 6H, Me-C-2)
d	28.3	143.2	$C_{23}H_{22}ClNO_2$	3420, 1708, 1594	7.26–7.00 (m, 9H, ArH), 3.77 (s, 2H, H-3), 3.62 (s, 2H, CH_2-C-5), 2.87 (s, 2H, H-1), 1.31 (s, 6H, Me-C-2)
e	75.5	163.0	$C_{23}H_{22}ClNO_2$	3420, 1706, 1241	7.28–7.02 (m, 9H, ArH), 3.76 (s, 2H, H-3), 3.59 (s, 2H, CH_2-C-5), 2.86 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
f	55.8	143.5	$C_{23}H_{21}Cl_2NO_2$	3425, 1709, 1463	7.41–6.95 (m, 8H, ArH), 3.71 (s, 2H, H-3), 3.42 (s, 2H, CH_2-C-5), 2.87 (s, 2H, H-1), 1.27 (s, 6H, Me-C-2)
g	40.0	161.5	$C_{23}H_{21}Cl_2NO_2$	3445, 1706, 1464	7.34–7.02 (m, 8H, ArH), 3.75 (s, 2H, H-3), 3.59 (s, 2H, CH_2-C-5), 2.85 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
h	5.0	157.4	$C_{23}H_{21}Cl_2NO_2$	3435, 1707, 1415	7.35–6.97 (m, 8H, ArH), 3.76 (d, J = 2.9, 2H, H-3), 3.48 (d, J = 1.8, 2H, CH_2-C-2), 2.90 (d, J = 1.8, 2H, H-1), 1.30 (d, J = 3.9, 6H, Me-C-2)
i	84.0	181.5	$C_{23}H_{20}Cl_3NO_2$	3420, 1707, 1449	7.32–6.94 (m, 7H, ArH), 3.75 (d, J = 1.5, 2H, H-3), 3.48 (d, J = 2.5, 2H, CH_2-C-5), 2.89 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
j	58.8	167.4	$C_{27}H_{31}NO_2$	3420, 1700, 1339	7.35–6.95 (m, 9H, ArH), 3.73 (s, 2H, H-3), 3.58 (s, 2H, CH_2-C-5), 2.83 (s, 2H, H-1), 1.31 (s, 15H, t-But-Ar + Me-C-2)
k	60.7	173.4	$C_{23}H_{22}N_2O_4$	3445, 1701, 1335	8.17–8.03 (AA', 2H, ArH), 7.43–6.87 (BB'/m, 7H, ArH), 3.75 (s, 2H, H-3), 3.60 (s, 2H, CH_2-C-5), 2.83 (s, 2H, H-1), 1.32 (s, 6H, Me-C-2)
l	73.4	dec.	$C_{23}H_{24}N_2O_2$	3410, 1715, 1150	7.93 (br, 2H, NH_2), 7.26–7.13 (m, 9H, ArH), 3.75 (s, 2H, H-3), 3.50 (s, 2H, CH_2-C-5), 2.85 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
m	57.0	155.0	$C_{23}H_{22}FNO_2$	3420, 1707, 1213	7.21–6.94 (m, 9H, ArH), 3.76 (s, 2H, H-3), 3.58 (s, 2H, CH_2-C-5), 2.87 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
n	11.0	137.1	$C_{24}H_{25}NO_3$	3440, 1703, 1243	7.00–6.50 (m, 9H, ArH), 3.67 (s, 3H, OCH_3), 3.60 (s, 2H, H-3), 3.47 (s, 2H, CH_2-C-5), 2.75 (s, 2H, H-1), 1.25 (s, 6H, Me-C-2)
o	16.0	158.9	$C_{23}H_{22}ClNO_2$	3405, 1675, 1270	7.33–6.95 (m, 9H, ArH), 3.75 (s, 2H, H-3), 3.61 (s, 2H, CH_2-C-5), 2.83 (s, 2H, H-1), 1.30 (s, 6H, Me-C-2)
p	50.0	170.0	$C_{21}H_{18}ClNO_2$	1708	7.30–7.03 (m, 9H, ArH), 4.03–3.97 (t, J = 7.0, 2H, H-3), 3.58 (s, 2H, CH_2-C-5), 3.07–3.00 (t, J = 7.0, 2H, H-1), 2.58–2.42 (m, 2H, H-2)
q	56.0	183 dec.	$C_{23}H_{23}NO_3$	3410, 1690, 1250	7.20–6.58 (m, 10H, ArH + OH), 3.60 (s, 2H, H-3), 3.50 (s, 2H, CH_2-C-5), 2.78 (s, 2H, H-1), 1.26 (s, 6H, Me-C-2)
r	52.0	163	$C_{25}H_{28}N_2O_3$	3420, 1700, 1680	7.68–6.98 (m, 10H, ArH + CONH-Ar), 3.75 (s, 2H, H-3), 3.48 (s, 2H, CH_2-C-5), 2.80 (s, 2H, H-1), 2.21 (s, 3H, CONH-CH_3), 1.29 (s, 6H, Me-C-2)

preliminary X-ray structure analysis of prostaglandin-H synthase with a resolution of about 8 Å; in the near future, more precise results should be available that make enzyme-based molecular modeling approaches possible. Preliminary studies are ongoing.

Experimental Section

Analytical TLC plates were purchased from Macherey + Nagel, Polygram Alox N/UV_{254} and Sil G/UV_{254}. NMR spectra were obtained at 200 MHz on a Bruker AC 200 in $CDCl_3$. Melting points were taken using a Mettler FP 5 apparatus and were uncorrected. Elemental analyses for C, H, and N were obtained from a Heraeus CHN-Rapid instrument. IR spectra were obtained using a Shimadzu IR-470.

Synthesis of 2,3-Dihydro-1*H*-pyrrolizines (1). General Procedure for the Preparation of 1a–q. To a well-stirred suspension of 0.5 mol of substituted ω-bromoacetophenone (substituents are given in Table 1 of the supplementary material, R[1]) in 1.4 L of diethyl ether was added the solution of 0.5 mol of 2-benzyl-4,4-dimethyl-Δ^1-pyrroline in 800 mL of dry ethanol. Under exclusion of moisture and protection from light, the slightly alkaline solution was stirred at room temperature for 24 h. After that time 0.35 L of saturated $NaHCO_3$ solution was added, and stirring was continued for 12 h. Workup was done by addition of water (2 L), separation, and repeated extraction of the aqueous layer with diethyl ether. After drying over Na_2SO_4 and evaporation of the solvent, the product was suspended in methanol (300 mL) and filtered off.

Varying from this general procedure substance **1o** was prepared with 0.5 mol of ω-bromoacetophenone and 0.5 mol of 2-(4-chlorobenzyl)-4,4-dimethyl-Δ^1-pyrroline, and substance **1p** was prepared with 0.5 mol of ω-bromo-4-chloroacetophenone and 0.5 mol of 2-benzyl-Δ^1-pyrroline.

Synthesis of Ethyl 2,3-Dihydro-1*H*-pyrrolizin-5-yl)acetate Derivatives (2). General Procedure for the Preparation of 2a–q. To the boiling solution of 0.66 mol of pyrrolizine in 50 mL of dry toluene, was added 0.2 mol of ethyl diazoacetate in small amounts (1–2 g), each addition followed by a small portion (0.2–0.3 g) of copper powder (total amount: 2.0 g = 0.03 mol). After addition was complete (after about 1 h), boiling was continued for a further 15 min. The mixture was allowed to cool down at room temperature, and the solution was evaporated under reduced pressure. Purification was carried out by column chromatography on silica gel (elution: *n*-hexane/CH_2Cl_2, 1:1).

Synthesis of (2,3-Dihydro-1*H*-pyrrolizin-5-yl)acetic Acid Derivatives (3). General Procedure for the Preparation of 3a–r. At a bath temperature of 80 °C, 15 mmol of ester was dissolved in 40 mL of ethanol. Sodium hydroxide solution (8 mL, 10% in water) was added, and the whole mixture was allowed

to boil for a further 10 min. After cooling down, the solution was acidified with phosphorous acid and extracted with diethyl ether/CH_2Cl_2, 3:1. Drying over Na_2SO_4 and evaporation of the solvent gave the crude product, which was washed with isopropyl ether and filtered off. **3r** was prepared from **3l** by acetylation with $(AcO_2)O$/pyridine according to ref 24.

Determination of CO and 5-LO Inhibition. Inhibition of CO and 5-LO was determined in thrombocyte (CO) or PMNL (5-LO) intact cell assay, isolated by a ficoll gradient centrifugation from fresh bovine or human blood. The cells were incubated with the compounds **3a–p** and stimulated with Ca-ionophore A 23187. 12-HHT, PGE_2, and LTB_4 were measured by a HPLC method. Statistical analysis (Student test) showed significant effects at >15% inhibition; IC_{50} values were determined graphically and are summarized in Table 1. For experimental details see ref 16.

Supplementary Material Available: Tables containing substituents, yields, melting points, formulas and IR and ^1H NMR spectral data for **1a–q** and **2a–q** and details of HPLC conditions (9 pages). Ordering information is given on any current masthead page.

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