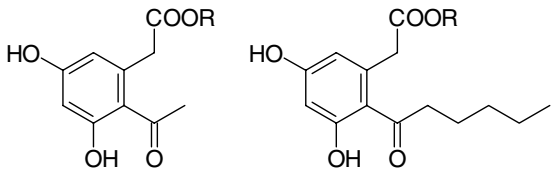
Department für Pharmazie – Zentrum für Pharmaforschung, University of Munich[1], and Institut für Pharmazie, University of Tübingen[2], Germany

Effects of natural products containing acylresorcinol partial structures on cyclooxygenases and 5-lipoxygenase

F. BRACHER[1], J. KRAUSS[1] and S. LAUFER[2]

Dedicated to Professor K. Görlitzer, Braunschweig, on the occasion of his 60th birthday

In the course of our ongoing studies on the chemistry and biological activities of polyketide-derived natural products [1–3] we recently described a convenient method for the preparation of the acylresorcinols curvulin (**1**) and curvulinic acid (**2**), both isolated from the fungus *Curvularia siddiqui* [4] and of secocurvularin (**3**), isolated from a fungus emerged from inside of the encrusting sponge *Spirastrella vagabunda* [5]. Moreover, we prepared the carboxylic acid **4**, derived from the ester **3** [6].



1 R = C_2H_5
2 R = H

3 R = C_2H_5
4 R = H

Products **1**–**4** contain structural elements of two different classes of compounds that inhibit enzymes of the arachidonate cascade, hence exhibiting antiphlogistic activities. On the one side, our compounds represent arylacetic acids (and esters thereof) with structural similarity to established nonsteroidal antiinflammatory drugs acting on cyclooxygenases, e.g. diclofenac. On the other side, **1**–**4** contain a resorcinol partial structure that is common to a number of substances with inhibitory effects on prostaglandin biosynthesis (e.g. resveratrol [7], des-*O*-methyllasiodiplodin [8]) and phospholipase A_2 [9].

This prompted us to investigate the effects of compounds **1**–**4** on enzymes involved in the arachidonate cascade, namely cyclooxygenase 1 (COX-1), cyclooxygenase 2 (COX-2), and 5-lipoxygenase (5-LOX). Screenings on COX-1 were performed in human platelets, those on 5-LOX in human PMNLs [10]. Screenings on COX-2 were done on human blood mononuclear cells as described earlier [11]. The results are presented in the Table.

Carboxylic acid **4** showed significant inhibition of COX-1, whereas curvulinic acid (**2**) and the esters **1** and **3** were inactive. The activity of **4** might be due to its arylacetic acid partial structure. COX-2 was not inhibited by any of the compounds. In the 5-LOX assay both arylacetic acids were inactive, but both esters showed inhibitory effects. The hexanoyl resorcinol secocurvularin (**3**) showed significantly higher inhibition than the acetyl resorcinol curvulin (**1**). So, a lipophilic side chain seems to favor 5-LOX inhibition by these esters. Comparing with 5-LOX-inhibitors in clinical trials, e.g. ZD-2138 [12], **3** is only a week inhibitor. But **3** and **4** can serve as leads for further modifications to obtain new inhibitors of 5-LOX and COX-1.

Table: Effects of compounds 1–4 on COX-1, COX-2 and 5-LOX

Compd.	IC_{50} (μM)		
	COX-1	COX-2	5-LOX
1	n.i.*	n.i.	8.5
2	n.i.	n.i.	n.i.
3	n.i.	n.i.	3.2
4	2.2	n.i.	n.i.
Diclofenac [11]	0.05	0.03	n.t.**
ML-3000 [10]	0.22	n.t.	0.37
ZD-2138 [12]	n.i.	n.i.	0.02
Celecoxib [13]	15	0.04	n.i.

* no inhibition; ** not tested

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Prof. Dr. Franz Bracher
Ludwig-Maximilians-Universität München
Department für Pharmazie
Zentrum für Pharmaforschung
Butenandtstr. 5–13
D-80333 Munich
Franz.Bracher@cup.uni-muenchen.de