Pharm. Pharmacol. Commun. 2000, 6: 217–221
Received November 2, 1999
Accepted November 8, 1999

Synthesis and Activity of Fluorinated Derivatives of Sulindac Sulphide and Sulindac Sulphone

MANFRED JUNG, ALAN F. WAHL*, WERNER NEUPERT†, GERD GEISSLINGER† AND PETER D. SENTER*

Westfälische Wilhelms-Universität Münster, Department of Pharmaceutical Chemistry, Hittorfstr. 58-62, D-48149 Münster, Germany; **Seattle Genetics, Inc., 22215 26th Avenue SE, Bothell, WA 98021, USA and* †*Zentrum der Pharmakologie, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, Germany*

Abstract

The synthesis of fluorinated derivatives of the sulphide and sulphone metabolites of sulindac, a non-steroidal anti-inflammatory agent with chemopreventative activity, is reported.

The key step in the synthesis is a Pummerer-rearrangement of the parent sulindac sulphoxide using (diethylamino)sulphur trifluoride as an activating agent and as a source of the fluoride nucleophile. The reaction leads to the formation of the 4-fluoromethylthio and 4-fluoromethylsulphonyl derivatives of sulindac (**4a** and **4b**, respectively). Sulindac sulphide is 2·5 times more potent as a COX-1 inhibitor compared with its fluorinated counterpart **4a**. The sulphones were inactive as COX-1 inhibitors, and none of the compounds inhibited COX-2 concentrations up to 0·1 mM. Cytotoxicity assays showed that **4a** and **4b** were as cytotoxic as sulindac sulphide and sulindac sulphone on 3719 colorectal carcinoma cell lines. Compound **4b** was the most potent compound on RCA cells with an IC50 of 95 μM (sulindac sulphide 140 μM, sulindac sulphone 175 μM).

Fluorinated sulindac derivatives warrant further investigation since we have shown that cytotoxic activity can be retained or even increased independently from COX-inhibitory properties. This could help minimize the undesired side-effects associated with chronic sulindac administration.

Inhibition of arachidonic acid pathways is one way to interfere with carcinogenesis. This has been studied extensively in numerous in-vitro and in-vivo models, and in the case of acetylsalicylic acid, activity has been documented in man (Kahn & Morrison 1997). One particularly interesting compound from the class of non-steroidal anti-inflammatory agents with respect to cancer prevention is sulindac (**1a**) (Kelloff et al 1985; Wattenberg 1997; Hakama 1998). This agent suppresses familial adenomatous polyposis (FAP), a premalignant disease that can lead to colon cancer (Giardiello et al 1993). The active form of sulindac in terms of anti-inflammatory activity is the sulphide **1b**, which is formed in the gastrointestinal tract. Sulphone **1c** accounts for a large percentage of the sulindac species in the blood (Duggan et al 1977; Elder & Paraskeva 1997). In contrast, **1b** is a cyclooxygenases (COX) inhibitor. Both agents are active in suppressing chemically induced rat mammary carcinogenesis (Thompson et al 1995). Recent studies suggest that COX inhibition is not necessary for the anticancer activity of sulindac. The mechanisms by which these agents exert anticancer activity are not well understood. Some of the suggested mechanisms include increased production of ceramide (Chan et al 1998), induction of apoptosis (Piazza et al 1995; Shiff et al 1995), PPAR-α and -γ agonistic activity (Lehmann et al 1997), suppression of PPAR-δ dependent processes (He et al 1999), alterations on mitochondrial membranes (Waddell 1998), inhibition of growth factor induced angiogenesis (Verheul et al 1999), and interaction with the ras/raf-pathway (Herrmann et al 1998).

As part of a programme for the development of new cancer chemoprevention drugs, we synthesized new derivatives and analogues of sulindac (**1a**). Since the total synthesis of **1a** is lengthy (Shuman et al 1977), we chose to modify the commercially available material, with a focus on alterations of the sulphoxide group. This molecular site apparently influences biological activity, given the differences

Correspondence: M. Jung, Westfälische Wilhelms-Universität Münster, Department of Pharmaceutical Chemistry, Hittorfstr. 58-62, D-48149 Münster, Germany.
E-Mail: jungm@uni-muenster.de

in activity between sulphide **1b** and sulphone **1c**. It was thought that slight modifications at the sulphoxide position would be synthetically practical and would lead to new molecules of biological interest.

The Pummerer rearrangement is a powerful tool for the modification of sulphoxide groups, leading to α-substituted sulphides that can subsequently be oxidized to form substituted sulphoxides and sulphones (De Lucchi et al 1991). We applied the Pummerer rearrangement reaction to **1a** using (diethylamino)sulphur trifluoride (DAST) (McCarthy et al 1985). This leads to the formation of α-fluoro-substituted sulphoxides that can be further modified to form substituted sulphides and sulphones. It has been previously shown that substitution of hydrogen by fluorine can influence the biological activity of drugs without affecting the overall molecular size (Welch & Eswarakrishnan 1991; Filler et al 1993). In this study we describe the synthesis and biological properties of α-fluoro-substituted derivatives of sulindac (**1a**).

Materials and Methods

Chemistry

Chloroform was dried using molecular sieves (3Å). Compound **1a** is commercially available from Sigma. Melting points are uncorrected. The following instruments were used: Perkin Elmer CHN-Analyser 240 for elemental analyses, Shimadzu 470 for infrared spectroscopy, Varian Gemini 200 (200 MHz) for ^{1}H NMR, Varian Gemini 200 (50·29 MHz) for ^{13}C NMR, Varian MAT 44S and Finnigan MAT 312 for mass spectrometry. Silica gel 60, 230–400 mesh (Merck), was used for flash chromatography.

*Methyl 5-fluoro-2-methyl-1-Z-(4-methylsulphinyl-benzylidene)-3-indenylacetate (**2**)*

Compound **1a** (5 g) was dissolved in 200 mL methanol and 1 mL concentrated H_2SO_4 was added. The mixture was heated to reflux for 6 h. After cooling to room temperature the mixture was evaporated and the resulting solid was recrystallized from CH_2Cl_2/hexane. The identity and purity of **2** as previously described by Jones (1975) was determined using IR, MS, ^{1}H and ^{13}C NMR.

*Methyl 5-fluoro-1-Z-(4-fluoromethylthio-benzylidene)-2-methyl-3-indenylacetate (**3a**)*

To a solution of **2** (1·85 g, 5 mmol) in 25 mL of $CHCl_3$ in an oven dried flask purged with N_2, DAST (1·32 mL, 1·61 g, 10 mmol) and $ZnBr_2$ (34 mg, 0·15 mmol) were added. After stirring at room temperature for 24 h, 20 mL 5 % aqueous $NaHCO_3$ was added. The organic phase was separated, dried over Na_2SO_4 and evaporated. The desired product (**3a**) was obtained as yellow crystals after flash chromatography (ethyl acetate/hexane 1 : 3) and recrystallization from hexane/CH_2Cl_2 (1·34 g, 72%): mp 102°C; ^{1}H NMR ($CDCl_3$): $\delta = 2{\cdot}18$ (s, 3H, 2-CH_3), 3·56 (s, 2H, CH_2COOR), 3·70 (s, 3H, OCH_3), 5·80 (d, $^{2}J_{H,F} = 52{\cdot}6$ Hz, CH_2F), 6·52 (ddd, $^{3}J = 9{\cdot}3$ Hz, $^{3}J = 9{\cdot}1$ Hz, $^{4}J_{H,H} = 2{\cdot}3$ Hz, 1H, 6-H), 6·88 (dd, $^{3}J_{H,F} = 8{\cdot}9$ Hz, $^{4}J_{H,H} = 2{\cdot}3$ Hz, 1H, 4-H), 7·13 (s, 1H, Ar−CH = C), 7·23–7·31 (m, 1H, 7-H), 7·47–7·55 (m, 4H, CH_3SOAr−H); ^{13}C NMR ($CDCl_3$): $\delta = 10{\cdot}54$ (2-CH_3), 31·58 (*CH_2*COO), 52·22 (OCH_3), 87·98 (d, $^{1}J_{H,F} = 216{\cdot}6$ Hz, CH_2F), 105·91 (d, $^{2}J_{C,F} = 23{\cdot}8$ Hz, C-4), 110·66 ($^{2}J_{C,F} = 22{\cdot}7$ Hz, C-6), 123·68 (d, $^{3}J_{C,F} = 9{\cdot}0$ Hz, C-7), 129·12 (Ar− *CH* = C), 129·66 (d, $^{4}J_{C,F} = 3{\cdot}1$ Hz, C-7a), 129·95 and 130·25 (C-2′/C-6′, C-3′/C-5′), 131·16 (C-3), 134·58 (C-2), 135·89 (C-1′), 138·32 (C-1), 140·80 (C-4′), 146·58 (d, $^{3}U_{C,F} = 9{\cdot}1$ Hz, C-3a), 163·24 (d, $^{1}J_{C,F} = 246{\cdot}1$ Hz, C−F), 170·80 (CO); MS: $m/z = 372$, [M^+], 233 (100); IR (KBr): $\nu = 1720$ (CO), 1590 (C = C) cm^{-1}; Anal. ($C_{21}H_{18}F_2O_2S$) 372·44; calc. C 67·72 H 4·88; found C 67·62 H 5·04.

*Methyl 5-fluoro-1-Z-(4-fluoromethylsulphonyl-benzylidene)-2-methyl-3-indenylacetate (**3b**)*

Compound **3a** (740 mg, 2 mmol) and meta-chlorobenzoic acid (MCPBA) (990 mg, 4 mmol) were dissolved in 10 mL THF and stirred for 3 h at room temperature. After evaporation, flash chromatography (ethyl acetate/hexane 2 : 3) and recrystallization (hexane/CH_2Cl_2), yellow crystals of **3b** were obtained (610 mg, 75%): mp 141°C; ^{1}H NMR ($CDCl_3$): $\delta = 2{\cdot}21$ (s, 3H, 2-CH_3), 3·57 (s, 2H, CH_2COOR), 3·72 (s, 3H, OCH_3), 5·21 (d, $^{2}J_{H,F} = 47{\cdot}1$ Hz, CH_2F), 6·58 (ddd, $^{3}J_{H,F} = 8{\cdot}9$ Hz, $^{3}J_{H,H} = 8{\cdot}5$ Hz, $^{4}J_{H,H} = 2{\cdot}4$ Hz, 1H, 6-H), 6·88 (dd, $^{3}J_{H,F} = 8{\cdot}9$ Hz, $^{4}J_{H,H} = 2{\cdot}4$ Hz, 1H, 4-H), 7·28 (dd, $^{3}J_{H,F} = 5{\cdot}1$ Hz, $^{3}J_{H,H} = 8{\cdot}5$ Hz, 1H, 7-H), 7·13 (s, 1H, Ar−CH = C), 7·72–8·05 (m, 4H, CH_3SOAr−H); ^{13}C NMR ($CDCl_3$): $\delta = 10{\cdot}46$ (2-CH_3), 31·61 (*CH_2*COO), 52·23 (OCH_3), 92·07 (d, $^{1}J_{H,F} = 220{\cdot}4$ Hz, CH_2F), 106·42 (d, $^{2}J_{C,F} = 24{\cdot}0$ Hz, C-4), 110·01 ($^{2}J_{C,F} = 22{\cdot}8$ Hz, C-6), 123·71 (d, $^{3}J_{C,F} = 9{\cdot}1$ Hz, C-7), 126·78 (Ar− CH = C), 129·23 (C-7a), 129·29 and 130·35 (C-2′/C-6′, C-3′/C-5′), 132·63 (C-3), 135·31 (C-2), 138·05 (C-1′), 142·77 (C-1), 143·83 (C-4′), 146·94 (d, $^{3}J_{C,F} = 9{\cdot}1$ Hz, C-3a), 163·64 (d, $^{1}J_{C,F} = 247{\cdot}4$ Hz, C−F), 170·49 (CO); MS (70 eV); m/z (%) = 404 [M^+], 233 (100 %); IR (KBr): $\nu = 1720$ (CO), 1590 (C = C), 1310s (SO_2),

1150s (SO_2); Anal. ($C_{21}H_{18}F_2O_4S$) 404·44; calc. C 62·36 H 4·45; found C 62·20 H 4·43.

General procedure for ester cleavage

The ester was dissolved in tetrahydrofuran (THF) and two equivalents of LiOH were added as a 1 M aqueous solution. After stirring for 5 h at room temperature, 20 mL diethyl ether and 20 mL H_2O were added. The aqueous phase was separated and acidified with 2 M HCl (pH 2–3). The acidic solution was extracted with 3 × 30 mL ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated.

*5-Fluoro-1-Z-(4-fluoromethylthio-benzylidene)-2-methyl-3-indenylacetic acid (**4a**)*

Ester cleavage as described above was performed on **3a** (370 mg, 1 mmol). The crude product was purified by flash chromatography (ethyl acetate/CH_3OH 50 : 1, 0·5% HOAc). Recrystallization from CH_2CH_3OH/H_2O gave the desired product **4a** as yellow-orange powder (80 mg, 22%): mp 148°C; ^{1}H NMR (DMSO-d_6): $\delta = 2{\cdot}20$ (s, 3H, 2-CH_3), 3·58 (s, 2H, CH_2COOR), 5·80 (d, $^2J_{H,F} = 52{\cdot}8$ Hz, CH_2F), 6·58 (ddd, $^3J_{H,F} = 9{\cdot}2$ Hz, $^3J_{H,H} = 8{\cdot}7$ Hz, $^4J_{H,H} = 2{\cdot}4$ Hz, 1H, 6-H), 6·88 (dd, $^3J_{H,F} = 9{\cdot}1$ Hz, $^4J_{H,H} = 2{\cdot}5$ Hz, 1H, 4-H), 7·26 (s, 1H, Ar−CH = C), 7·28 (dd, $^3J_{H,F} = 5{\cdot}2$ Hz, $^3J_{H,H} = 8{\cdot}7$ Hz, 1H, 7-H), 7·45–7·56 (m, 4H, CH_3SOAr−H); ^{13}C NMR (DMSO-d_6): $\delta = 10{\cdot}53$ (2-CH_3), 31·28 (*CH_2*COO), 87·17 (d, $^1J_{H,F} = 216{\cdot}9$ Hz, CH_2F), 105·93 (d, $^2J_{C,F} = 24{\cdot}0$ Hz, C-4), 110·83 ($^2J_{C,F} = 22{\cdot}7$ Hz, C-6), 123·83 (d, $^3J_{C,F} = 8{\cdot}9$ Hz, C-7), 129·32 (Ar−*CH* = C), 129·69 (d, $^4J_{C,F} = 3{\cdot}1$ Hz, C-7a), 130·09 and 130·16 (C-2′/C-6′, C-3′/C-5′), 130·62 (C-3), 134·70 (C-2), 135·97 (C-1′), 138·75 (C-1), 140·81 (C-4′), 146·49 (d, $^3J_{C,F} = 9{\cdot}0$ Hz, C-3a), 163·33 (d, $^1J_{C,F} = 236{\cdot}4$ Hz, C−F), 175·11 (CO); MS: $m/z = 358$ [M^+], 233 (100); IR (KBr): $\nu = 1690$ (CO), 1590 (C = C) cm^{-1}; Anal. ($C_{20}H_{16}F_2O_2S$) 358·42; Calc. C 67·02 H 4·51; Found C 67·02 H 4·62.

*5-Fluoro-1-Z-(4-fluoromethysulphonylbenzylidene)-2-methyl-3-indenylacetic acid (**4b**)*

Ester cleavage as described above was performed on **3b** (202 mg, 0·5 mmol). Recrystallization from CH_2CH_3OH/H_2O gave the desired product as a yellow powder (120 mg, 62%): mp 176°C; ^{1}H NMR (DMSO-d_6): $\delta = 2{\cdot}21$ (s, 3H, 2-CH_3), 3·60 (s, 2H, CH_2COOR), 5·21 (d, $^2J_{H,F} = 47{\cdot}2$ Hz, CH_2F), 6·58 (ddd, $^3J_{H,F} = 9{\cdot}1$ Hz, $^3J_{H,H} = 8{\cdot}4$ Hz, $^4J_{H,H} = 2{\cdot}4$ Hz, 1H, 6-H), 6·89 (dd, $^3J_{H,F} = 8{\cdot}8$ Hz, $^4J_{H,H} = 2{\cdot}4$ Hz, 1H, 4-H), 7·07 (dd, $^3J_{H,F} = 5{\cdot}1$ Hz, $^3J_{H,H} = 8{\cdot}4$ Hz, 1H, 7-H), 7·14 (s, 1H, Ar−CH = C), 7·71–7·77 (m, 4H, CH_3SOAr−H); ^{13}C NMR (CH_3OH-d_4): $\delta = 10{\cdot}37$ (2-CH_3), 32·12 (*CH_2*COO), 93·52 (d, $^1J_{H,F} = 215{\cdot}6$ Hz, CH_2F), 107·13 (d, $^2J_{C,F} = 24{\cdot}4$ Hz, C-4), 111·48 ($^2J_{C,F} = 23{\cdot}9$ Hz, C-6), 124·72 (d, $^3J_{C,F} = 9{\cdot}2$ Hz, C-7), 128·55 (Ar−*CH* = C), 129·82 (C-7a), 130·32 and 131·45 (C-2′/C-6′, C-3′/C-5′), 136·93 (C-2), 139·31 (C-1′), 143·69 (C-1), 145·16 (C-4′), 148·65 (d, $^3J_{C,F} = 8{\cdot}0$ Hz, C-3a), 164·84 (d, $^1J_{C,F} = 245{\cdot}4$ Hz, C−F), 174·00 (CO); MS: $m/z = 390$ [M^+], 233 (100); IR (KBr): $\nu = 1690$ (CO), 1590 (C = C), 1310 (SO_2), 1150 (SO_2) cm^{-1}; Anal. ($C_{20}H_{16}F_2O_4S$) 390·41; Calc. C 61·52 H 4·14; Found C 61·79 H 4·47.

Inhibition of cyclooxygenases

Inhibition of cyclooxygenase activity was studied using a whole blood assay as described previously (Panara et al 1995; Neupert et al 1997). COX-1 inhibition was analysed by measuring immunoreactive thromboxan B_2 (irTXB_2) and COX-2 (after induction with LPS) by monitoring immunoreactive protaglandin E_2 (irPGE_2), both via enzyme immunoassay. For COX-2 assessment aspirin was added to suppress COX-1 contribution.

Growth inhibition of RCA colon cancer cells

The RCA (Ricinus communis agglutinin) human colon cancer cells was provided by M. Brattain, University of Texas, San Antonio. The 3719 human colorectal carcinoma cell line was established from a freshly surgically removed colorectal carcinoma tumour. The cell lines were plated at approximately 5000 cells/well into 96 well tissue culture plates in 150 μL of RPMI medium containing 10% foetal bovine serum, 60 $\mu g\,mL^{-1}$ penicillin and 0·1 $mg\,mL^{-1}$ streptomycin. After adhering overnight at 37°C, the cells were exposed to varying concentrations of the drugs for 72 h. XTT tetrazolium dye was added to the wells, and after 6 h, dye reduction was measured in a plate reader.

Results and Discussion

Sulindac methyl ester **2** was treated with DAST and catalytic amounts of zinc bromide. The desired α-fluoro sulphide **3a** was isolated after chromatography in 72% yield. Oxidation of **3a** with metachloroperbenzoic acid led to a 75% yield of the α-fluoro sulphone **3b**. Hydroxide mediated cleavage of the esters **3a** and **3b** gave the respective acids **4a**

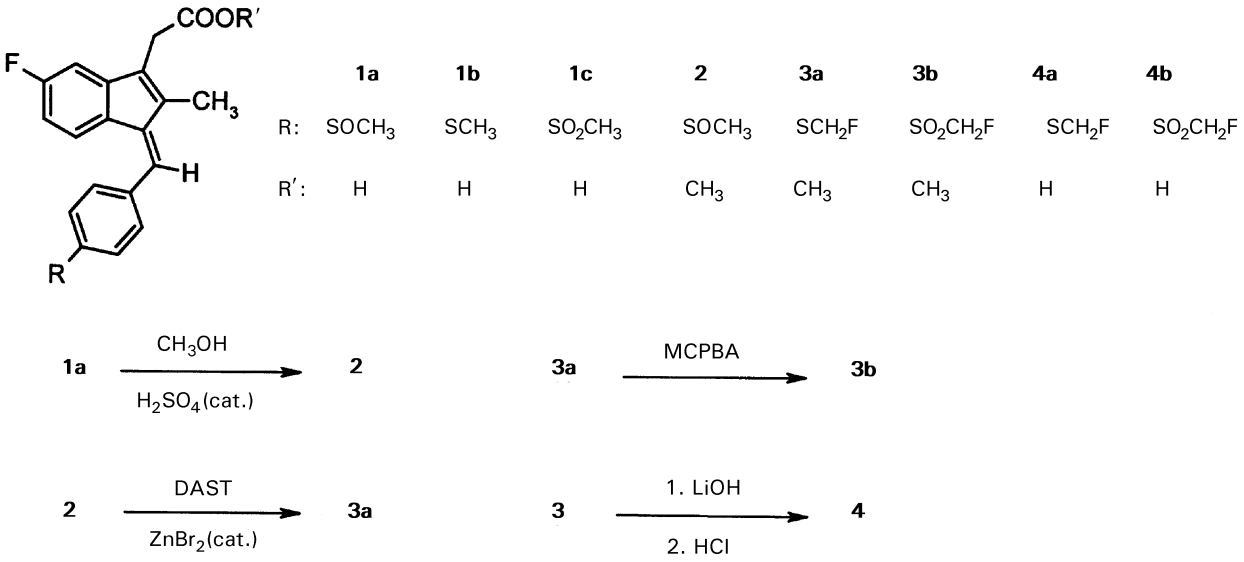

Figure 1. Structure and synthesis of the fluorinated derivatives of sulindac metabolites.

and **4b**. All compounds were obtained as crystalline solids that were analytically pure (Figure 1).

The compounds were then investigated for their ability to inhibit COX-1 and 2 using enzyme immunoassays for the quantification of respective metabolites ($irTXB_2$ for COX-1 and $irPGE_2$ for COX-2) as described previously (Panara et al 1995; Neupert et al 1997). None of the compounds displayed significant inhibition of COX-2. Sulindac sulphide (**1b**) and its fluorinated derivative **4a** were both active as inhibitors of COX-1, with **1b** (IC50 2·6 μM) being 2·5 times more potent than **4a** (IC50 6·4 μM). Neither of the sulphones **1c** or **4b** inhibited COX-1 at the highest concentrations tested (Table 1).

Cytotoxicity assays were performed using the RCA and 3719 human colorectal carcinoma cell lines. The cells were exposed to the drugs for 72 h, and cell viability was determined using the tetrazolium stain XTT, which gives a readout of mitochondrial membrane integrity. The IC50 values of the sulindac derivatives **1b**, **1c**, **4a** and **4b** were approximately the same on the 3719 cell line. On the RCA cells the fluoro sulphone **4b** (IC50 of 95 μM) was more active than the other agents. The observed IC50 values are in the range of sulindac concentrations that have previously been shown to induce apoptosis in colon cancer cells (120 μM in HAT-29 cells; Piazza et al 1995) (Table 1).

Table 1. Cox-inhibition and cytotoxic activity of sulindac metabolites and derivatives.

Assay	IC50 (μM)			
	1b	**1c**	**4a**	**4b**
COX-1 inhibition	2·6	> 100[a]	6·4	> 100[a]
COX-2 inhibition	> 100[a]	> 100[a]	> 100[a]	> 100[a]
3719 growth inhibition	125	125	125	125
RCA growth inhibition	140	175	140	95

[a]Less than 20% inhibition at 100 μM.

Several studies have shown that long term chronic use of NSAIDs can be effective in reducing the incidence and death rate from colorectal carcinoma (Elder & Paraskeva 1997). Sulindac (**1a**) is one such agent that has been shown to reduce polyp formation in patients with familial adenomatous polyposis (Shiff et al 1995). While many of the chemopreventive agents actively inhibit COX-1 and/or COX-2, there is now evidence that COX inhibition is not required for the activity of **1a** and its metabolites. We (Table 1), and others (Thompson et al 1997) have shown that sulindac sulphone (**1c**), an agent that is chemopreventive in rat models of breast and colorectal carcinoma, does not inhibit either of the COX enzymes. COX-1 inhibition by sulindac sulphide (**1b**) may actually be detrimental for long term administration, since the enzyme is constitutively expressed, and inhibitors of COX-1 lead to significant gastrointestinal toxicity. While the use of selective COX-2 inhibitors might be one possibility to avoid side effects (Oshima et al 1996), we are aiming to establish compounds with increased proapoptotic properties that are independent of inhibition of prostaglandin synthesis. We have demonstrated that the fluoro derivative of sulindac sulphide **4a** retains, or even has slightly increased cytotoxic activity on colorectal cell lines, but displays 2·5-fold less inhibitory activity on COX-1 than sulindac sulphide **1b**. Additionally, the fluorinated sulphone **4b** shows an increased cyto-

toxicity on RCA cells and retained activity on the 3719 cells without displaying COX-inhibitory properties. Therefore, fluorinated derivatives of sulindac metabolites constitute interesting prototypes for further structure–activity studies. These may lead to new agents for cancer chemoprevention with reduced undesired side-effects compared with the clinically approved agent from which they are derived.

Acknowledgements

Manfred Jung thanks B. Unterhalt for his generous support and also the Fonds der Chemischen Industrie and the DPhG-Stiftung für den Wissenschaftlichen Nachwuchs im Stifterverband für die Deutsche Wissenschaft for funding. We thank Dr. G. Winde, Department of General Surgery, University of Münster, for the generous gift of compound **1a**.

References

Chan, T. A., Morin, P. J., Vogelstein, B., Kinzler, K. W. (1998) Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. Proc. Natl Acad. Sci. USA 95: 681–686

De Lucchi, O., Miotti, U., Modena, G. (1991) The Pummerer reaction of sulphinyl compounds. Org. Reactions 40: 157–405

Duggan, D. E., Hooke, K. F., Risley, E. A. Shen, T. Y., Arman, C. G. (1977) Identification of the biologically active form of sulindac. J. Pharmacol. Exp. Ther. 201: 8–13

Elder, D. J. E., Paraskeva, C. (1997) NSAIDS to prevent colorectal cancer: a question of sensitivity. Gastroenterology 113: 1999–2003

Filler, R., Kobayashi, K., Yagupolskii L. M. (eds) (1993) Organofluorine compounds. In: Medicinal Chemistry and Biomedical Applications. Elsevier, Amsterdam

Giardiello, F. M., Hamilton, S. R., Krush, A. J., Piantadosi, S., Hylind, L. M., Celano, P., Booker, S. V., Robinson, C. R., Offerhaus, G. J. (1993) Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N. Engl. J. Med. 328: 1313–1316

Hakama, M. (1998) Chemoprevention of cancer. Acta Oncol. 37: 227–230

He, T. C., Chan, T. A., Vogelstein, B., Kinzler, K. W. (1999) PPAR delta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. Cell 99: 335–345

Herrmann, C., Block, C., Geisen, C., Haas, K., Weber, C., Winde, G., Moroy, T., Müller, O. (1998) Sulindac sulfide inhibits ras signaling. Oncogene 17: 1769–1776

Jones, H. (1975) 5-Fluoro-2-methyl-1-(p-methysulfinylbenzylidene)-indenyl-3-acetic acid. U.S. Pat. 3869507

Kahn, M. J., Morrison, D. G. (1997) Chemoprevention for colorectal carcinoma. Hematol. Oncol. Clin. North Am. 11: 779–794

Kelloff, G. J., Boone, C. W., Steele, V. E., Fay, J. R., Lubet, R. A., Crowell, J. A., Sigman, C. C. (1995) Mechanistic considerations in chemopreventive drug development. J. Cell. Biochem. Suppl. 20: 1–24

Lehmann, J. M., Lenhard, J. M., Oliver, B. B., Ringold, G. M., Kliewer, S. A. (1997) Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. J. Biol. Chem. 272: 3406–3410

McCarthy, J. R., Peet, N. P., LeTourneau, M. E., Inbasekaran, M. (1985) (Diethylamino)sulfur trifluoride in organic synthesis. 2. The transformation of sulfoxides to α-fluoro thioethers. J. Am. Chem. Soc. 107: 735–737

Neupert, W., Brugger, R., Euchenhofer, C., Brune, K., Geisslinger, G. (1997) Effects of ibuprofen enantiomers and its coenzyme A thioesters on human prostaglandin endoperoxide synthases. Br. J. Pharmacol. 122: 487–492

Oshima, M., Dinchuk, J. E., Kargman, S. L., Oshima, H., Hancock, B., Kwong, E., Trzaskos, J. M., Evans, J. F., Taketo, M. M. (1996) Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell 87: 803–809

Panara, M. R., Greco, A., Santini, G., Sciulli, M. G., Rotondo, M. T., Padovano, R., Digiamberardino, M., Cipollone, F., Cuccurullo, F., Patrono, C., Patrignani, P. (1995) Effects of the novel antiinflammatory compounds, N-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulfonamide (Ns-398) and 5-methanesulphonamido-6-(2,4-difluorothiophenyl)-1-indanone (L-745,337), on the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. Br. J. Pharmacol. 116: 2429–2434

Piazza, G. A., Rahm, A. L. K., Krutzsch, M., Sperl, G., Paranka, N. S., Gross, P. H., Brendel, K., Burt, R. W., Alberts, D. S., Pamukcu, R., Ahnen, D. J. (1995) Antineoplastic drugs sulindac sulfide and sulfone inhibit cell growth by inducing apoptosis. Cancer Res. 55: 3110–3116

Shiff, S. J., Qiao, L., Tsai, L. L., Rigas, B. (1995) Sulindac sulfide, an aspirin-like compound, inhibits proliferation, causes cell cycle quiescence, and induces apoptosis in HT-29 colon adenocarcinoma cells. J. Clin. Invest. 96: 491–503

Shuman, R. F., Pines, S. H., Shearin, W. E., Czaja, R. F., Abramson, N. L., Tull, R. (1977) A sterically efficient synthesis of (Z)-5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid and its S-oxide, sulindac. J. Org. Chem. 42: 1914–1919

Thompson, H. J., Briggs, S., Paranka, N. S., Piazza, G. A., Brendel, K., Gross, P. H., Sperl, G. J., Pamukcu, R., Ahnen, D. J. (1995) Inhibition of mammary carcinogenesis in rats by sulfone metabolite of sulindac. J. Natl Cancer. Inst. 87: 1259–1260

Thompson, H. J., Jiang, C., Lu, J., Mehta, R. G., Piazza, G. A., Paranka, N. S., Pamukcu, R., Ahnen, D. J. (1997) Sulfone metabolite of sulindac inhibits mammary carcinogenesis. Cancer Res. 57: 267–271

Verheul, H. M., Panigraphy, D., Yuan, J., D'Amato, R. J. (1999) Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumor growth in rabbits. Br. J. Cancer 79: 114–118

Waddell, W. R. (1998) Stimulation of apoptosis by sulindac and piroxicam. Clin. Sci. Colch. 95: 385–388

Wattenberg, L. W. (1997) An overview of chemoprevention: current status and future prospects. Proc. Soc. Exp. Biol. Med. 216: 133–141

Welch, J. T., Eswarakrishnan, S. (1991) Fluorine in Bioorganic Chemistry. Wiley, New York