THE ANTILEUKOTRIENIC DERIVATIVES AND HOMOLOGUES OF [(QUINOLIN-2-YLMETHOXY)SULFANYL]BENZOIC ACIDS WITH REDUCED LIPOPHILICITY

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Dedicated to Professor Otto Exner, DrSc. on the occasion of his 80th birthday.

A series of ({[(quinolin-2-ylmethoxy)phenyl]sulfanyl}phenyl)acetic acids **2** and *S*-oxidized derivatives of {[(quinolin-2-ylmethoxy)phenyl]sulfanyl}benzoic acids **3** were prepared and their antileukotrienic and antiasthmatic activities evaluated. Regression analysis led to the conclusion that the antileukotrienic activities of compounds **2** correspond to the relationships between these activities and lipophilicity, derived for the previously synthesized series of substituted (arylsulfanyl)benzoic acids **1A**, **1B** and **1C**. Acids **3** are outliers from these relationships, probably due to a somewhat different mechanism of action. A higher antiasthmatic activity was observed in some [(arylsulfanyl)phenyl]acetic acids **2** in comparison with the corresponding analogs bearing the (arylsulfanyl)benzoic acid moiety. The inhibition of 5-lipoxygenase activated protein (FLAP) was determined for these compounds, and the influence of the direct inhibition of LTB_4 biosynthesis is discussed to explain the differences in the antiasthmatic effect of the compounds under study.

Keywords: [(Phenylsulfanyl)phenyl]acetic acids; Arylacetic acids; Quinolines; Antileukotrienic activities; FLAP inhibition; Lipophilicity; Regression analysis; Antiasthmatic effect.

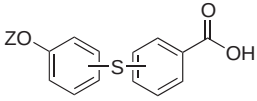
Asthma is a chronic inflammation condition of the airways, which affects about 5% of the population in industrialized areas. Asthmatic reactions, characterized by bronchial hyperresponsiveness, are induced by a wide range of inflammatory mediators. During the recent two decades, leuko-

trienes (LT) have been identified as important bronchoconstrictors, the pharmacological effects of which mimic the pathological changes accompanying asthma[1,2]. Leukotriene receptor antagonists and leukotriene biosynthesis inhibitors have provided a new therapeutic approach to the treatment of asthma[3,4]. A vast number of antileukotrienics[5] of extensive structural variability has been studied in the treatment of allergic diseases of the respiratory system. Some of them, such as the 5-lipoxygenase (5-LO) inhibitor zileuton[6] and cysteinyl LT antagonists zafirlukast[7] and montelukast[8,9] have been registered for the treatment of asthma. Numerous compounds bearing the quinoline fragment as a lipophilic moiety are known to bind tightly to the cysteinyl LT receptors[8–12] or are studied[13,14] as inhibitors of 5-LO. In our previous paper[15], we described the synthesis and biological evaluation of a series of (phenylsulfanyl)benzoic acid derivatives **1**, bearing the hydrophobic moieties of quinoline (**1A**), 2-hydroxy-3-propylacetophenone (**1B**) and 2,4-difluorobiphenyl (**1C**). The relationships between log P_{calc} values and antileukotrienic activities were described by regression equations: (*1*) for the inhibition of LTB_4 biosynthesis, (*2*) and (*3*) for the binding to LTD_4 and LTB_4 receptors, respectively. *C* is molar concentration of a compound causing 50% inhibition and log P_{calc} are the calculated values of the logarithms of the partition coefficients in the octanol–water system (*n* is number of compounds, *r*, *s* and *F* are statistical criteria, cf. Experimental).

	n	*r*	*s*	*F*	Eq.
$\log (1/C) = -0.643\ (\pm 0.300) \log P_{calc} + 10.964\ (\pm 2.323)$	24	0.779	0.549	36.37	(*1*)
$\log (1/C) = -0.643\ (\pm 0.341) \log P_{calc} + 10.019\ (\pm 2.518)$	19	0.785	0.480	30.00	(*2*)
$\log (1/C) = 5.222\ (\pm 2.550) \log P_{calc} - 0.345\ (\pm 0.174)(\log P_{calc})^2 - 14.461\ (\pm 10.138)$	20	0.842	0.229	24.19	(*3*)

The results of the regression analysis led to the conclusion that these activities are probably negatively influenced by the high lipophilicity of the compounds under study. In accord with this finding, the most active compounds – in antileukotrienic, antiinflammatory and antiasthmatic effects – belong[16] to the quinoline derivatives **1A**. We synthesized analogs of compounds **1A** with structural changes directed towards the decrease in total lipophilicity. The homologous arylacetic acids **2** and the *S*-oxidized analogs **3** were prepared in order to obtain derivatives of compounds **1** with reduced lipophilicity. Several quinoline derivatives[5,17–19] were shown as potent inhibitors of 5-lipoxygenase-activating protein (FLAP), responsible for the translocation of 5-lipoxygenase from cytosol to the cell membrane and its activation[20]. Therefore, our most active quinoline derivatives were also

studied from this point of view. For this purpose, the determination of LTB_4 biosynthesis in the cellular and subcellular system was necessary. A higher inhibition of FLAP is directly proportional to the ratio $(IC_{50})_S/(IC_{50})_C$, where the subscripts S and C denote the activities in subcellular and cellular systems, respectively. The possibility of the utilization of FLAP inhibitors in gastric cancer prevention and therapy has recently been reported[21,22]. A comparison of antileukotrienic activities and antiasthmatic effect of compounds **2** and **3** with the previous series of compounds **1** and especially **1A** was the main goal of this study.



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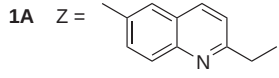
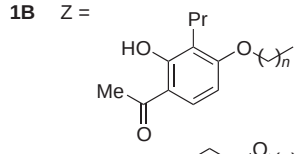
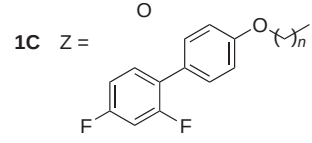




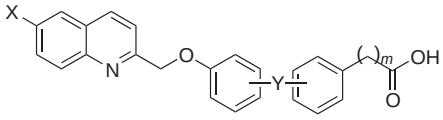


RESULTS AND DISCUSSION

Arylacetic acids **2** were prepared from the methyl esters of the corresponding {[(hydroxyphenyl)sulfanyl]phenyl}acetic acids **5** and 2-(chloromethyl)-quinoline **4a** or its 6-chloro derivative **4b**, and by subsequent hydrolysis of the intermediate methyl ester **6**. The desired {[(methoxyphenyl)sulfanyl]-phenyl}acetic acids **7** were prepared by the homologation of the corresponding benzoic acids according to a literature method[23], and fusion with pyridine hydrochloride[24] was used for their *O*-demethylation to yield the corresponding acids **8** (Scheme 1). The intermediate methyl esters of [(hydroxyphenyl)sulfinyl]benzoic acids **9** and their sulfonyl analogs were prepared from the corresponding sulfanyl derivatives[15] **10** by the oxidation with 3-chloroperbenzoic acid or hydrogen peroxide, analogously to a literature method[25]. The reaction of esters **9** with 2-(chloromethyl)quinoline **4a** and its 6-chloro derivative **4b** followed by the hydrolysis of esters **11** gave acids **3** (Scheme 2).

All synthesized compounds were subjected to evaluation of antileukotrienic activity by testing the inhibition of LTB_4 biosynthesis in vitro as a criterion of 5-LO inhibition, and affinities to LTB_4 and LTD_4 receptors,

which are the prerequisite for antagonistic activities towards those LT. The results of antileukotrienic activity evaluation are summarized in Table I. The oxidized analogs **3b** and **3c** were also employed as the standards of possible metabolites for the study of the biotransformation[26] of the most active[15,16] quinoline derivative **1Aa**.



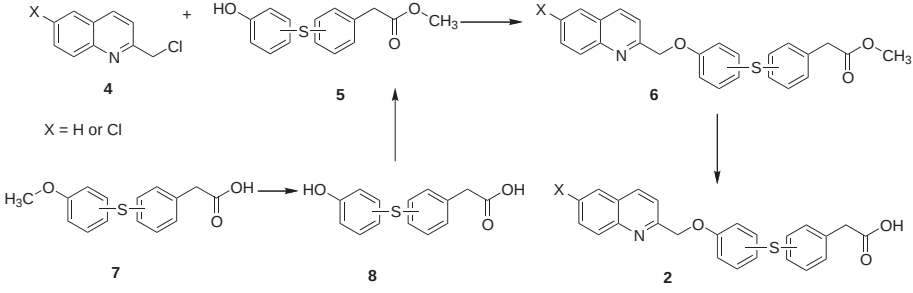
2: Y = S, *n* = 1
3: Y = SO, SO_2; *m* = 0, 1

Compound	*m*	X	Y	Relative position of S to	
				O	COOH (CH_2COOH)
2a	1	H	S	*p*	*o*
2b	1	Cl	S	*p*	*o*
2c	1	H	S	*p*	*p*
2d	1	Cl	S	*p*	*p*
2e	1	H	S	*m*	*o*
2f	1	Cl	S	*m*	*o*
3a	0	H	SO	*p*	*o*
3b	0	H	SO	*p*	*p*
3c	0	H	SO_2	*p*	*p*
3d	0	H	SO	*m*	*o*
3e	1	H	SO	*p*	*p*

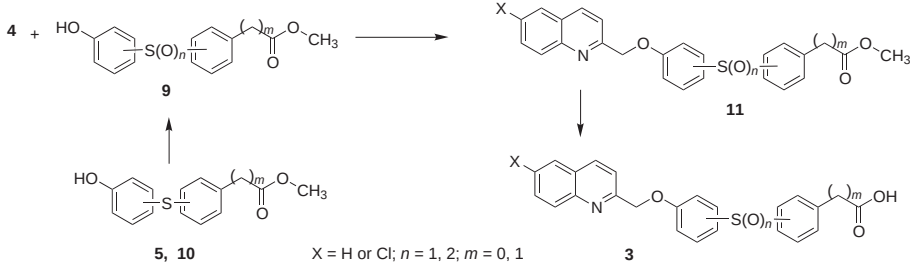
It should be emphasized that the antileukotrienic activities of the homologous phenylacetic acids **2** correspond in all instances to the originally obtained dependences of their effects on lipophilicity, expressed by Eqs (*1*)–(*3*) for compounds **1**. In the extended series of acids **1** and **2**, Eq. (*4*) was derived for the inhibition of LTB_4 biosynthesis, Eq. (*5*) for LTD_4 receptor binding, and Eq. (*6*) for LTB_4 receptor binding. The concentrations *C* have the same meaning as in the corresponding equations (*1*), (*2*) and (*3*). The character of the dependences of antileukotrienic activities on lipophilicity did not change.

	n	*r*	*s*	*F*	Eq.
$\log(1/C) = -0.575\ (\pm 0.234)\ \log P + 10.447\ (\pm 1.734)$	30	0.810	0.489	56.2	(*4*)
$\log(1/C) = -0.720\ (\pm 0.271)\ \log P + 10.622\ (\pm 1.918)$	25	0.858	0.442	68.1	(*5*)
$\log(1/C) = 4.181\ (\pm 2.500)\ \log P - 0.275\ (\pm 0.175)(\log P)^2 - 10.693\ (\pm 8.778)$	26	0.816	0.262	26.0	(*6*)

Unfortunately, the antileukotrienic activities of the *S*-oxidized derivatives **3** with significantly lower lipophilicities do not correspond either to both the original relationships (Eqs (*1*) and (*2*)) or the corresponding Eqs (*4*) and (*5*). We assume that the sulfinyl and sulfonyl groups participate in the binding to the receptors, and their mechanism of action is somewhat different from that of compounds **1** and **2**. From practical point of view, both metabolites (**3a**, **3c**) of the most active compound[15,16] of the quinoline derivatives (**1Aa**) are less active than their parent compound.



SCHEME 1



SCHEME 2

The antiasthmatic effect of three selected homologues (**2c**, **2d**, **2f**) of the most active benzoic acid derivatives **1Aa**, **1Ac** and **1Ag** was evaluated in the model of bronchospasm, induced by LTD_4. The results for the above-mentioned compounds are summarized in Table II.

A significant difference in the inhibition of bronchospasm can be observed in the pair of compounds **2c** and **1Aa**. Regardless of higher antileukotrienic activities (cf. Table III) of **1Aa**, compound **2c** has a remarkably better antiasthmatic effect. The additional two pairs of compounds, **2d**, **1Ae** and **2f**, **1Ag** display a higher antiasthmatic effect for sulfanylphenylacetic acid derivatives **2d** and **2f**. Two explanations, applying individually or, in part, simultaneously, can be offered for the differences in the inhibition of bronchospasm:

1. A lower lipophilicity of compounds **2** in comparison with the benzoic acid derivatives **1A** can play a role in a better bioavailability of **2** at the site of action. But a small decrease in log *P* (0.1 for **2f** and 0.4 for **2c** and **2d**) seems to be insufficient to account for this change of the antiasthmatic effect.

TABLE I
Antileukotrienic activities of compounds **2** and **3**

Compound	Inhibition of LTB_4 biosynthesis		Inhibition of LTB_4 receptor binding		Inhibition of LTD_4 receptor binding		log P_{calc}
	IC_{50}[a]	$\log(1/IC_{50})+6$	IC_{50}[a]	$\log(1/IC_{50})+6$	IC_{50}[a]	$\log(1/IC_{50})+6$	
2a	0.16	6.796	22.5	4.648	0.18	6.745	5.66
2b	0.68	6.167	35.0	4.456	1.0	6.000	6.31
2c	0.05	7.301	53.5	4.272	0.1	7.000	5.66
2d	0.12	6.921	11.5	4.939	3.2	5.495	6.31
2e	0.07	7.155	86.3	4.064	0.29	6.538	5.66
2f	0.46	6.337	63.0	4.201	1.1	5.959	6.31
3a	5.30	5.276	5[b]	–	5.01	5.301	3.54
3b	0.05	7.301	10[b]	–	0.19	6.721	3.89
3c	4.20	5.377	13.1	4.883	0.15	6.824	4.43
3d	7[b]	–	17[b]	–	8.44	5.076	3.54
3e	13.1	4.883	20[b]	–	0.14	6.854	3.44

[a] Concentration in μmol/l causing 50% inhibition; [b] % inhibition at the concentration of 20 μmol/l, the compounds are not included in the regression analysis.

TABLE II
Inhibition of bronchospasm induced by LTD_4

Compound	Dose, mg/kg	% of inhibition at time *t*, min			log P_{calc}
		2	4	10	
2c	100	73	77	89	5.66
	50	83	86	89	
	12.5	61	65	74	
2d	100	27	35	56	6.31
	50	20	25	37	
2f	100	29	42	60	6.31
	50	20	26	35	
1Aa	100	69	70	75	6.11
	50	32	38	45	
1Ae	100	14	33	43	6.75
	50	10	12	18	
1Ag	100	6	38	54	6.41
	50	12	25	28	

Compounds **1Aa**, **1Ae** and **1Ag** correspond to **2c**, **2d** and **2f**, respectively, with regard to the positions of COOH (CH_2COOH), and O to S

TABLE III
Inhibition of 5-lipoxygenase activating protein (FLAP) of selected compounds **2** and **1A**

Compound	Inhibition of LTB_4, C [a]			Inhibition of LTD_4 binding C [a]
	Cellular	Subcellular	S/C [b]	
2c	0.05	1.38	24.6	0.1
2d	0.12	0.70	5.8	3.2
2f	0.46	1.84	4.0	1.15
1Aa	0.01	2.35	235.0	0.07
1Ae	0.17	6.85	40.3	3.80
1Ag	0.08	2.62	32.8	0.27

[a] In μmol/l; [b] the ratio of subcellular and cellular concentrations.

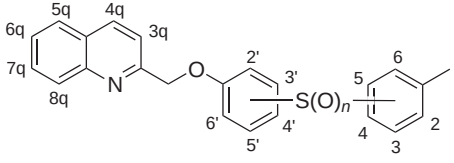
2. Significant differences in both groups of compounds were found in the inhibition of FLAP. From the results summarized in Table III, it is apparent that the phenylacetic acid derivatives **2** are more likely direct inhibitors of 5-lipoxygenase (5-LO), while benzoic acid derivatives **1A** are rather inhibitors of FLAP.

A direct inhibition of 5-LO is probably more important for bronchospasm inhibition. A proper extent of LTB_4 biosynthesis inhibition, and also of LTD_4 receptor binding must be taken into account as well.

From the results, we can draw the following conclusions: (i) the antileukotrienic activities of acids **2** correspond to the previously derived[15] relationships between these activities and lipophilicity; this conclusion is not valid for the sulfinyl and sulfonyl derivatives **3**; (ii) a higher antiasthmatic effect compared with the original compounds **1A**, evaluated by the inhibition of bronchospasm, induced by LTD_4, was found for compounds **2**; (iii) the differences in bioavailability and probably the more pronounced direct inhibition of 5-LO can play a role in the above-mentioned change of the antiasthmatic effect.

EXPERIMENTAL

Melting points were determined on a Boetius-type Kofler block and are not corrected. The ^{1}H NMR spectra of 6% solutions of the compounds in deuteriochloroform (or in hexadeuteriodimethyl sulfoxide) containing tetramethylsilane or 3-(trimethylsilyl)propanoic acid-d_5 as internal standard and ^{13}C NMR spectra of 2% solutions of the compounds in hexadeuteriodimethyl sulfoxide were measured on a Bruker-250-DPX, 250 MHz. Chemical shifts are given in ppm (δ-scale), coupling constants *J* in Hz. The following numbering was used for ^{1}H NMR spectra of compounds **2** and **3**:



The purity of compounds **5** and **9** was evaluated by HPLC on an Alliance Waters 2695 liquid chromatograph (Waters Assoc., Milford (MA), U.S.A.) with UV detection (Waters 2487 dual detector) at 251 μm. Cromasil C18 100 A (300 mm × 4.6 mm) was obtained from Chromservis (Czech Republic). Gradient chromatography was performed with water (Q plus, Millipore, Germany), acetonitrile (Merck, Darmstadt, Germany) with 0.1% of phosphoric acid (Merck, Darmstadt) as a mobile phase. The eluent flow rate was 1 ml/min.

The values of log P_{calc} were calculated using the KOWWIN Program, Version 1.63 (Syracuse Research Corp., U.S.A.).

The coefficients in the regression equations were calculated from experimental results by multiple regression analysis and their statistical significance was tested by the Student *t*-test. Statistical significance of the regression equations was tested by standard deviations (*s*), coefficients of multiple correlation (*r*) and the Fisher–Snedecor criterion (*F*). The level of statistical significance *p* was better than 0.005 for both the whole equations and individual variables.

Biological Evaluation

Inhibition of LTB_4 biosynthesis: the production of LTB_4 was determined in rat polymorphonuclear cells from the pleural exudate, elicited by heat-inactivated rat serum[27]. The cells were stimulated with Ca^{2+} ionophore A23187 (Sigma) and incubated with various concentrations of the tested compounds. For the evaluation of inhibition in a subcellular system, the cell suspension was centrifuged for 5 min at 1000 g, homogenized by sonification and again centrifuged. The supernatant was incubated with the tested compounds[28,29]. LTB_4 was determined in both cases in the supernatants using a commercial RIA kit (Amersham). The in vitro activity was expressed as the concentration *C* (μM) giving rise to 50% inhibition of LTB_4 biosynthesis. For the LTB_4 receptor binding study, a slightly modified method of Cheng et al.[30] was used. The membrane fraction was prepared from the male guinea pig spleen; 2 mg of the membranes were incubated with 0.3 nM ^{3}H-LTB_4 in 100 μl of the incubating mixture at 25 °C for 30 min. Nonspecific binding was determined in the presence of 0.1 μM of LTB_4. The membranes were filtered through Whatman GF/C paper and washed with buffer three times; the radioactivity was measured by liquid scintillation spectrometry and the specific binding of ^{3}H-LTB_4 to the receptor was determined. The LTD_4 receptor binding study was performed by the method of Bruns et al.[31] The membrane fraction was prepared from the male guinea pig lungs; 4 mg of this fraction were incubated with 0.4 nM of ^{3}H-LTD_4 in 100 μl of the incubating mixture at 25 °C for 60 min. Nonspecific binding was determined in the presence of 0.1 μM of LTD_4. Filtration of the membranes, washing and measurement of radioactivity were the same as in the previous determination. The in vitro activities were expressed as the concentrations *C* (μM) giving rise to 50% inhibition of LTB_4 (LTD_4) binding to the receptor. Six points at different concentrations were used for the calculation of *C*.

The method of Jones and Masson[32] was used for the evaluation of the inhibition of bronchoconstriction, induced by the intravenous injection of 0.5 μg/kg of LTD_4 to a guinea pig. The tested compound was administered in the doses of 12.5, 50, 100 mg/kg p.o., 60 min before the application of albumin or LTD_4. The effect was expressed as the percentage of the inhibition of bronchospasm relative to the untreated control.

Methyl {2-[(4-Hydroxyphenyl)sulfanyl]phenyl}acetate (**5a**)

{2-[(4-Methoxyphenyl)sulfanyl]phenyl}acetic acid (**7a**) was prepared from the corresponding benzoic acid[15] according to ref.[23] in 63% overall yield, m.p. 102–105 °C (lit.[23] m.p. 103–104 °C). {2-[(4-Hydroxyphenyl)sulfanyl]phenyl}acetic acid (**8a**) was prepared from **7a** by melting with pyridine hydrochloride according to ref.[24] in the yield of 89%, m.p. 183–185 °C (lit.[24] m.p. 184–186 °C). For $C_{14}H_{12}O_3S$ (260.2) calculated: 64.61% C, 4.65% H, 12.30% S; found: 64.35% C, 4.82% H, 12.03% S. **8a** (19.4 g, 0.075 mol) and 4-methylbenzene-1-sulfonic acid (2.1 g) in methanol (210 ml) were treated at reflux for 6 h; methanol was evaporated and the residual oil dissolved in ether (270 ml). The solution was washed with water (3 ×

100 ml), ether evaporated and the solid purified on a silica gel column using dichloromethane as a mobile phase. Evaporation gave **5a** (14.2 g, 70%), m.p. 126–128 °C. ^{1}H NMR ($CDCl_3$): 3.75 s (CH_2COO); 5.63 s (OH). For $C_{15}H_{14}O_3S$ (274.3) calculated: 65.69% C, 5.15% H, 11.67% S; found: 65.40% C, 5.35% H, 11.39% S.

Methyl Esters **5b** and **5c**

These esters were prepared similarly.

Methyl {4-[(4-hydroxyphenyl)sulfanyl]phenyl}acetate (**5b**). Methoxy acid **7b** was prepared from the corresponding benzoic acid[15] in 21% overall yield, m.p. 88–90 °C. ^{1}H NMR ($CDCl_3$): 3.42 s (CH_2COO); 3.78 s (CH_3O). For $C_{15}H_{14}O_3S$ (274.3) calculated: 65.69% C, 5.15% H, 11.67% S; found: 65.50% C, 5.38% H, 11.42% S. **7b** was demethylated to give **8b** in 93% yield, m.p. 182–184 °C. ^{1}H NMR (DMSO-d_6): 3.53 s (CH_2COO). After esterification and column chromatography, ester **5b** was prepared in 70% yield, m.p. 76–78 °C. ^{1}H NMR ($CDCl_3$): 3.58 s (CH_2COO); 3.68 s ($COOCH_3$); 5.72 s (OH). For $C_{15}H_{14}O_3S$ (274.3) calculated: 65.69% C, 5.15% H, 11.67% S; found: 65.48% C, 5.27% H, 11.49% S.

Methyl {2-[(3-hydroxyphenyl)sulfanyl]phenyl}acetate (**5c**). Methoxy acid **7c** was prepared from the corresponding benzoic acid[15] in 51% overall yield, m.p. 63–65 °C. ^{1}H NMR ($CDCl_3$): 3.65 s (CH_2COO); 3.82 bs (OCH_3). For $C_{15}H_{14}O_3S$ (274.3) calculated: 65.69% C, 5.15% H, 11.67% S; found: 65.32% C, 5.40% H, 11.38% S. The corresponding hydroxy acid **8c** was obtained in 77% yield, m.p. 163–165 °C. For $C_{14}H_{12}O_3S$ (260.4) calculated: 64.60% C, 4.65% H, 12.32% S; found: 64.30% C, 4.85% H, 12.10% S, and gave, after esterification, the expected ester **5c** in 79% yield, m.p. 54–56 °C. ^{1}H NMR ($CDCl_3$): 3.85 s (CH_2COO); 5.60 bs (OH). For $C_{15}H_{14}O_3S$ (274.3) calculated: 65.69% C, 5.15% H, 11.67% S; found: 64.79% C, 5.25% H, 11.44% S.

{2-[4-(Quinolin-2-ylmethoxy)phenylsulfanyl]phenyl}acetic Acid (**2a**)

A mixture of **5a** (5.9 g, 0.018 mol), **4a** (3.2 g, 0.018 mol; prepared[33] from 2-methylquinoline by chlorination; the degree of chlorination was checked by TLC), anhydrous potassium carbonate (6.5 g) and potassium iodide (0.2 g) in butan-2-one (70 ml) was stirred under reflux for 8 h. The hot mixture was filtered with charcoal, and the filtrate evaporated. The solid residue was crystallized from methanol to yield methyl ester **6a** (5.9 g, 81%), m.p. 100–102 °C. ^{1}H NMR ($CDCl_3$): 3.64 s (CH_3OCO); 3.83 s (CH_2COO); 5.36 s (CH_2O); 6.97 d, J = 8.8 (H2′, 6′); 7.20 m (H3, 4, 5, 6); 7.25 d, J = 8.8 (H3′, 5′); 7.54 m (H6q); 7.64 d, J = 8.8. (H3q); 7.73 m (H7q); 7.82 dd, J = 1.3, 8.5 (H5q); 8.08 d, J = 8.5 (H8q); 8.18 d, J = 8.8 (H4q). A mixture of ester **6a** (5.9 g, 0.014 mol) in ethanol (75 ml) and potassium hydroxide (1.5 g, 0.027 mol) in water (10 ml) was stirred under reflux for 30 min; ethanol was then evaporated, the residue diluted with water (100 ml), and the turbid solution filtered with charcoal. After acidification with acetic acid to pH 4.5, the precipitated crude product was crystallized from ethanol giving **2a** (3.0 g, 53%), m.p. 179–181 °C. ^{1}H NMR (DMSO-d_6, 60 °C): 3.77 s (CH_2COO); 5.38 s (CH_2O); 7.13–7.37 m (H3, 4, 5, 6); 7.10 d, J = 8.5 (H2′, 6′); 7.30 d, J = 8.5 (H3′, 5′); 7.61 m (H6q); 7.67 d, J = 8.2 (H3q); 7.78 m (H7q); 7.98 dd, J = 0.9, 8.7 (H5q); 8.03 d, J = 8.5 (H8q); 8.40 d, J = 8.2 (H4q). ^{13}C NMR: 71.19, 116.30, 119.73, 125.47, 126.78, 127.14, 127.17, 127.38, 128.06, 128.11, 128.73, 130.05, 131.10, 131.39, 133.83, 135.53, 136.60, 137.23, 147.14, 157.42, 158.27, 172.20. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 71.67% C, 4.94% H, 3.41% N, 7.77% S.

Acids **2b**, **2c**, **2d**, **2e** and **2f**

These acids were prepared similarly.

[2-({4-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)phenyl]acetic acid (**2b**). Ester **6b** was prepared from **5a** and **4b** (prepared similar to **4a**) in the yield of 89%, m.p. 92–93 °C (butan-2-one–hexane 1:1). ^{1}H NMR ($CDCl_3$): 3.66 s (CH_3OCO); 3.84 s (CH_2COO); 5.33 s (CH_2O); 6.95 d, *J* = 9.1 (3′, 5′); 7.22 m (H3, 4, 5, 6, 2′, 6′); 7.66 m (H3q, 7q); 7.80 d, *J* = 2.5 (H5q); 8.00 d, *J* = 8.8 (H8q); 8.09 d, *J* = 8.5 (H4q). Ester **6b** was hydrolyzed to give **2b** in the yield of 64%, m.p. 204–206 °C (ethanol). ^{1}H NMR (DMSO-d_6): 3.79 s (CH_2COO); 5.36 s (CH_2O); 7.09 d, *J* = 8.5 (H3′, 5′); 7.20 m (H3, 4, 5, 6); 7.30 d, *J* = 8.5 (H2′, 6′); 7.66 m (H3q, 7q); 8.02 d, *J* = 9.1 (H5q); 8.07 d, *J* = 2.5 (H8q); 8.36 d, *J* = 8.5 (H4q). ^{13}C NMR: 39.28, 71.00, 116.28, 120.72, 125.56, 126.81, 127.17, 128.04, 128.12, 130.54, 130.82, 131.10, 131.12, 131.38, 133.79, 135.56, 136.54, 136.61, 145.54, 158.06, 158.17, 172.18. For $C_{24}H_{18}ClNO_3S$ (435.9) calculated: 66.12% C, 4.16% H, 8.13% Cl, 3.21% N, 7.36% S; found: 66.25% C, 4.13% H, 8.25% Cl, 3.12% N, 7.15% S.

(4-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfanyl}phenyl)acetic acid (**2c**). Ester **6c** was prepared from **5b** and **4a** in nearly quantitative yield as an oil. ^{1}H NMR ($CDCl_3$): 3.55 s (CH_2COO); 3.66 s (CH_3OCO); 5.37 s (CH_2O); 7.00 d, *J* = 8.8; 7.14 AA′BB′ system (H2, 3, 5, 6, 3′, 5′); 7.37 d, *J* = 8.8 (H2′, 6′); 7.53 m (H6q); 7.64 d, *J* = 8.5 (H3q); 7.72 m (H7q); 7.81 dd, *J* = 1.6, 8.2 (H5q); 8.08 dd, *J* = 1.3, 8.5 (H8q); 8.17 d, *J* = 8.5 (H4q). Ester **6c** was hydrolyzed into **2c** in the yield of 79%, m.p. 176–178 °C (ethanol). ^{1}H NMR (DMSO-d_6): 3.54 s (CH_2COO); 5.39 s (CH_2O); 7.14 d, *J* = 8.8; 7.19 AA′BB′ system (H2, 3, 5, 6, 3′, 5′); 7.39 d, *J* = 8.8 (H2′, 6′); 7.61 ddd, *J* = 1.2, 6.9, 8.1 (H6q); 7.67 d, *J* = 8.5 (H3q); 7.78 ddd, *J* = 1.5, 6.9, 8.4 (H7q); 7.98 dd, *J* = 1.1, 8.1 (H5q); 8.03 bd (H8q); 8.39 d, *J* = 8.5 (H4q). ^{13}C NMR: 71.17, 116.35, 119.73, 124.80, 126.78, 127.13, 127.38, 128.11, 128.73, 128.79, 130.04, 130.50, 133.96, 134.70, 135.19, 137.24, 147.14, 157.39, 158.54, 172.72. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 72.13% C, 4.89% H, 3.40% N, 7.82% S.

[4-({4-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)phenyl]acetic acid (**2d**). Ester **6d** was prepared from **5b** and **4b**, in the yield of 77%, m.p. 97–99 °C (butan-2-one–hexane 1:1). ^{1}H NMR ($CDCl_3$): 3.65 s (CH_3OCO); 3.84 s (CH_2COO); 5.33 s (CH_2O); 7.66 m (H3q, H7q); 7.80 d, *J* = 2.5 (H5q); 8.00 d, *J* = 8.8 (H8q); 8.09 d, *J* = 8.5 (H4q). Ester **6d** was hydrolyzed into **2d** with the yield of 70%, m.p. 215–217 °C (ethanol). ^{1}H NMR (DMSO-d_6): 3.44 s (CH_2COO); 5.37 s (CH_2O); 7.10 d, *J* = 9.0 (H3′, 5′); 7.14 d, *J* = 9.0 (H3, 5); 7.18 d, *J* = 8.5 (H2, 6); 7.35 d, *J* = 8.9 (H2′, 6′); 7.73 d, *J* = 8.6 (H3q); 7.78 dd, *J* = 2.4, 9.0 (H7q); 8.04 d, *J* = 9.0 (H5q); 8.14 d, *J* = 2.4 (H8q); 8.41 d, *J* = 8.7 (H4q). For $C_{24}H_{18}ClNO_3S$ (435.9) calculated: 66.12% C, 4.16% H, 8.13% Cl, 3.21% N, 7.36% S; found: 66.18% C, 4.30% H, 8.27% Cl, 3.36% N, 7.08% S.

(2-{[3-(Quinolin-2-ylmethoxy)phenyl]sulfanyl}phenyl)acetic acid (**2e**). Ester **6e** was prepared from **5c** and **4a**, purified by chromatography on silica gel using chloroform as eluent, in the yield of 92%, m.p. 90–93 °C. ^{1}H NMR ($CDCl_3$): 3.60 s (CH_3OCO); 3.79 s (CH_2COO); 5.28 s (CH_2O); 6.80 m (H2′, 4′, 6′); 7.15 m, 7.25 m (H3, 4, 5, 5′); 7.41 dd, *J* = 1.3, 7.9 (H6); 7.53 m, 7.58 d, *J* = 8.5 (H3q, 6q); 7.72 m (H7q); 7.81 dd, *J* = 1.3, 8.5 (H5q); 8.05 d, *J* = 8.5 (H8q); 8.14 d, *J* = 8.5 (H4q). Hydrolysis of ester **6e** gave, after purification on silica gel using chloroform as eluent, acid **2e** in 57% yield, m.p. 165–167 °C. ^{1}H NMR (DMSO-d_6): 3.74 s (CH_2COO); 5.31 s (CH_2O); 6.82 m (H2′, 6′); 6.95 m (H4′); 7.20–7.40 m (H3, 4, 5, 6, 5′); 7.59 d, *J* = 8.8, 7.59 m (H3q, 6q); 7.76 m (H7q); 7.94 dd, *J* = 1.3, 8.5 (H5q); 8.02 d, *J* = 8.5 (H8q); 8.33 d, *J* = 8.8 (H4q). ^{13}C NMR: 39.50, 70.85, 113.21, 115.09, 120.61, 121.50, 126.78,

128.08, 128.24, 128.81, 130.45, 130.48, 130.82, 131.10, 131.67, 133.03, 134.36, 136.54, 137.95, 138.15, 145.52, 158.00, 158.79, 172.23. For $C_{24}H_{19}NO_3S \cdot 1/2H_2O$ (410.5) calculated: 70.22% C, 4.91% H, 3.41% N, 7.81% S; found: 70.13% C, 4.75% H, 3.34% N, 7.85% S.

[2-({3-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)phenyl]acetic acid (**2f**). Ester **6f** was prepared from **5c** and **4b**, isolated as an oil in 92% yield. ^{1}H NMR ($CDCl_3$): 3.59 s (CH_3OCO); 3.79 s (CH_2COO); 5.23 s (CH_2O); 6.77 m (H2′, 4′, 6′); 7.18 bm (H3, 4, 5, 5′); 7.40 dd, *J* = 1.6, 7.5 (H6); 7.56 d, *J* = 8.2 (H3q); 7.61 dd, *J* = 2.5, 8.8 (H7q); 7.73 d, *J* = 2.5 (H5q); 7.95 d, *J* = 8.8 (H8q); 7.99 d, *J* = 8.2 (H4q). Ester **6f** was hydrolyzed into acid **2f** in the yield of 56%, m.p. 167–169 °C (ethanol–water 4:1). ^{1}H NMR (DMSO-d_6, 60 °C): 3.72 s (CH_2COO); 5.29 s (CH_2O); 6.78 m (H2′, 6′); 6.94 m (H4′); 7.28 m (H3, 4, 5, 6, 5′); 7.64 d, *J* = 8.5 (H3q); 7.77 dd, *J* = 2.2, 9.1 (H7q); 8.01 d, *J* = 9.1 (H5q); 8.10 d, *J* = 2.2 (H8q); 8.35 d, *J* = 8.5 (H4q). For $C_{24}H_{18}ClNO_3S \cdot H_2O$ (453.9) calculated: 63.50% C, 4.44% H, 7.81% Cl, 3.08% N, 7.06% S; found: 63.67% C, 4.53% H, 8.03% Cl, 2.95% N, 7.02% S.

Methyl 2-[(4-Hydroxyphenyl)sulfinyl]benzoate (**9a**)

3-Chloroperbenzoic acid (10.4 g, 0.06 mol) was added to a suspension of methyl 2-[(4-hydroxyphenyl)sulfanyl]benzoate (**10a**; 16.0 g, 0.06 mol; prepared according to ref.[11]) in dichloromethane (230 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, filtered, and the filtrate evaporated. The crude solid was purified by crystallization from methanol, giving 7.9 g (47%) of **9a**, m.p. 202–204 °C, HPLC purity 99%. ^{1}H NMR (DMSO-d_6): 3.84 s (COOMe); 9.91 bs (OH). For $C_{14}H_{12}O_4S$ (276.3) calculated: 60.85% C, 4.38% H, 11.61% S; found: 60.69% C, 4.52% H, 11.45% S.

Methyl Esters **9b**, **9c** and **9d**

These methyl esters were prepared similarly.

Methyl 4-[(4-hydroxyphenyl)sulfinyl]benzoate (**9b**). From methyl 4-[(4-hydroxyphenyl)-sulfanyl]benzoate (**10c**); the crude solid was purified by chromatography on silica gel using dichloromethane–ethyl acetate (5–40%) as the eluent. **9b** was isolated in 56% yield, m.p. 195–197 °C, HPLC purity 99%. ^{1}H NMR (DMSO-d_6): 3.86 s (COOMe); 9.90 bs (OH). For $C_{14}H_{12}O_4S$ (276.3) calculated: 60.85% C, 4.38% H, 11.61% S; found: 60.48% C, 4.62% H, 11.37% S.

Methyl 2-[(3-hydroxyphenyl)sulfinyl]benzoate (**9c**). From methyl 2-[(3-hydroxyphenyl)-sulfanyl]benzoate (**10b**); the crude solid was purified by chromatography on silica gel using dichloromethane–ethyl acetate (5–10%) as the eluent. **9c** was isolated in 51% yield, m.p. 135–137 °C, HPLC purity 99%. ^{1}H NMR ($CDCl_3$, 60 °C): 3.92 s (COOMe); 7.12 bs (OH). For $C_{14}H_{12}O_4S$ (276.3) calculated: 60.85% C, 4.38% H, 11.61% S; found: 60.61% C, 4.45% H, 11.29% S.

Methyl {4-[(4-hydroxyphenyl)sulfoxy]phenyl}acetate (**9d**). From methyl ester **5b**; the crude product was purified by chromatography on silica gel using dichloromethane–ethyl acetate (10–30%) as the eluent. **9d** was isolated in 87% yield, m.p. 120–123 °C, HPLC purity 97%. ^{1}H NMR (DMSO-d_6): 3.62 s (COOMe); 3.66 s (CH_2COO); 6.78 dt, *J* = 1.8, 8.8 (H2′, 6′); 7.30–7.40 m (H3, 5, 3′, 5′); 7.49 dt, *J* = 1.8, 8.8 (H2, 6). For $C_{15}H_{14}O_4S$ (290.3) calculated: 62.05% C, 4.86% H, 11.05% S; found: 62.58% C, 5.12% H; 10.71% S.

Methyl 4-[(4-Hydroxyphenyl)sulfonyl]benzoate (**9e**)

30% aqueous hydrogen peroxide (40 ml) was added to a suspension of **10c** (13.0 g, 0.05 mol) in acetic acid (300 ml), and the mixture was stirred at 20 °C for 12 h. The clear solution was poured into ice water (600 ml), the precipitated **9d** was filtered off, and washed thoroughly with water; 10.6 g (73%) of **9d** was isolated, m.p. 186–188 °C, HPLC purity 99%. ^{1}H NMR (DMSO-d_6): 3.89 s (COOMe); 10.73 bs (OH). For $C_{14}H_{12}O_4S$ (292.3) calculated: 57.52% C, 4.14% H, 10.96% S; found: 57.33% C, 4.37% H, 10.82% S.

2-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfinyl}benzoic Acid (**3a**)

A mixture of **4a** (1.8 g, 0.01 mol) and **9a** (2.76 g, 0.01 mol), potassium carbonate (4.2 g) and potassium iodide (0.1 g) in butan-2-one (36 ml) was stirred under reflux for 10 h. The suspension was filtered, and the filtrate concentrated in vacuo. The obtained solid was crystallized from methanol (70 ml) to furnish methyl 2-{[4-(quinolin-2-ylmethoxy)phenyl]-sulfinyl}benzoate (**11a**) in 68% yield (2.9 g), m.p. 145–146 °C. ^{1}H NMR (DMSO-d_6): 3.82 s (COOMe); 5.34 s (CH_2O); 6.98 dt, *J* = 1.8, 8.8 (H2′, 6′); 7.45–7.50 m (H3, 5, 3′, 5′, 6q); 7.71 ddd, *J* = 1.1, 6.9, 8.3 (H3q); 7.81–8.02 m (H4, 6, 5q, 7q); 8.14 d, *J* = 8.4 (H8q); 8.45 dd, *J* = 1.1, 8.0 (H4q). A mixture of ester **11a** (2.9 g, 0.007 mol) in ethanol (35 ml) and potassium hydroxide (0.8 g, 0.014 mol) in water (5 ml) was stirred under reflux for 30 min. Water (90 ml) was added, and the turbid solution was filtered with charcoal. After acidification with acetic acid to pH 4.5, the precipitate was filtered off, and thoroughly washed with water. Acid **3a** was obtained in 83% yield (2.3 g), m.p. 219–221 °C. ^{1}H NMR (DMSO-d_6): 5.39 s (CH_2O); 7.14 bdt (H2′, 6′); 7.54–7.68 m (H3, 5, 3′, 5′, 6q); 7.77 ddd, *J* = 1.5, 6.9, 8.3 (H3q); 7.88–8.04 m (H4, 6, 5q, 7q); 8.31 dd, *J* = 1.1, 8.0 (H8q); 8.40 bd, *J* = 8.4 (H4q). ^{13}C NMR: 71.19, 115.40, 119.68, 124.05, 126.81, 127.36, 128.11, 128.11, 128.29, 128.71, 130.07, 130.70, 131.11, 133.75, 137.27, 139.00, 147.11, 148.82, 157.13, 160.10, 166.44. For $C_{23}H_{17}NO_4S$ (403.4) calculated: 68.47% C, 4.25% H, 3.47% N, 7.95% S; found: 68.30% C, 4.48% H, 3.58% N, 7.81% S.

Acids **3b**, **3c**, **3d** and **3e**

These acids were prepared similarly.

4-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfinyl}benzoic acid (**3b**). Ester **11b** was prepared from **4a** and **9b** in the yield of 52%, m.p. 156–158 °C (methanol). ^{1}H NMR ($CDCl_3$): 3.91 s (COOMe); 5.39 s (CH_2O); 7.08 bd, *J* = 8.5 (3, 5, 3′, 5′); 7.45 d, *J* = 8.5 (H2, 6); 7.56 t, *J* = 7.7 (H6q); 7.67 d, *J* = 8.6 (H3q); 7.75 t, *J* = 7.7 (H7q); 7.85 bd, *J* = 8.5 (H2′, 6′, 5q); 8.09 d, *J* = 8.6 (H8q); 8.21 d, *J* = 8.6 (H4q). For $C_{24}H_{19}NO_4S$ (417.5) calculated: 7.68% S; found: 7.55% S. Ester **11b** was hydrolyzed into **3b** in the yield of 94%, m.p. 211–212 °C. ^{1}H NMR (DMSO-d_6): 5.44 s (CH_2O); 7.21 ddt, *J* = 2.1, 8.8 (H3, 5, 3′, 5′); 7.50 dt, *J* = 2.2, 8.9 (H2, 6); 7.62 ddd, *J* = 1.4, 7.0, 8.4 (H6q); 7.70 d, *J* = 8.6 (H3q); 7.77 dd, *J* = 1.7, 8.4 (H7q); 7.84 dt, *J* = 2.0, 8.5 (H2′, 6′); 8.00 d, *J* = 9.3, 8.04 d, *J* = 9.3 (H5q, 8q); 8.42 d, *J* = 8.9 (H4q). For $C_{23}H_{17}NO_4S$ (403.4) calculated: 68.47% C, 4.25% H, 3.47% N, 7.95% S; found: 68.45% C, 4.41% H, 3.48% N, 7.91% S.

4-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfonyl}benzoic acid (**3c**). Ester **11c** was prepared from **4a** and **9e** in the yield of 88%, m.p. 188–190 °C (methanol). ^{1}H NMR ($CDCl_3$): 3.92 s (COOMe); 5.41 s (OCH_2); 7.12 dt, *J* = 1.8, 8.9 (H2, 6); 7.57 d, *J* = 8.5 (H3q, 6q); 7.74 ddd, *J* = 1.5, 6.8, 8.7 (H7q); 7.82 bt, *J* = 8.7 (H5q); 7.87 dt, *J* = 1.8, 8.8 (H3′, 5′); 7.95 dt, *J* = 1.8, 8.8

(H3, 5); 8.06 d, *J* = 8.7 (H8q); 8.12 dt, *J* = 1.8, 8.8 (H2′, 6′); 8.18 d, *J* = 8.7 (H4q). For $C_{24}H_{19}NO_4S$ (417.5) calculated: 7.68% S, found: 7.39% S. Ester **11c** was hydrolyzed into **3c** in the yield of 91%, m.p. >245 °C. ^{1}H NMR (DMSO-d_6): 5.48 s (CH_2O); 7.29 dt, *J* = 1.8, 8.9 (H2, 6); 7.58–7.67 m (H3q, 6q); 7.76 ddd, *J* = 1.4, 6.5, 8.6 (H7q); 7.90–8.05 m (H3, 5, 3′, 5′, 5q, 8q); 8.10 bd, *J* = 8.8 (H2′, 6′); 8.39 d, *J* = 8.2 (H4q). For $C_{23}H_{17}NO_4S$ (403.4) calculated: 65.86% C, 4.09% H, 3.34% N, 7.64% S; found: 65.70% C, 4.21% H, 3.38% N, 7.67% S.

2-{[3-(Quinolin-2-ylmethoxy)phenyl]sulfinyl}benzoic acid (**3d**). Ester **11d** was prepared from **4a** and **9c** in the yield of 89%, as a viscous oil after the purification by chromatography on silica gel using dichloromethane–ethyl acetate (10–30%) as the eluent. For $C_{24}H_{19}NO_4S$ (417.4) calculated: 7.68% S; found: 7.39% S. Ester **11d** was hydrolyzed into **3d** in the yield of 48%, m.p. 110–113 °C (methanol). ^{1}H NMR (DMSO-d_6): 5.44 s (OCH_2); 7.20 d, *J* = 8.2 (H4′); 7.25–7.35 m (H2′, 6′); 7.43 t, *J* = 7.9 (H5′); 7.56–7.73 m (H5, 3q, 6q); 7.79 t, *J* = 7.8 (H7q); 7.84 t, *J* = 6.9 (H4); 7.96 d, *J* = 7.7 (H6); 8.00–8.10 m (H 5q, 8q); 8.20 d, *J* = 7.8 (H3); 8.41 d, *J* = 8.5 (H4q). For $C_{23}H_{17}NO_4S{\cdot}CH_3OH$ (435.5) calculated: 66.18% C, 4.63% H, 3.02% N, 7.35% S; found: 66.42% C, 4.63% H, 3.22% N, 7.47% S.

(4-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfoxy}phenyl)acetic acid (**3e**). Ester **11e** was prepared from **4a** and **9d** in 44% yield, m.p. 148–150 °C (methanol). ^{1}H NMR ($CDCl_3$): 3.63 s (CH_2COO); 3.88 s (COOMe); 5.38 s (OCH_2); 7.08 d, *J* = 8.2 (H3′, 5′); 7.36 bd, *J* = 8.2 (H3, 5); 7.56 m (H2, 6, 2′, 6′, 3q, 6q); 7.73 t, *J* = 7.5 (H7q); 7.82 d, *J* = 8.2 (H5q); 8.07 d, *J* = 8.5 (H8q); 8.18 d, *J* = 8.5 (H4q). For $C_{25}H_{21}NO_4S$ (431.5) calculated: 7.42% S; found: 7.31% S. Ester **11d** was hydrolyzed into **3e** in the yield of 92%, m.p. 204–206 °C. ^{1}H NMR (DMSO-d_6): 3.64 s (CH_2COO); 5.42 s (CH_2O); 7.24 m (H3′, 5′); 7.42 bd, *J* = 8.5 (H3, 5); 7.59–7.70 m (H2, 6, 2′, 6′, 3q, 6q); 7.80 ddd, *J* = 1.6, 6.8, 8.5 (H7q); 8.02 m (H5q, 8q); 8.42 bd, *J* = 8.5 (H4q). ^{13}C NMR: 40.41, 71.30, 116.04, 119.73, 124.14, 126.62, 126.83, 127.39, 128.13, 128.75, 130.08, 130.69, 137.29, 137.74, 138.30, 144.61, 147.14, 157.14, 160.60, 172.38. For $C_{24}H_{19}NO_4S$ (417.5) calculated: 69.05% C, 4.59% H, 3.35% N, 7.68% S; found: 69.29% C, 4.92% H, 3.21% N, 7.55% S.

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REFERENCES

1. Hay D. W. P., Thorpy T. J., Undem B. J.: *Trends Pharmacol. Sci.* **1995**, *16*, 304.
2. Mayatepek E., Hoffmann G. F.: *Pediatr. Res.* **1995**, *37*, 1.
3. Smith L. J.: *Arch. Int. Med.* **1996**, *156*, 2181.
4. Bell R. L., Summers J. B., Harris R. R.: *Annu. Rep. Med. Chem.* **1997**, *32*, 91.
5. Brooks C. D. W., Summers J. B.: *J. Med. Chem.* **1996**, *39*, 2629.
6. Carter G. W., Young P. R., Albert D. H., Bouska J. B., Dyer R., Bell R. L., Summers J. B., Brooks D. W.: *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929.
7. Matassa V. G., Maduskuie T. P., Jr., Shapiro H. S., Hesp B., Snyder D. W., Aharony D., Krell R. D., Keith R. A.: *J. Med. Chem.* **1990**, *33*, 1781.
8. Jones T. R., Labelle M., Belley M., Champion E., Charette L., Evans J., Ford-Hutchinson W., Gauthier J.-Y., Lord A.: *Can. J. Physiol. Pharmacol.* **1995**, *73*, 191.
9. Ramires R., Caiaffa M. F., Tursi A., Haeggstrom J. Z., Macchia L.: *Biochem. Biophys. Res. Commun.* **2004**, *12*, 324.

10. Palomer A., Pascual J., Cabré F., Garcia M. L., Mauleón D.: *J. Med. Chem.* **2000**, *43*, 392.
11. Ferrari F., Mennuni L., Caselli G., Zanelli T., Makovec F.: *Eur. J. Pharmacol.* **2004**, *504*, 223.
12. Kolasa T., Gunn D. E., Bhatia P., Basha A., Craig R. A., Stewart A. O., Bouska J. B., Harris R. R., Hulkower K. I., Malo P. E., Bell R. L., Carter G. W., Brooks C. D. W.: *J. Med. Chem.* **2000**, *43*, 3322.
13. Gorlitzer K., Fabian J., Frohberg P., Drutkowski G.: *Pharmazie* **2002**, *57*, 243.
14. Gorlitzer K., Fabian J., Jones P. G., Frohberg P., Drutkowski G.: *Pharmazie* **2002**, *57*, 362.
15. Kuchař M., Kmoníček V., Panajotová V., Jandera A., Brůnová B., Junek R., Bucharová V., Čejka J., Šatínský D.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 2098.
16. Kuchař M., Kmoníček V., Zůnová H., Brůnová B., Panajotová V., Jandera A.: Czech 290693 (2002); U.S. 6,303,612 B1 (2003).
17. Hatzelmann A., Goossens J., Fruchtmann R., Mohrs K.-H., Raddatz S., Muller-Peddinghaus R.: *Biochem. Pharmacol.* **1994**, *47*, 2259.
18. Kolasa T., Gunn D. E., Bhatia P., Woods K. W., Gane T., Stewart A. O., Bouska J. B., Harris R. R., Hulkower K. E., Malo P. E., Bell R. L., Carter G. W., Brooks C. D. W.: *J. Med. Chem.* **2000**, *43*, 690.
19. Schuller H. M., Yhang L., Weddle D. L., Castongay A., Walker K., Miller M. S.: *J. Cancer Res. Clin. Oncol.* **2002**, *128*, 525.
20. Peters-Golden M., Brock T. G.: *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2003**, *69*, 99.
21. Wu X., Biswal S. S., Kehrer J. P.: *Cell Biol. Toxicol.* **2003**, *19*, 135.
22. Fau X. M., Tu S. P., Lem S. K., Wang W. P., Wu J., Wong W. M., Yuen M. F., Lin M. C., Kung H. F., Wong B. C.: *Gastroenterol. Hepatol.* **2004**, *19*, 31.
23. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: *Collect. Czech. Chem. Commun.* **1968**, *33*, 1895.
24. Šindelář K., Kakáč B., Svátek E., Metyšová J., Protiva M.: *Collect. Czech. Chem. Commun.* **1973**, *38*, 1579.
25. Sawyer J. S., Bach N. J., Baker S. R., Baldwin R. F., Borromeo P. S., Cockerham S. L., Fleisch J. H., Floreancig P., Froelich L. L., Jackson W. T., Marder P., Palkowitz J. A., Roman C. R., Saussy D. L., Jr., Schmittling E. A., Silbaugh S. A., Spaethe S. M., Stengel P. W., Sofia M. J.: *J. Med. Chem.* **1995**, *38*, 4411.
26. Wsol V., Szotáková B., Baliharová V., Šišpera L., Holčapek M., Kolářová L., Suchanová B., Kuchař M., Skálová L.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 689.
27. Palmer R. M. J., Salmon J. A.: *Immunology* **1983**, *50*, 65.
28. Cabré F., Carabazza A., Suesa N., Garcia A. M., Rotlan E., Gómez M., Tost D., Mauleón D., Carganico G.: *Inflamm. Res.* **1996**, *45*, 218.
29. Tateson J. E., Randall R. W., Reynold C. H., Jackson W. P., Bhattacherjee P., Salmon J. A., Garland L. G.: *Br. J. Pharmacol.* **1988**, *94*, 528.
30. Cheng J. B., Cheng E. I.-P., Kohi F., Townley R. G.: *J. Pharmacol. Exp. Ther.* **1986**, *236*, 126.
31. Bruns R. F., Thomsen W. J., Pugsley T. A.: *Life Sci.* **1983**, *33*, 645.
32. Jones T. R., Masson P.: *Prostaglandins* **1985**, *29*, 799.
33. Mathes W., Schuely H.: *Angew. Chem.* **1963**, *75*, 235.