DERIVATIVES OF (PHENYLSULFANYL)BENZOIC ACIDS WITH MULTIPLE ANTILEUKOTRIENIC ACTIVITY

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A series of derivatives of (phenylsulfanyl)benzoic acids bearing quinoline, 2,4-dihydroxy-3-propylacetophenone and 2,4-difluorobiphenyl moieties were prepared and their antileukotrienic activities evaluated. Some of the compounds were found to display multiple antileukotrienic effect in the inhibition of LTB_4 biosynthesis, binding to LTD_4 and LTB_4 receptors, superior to the standards (zileuton and zafirlukast) used. The compounds had an antiinflammatory effect, manifested with quinoline derivatives by a significant inhibition of bronchospasm induced by LTD_4 and/or albumin. The results of regression analysis correspond to the observation that the most active compounds belong to quinoline derivatives with the lowest lipophilicity. X-ray analysis of the quinoline compounds revealed that an intramolecular hydrophobic interaction of their aromatic rings does not occur in the solid state.

Keywords: (Phenylsulfanyl)benzoic acids; Antileukotrienic activity; Regression analysis; Lipophilicity; Antiinflammatory and antiasthmatic effects; QSAR.

Leukotrienes (LT) are an important group of biologically active compounds formed from arachidonic acid under the influence of 5-lipoxygenase (5-LO)[1]. Peptidoleukotrienes C_4 and D_4 were characterized[2] as components of the slowly reacting substance (SRS-A), which induces the inflammatory reaction in bronchoconstriction and increases the vascular permeability associated with acute hypersensitivity[3]. Furthermore, LTB_4 stimulates[4] the ag-

gregation and degranulation of neutrophiles, promotes[5] chemotaxis and chemokinesis of leukocytes and other cells which play an important role in the development of the inflammatory process. The LT antagonists and/or the inhibitors of LT biosynthesis can be therefore utilized[6] in the treatment of the allergic diseases of the respiratory system. A great number of anti-asthmatics with an antileukotrienic mechanism of action, such as the 5-LO inhibitor zileuton[7] or peptide LTD_4 antagonists zafirlukast[8] and montelukast[9] attest to the increasing importance of antileukotrienics in the treatment of asthma.

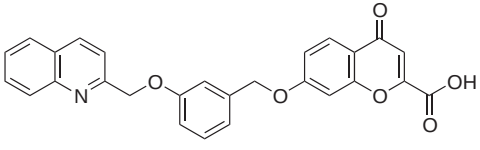
A majority of antileukotrienics possess common structural features, which can be summarized as follows[10]:

a) the hydrophobic region in the proximity of polar group is in the "western" part;

b) the "eastern" part is a carrier of an acidic group (carboxyl or its equivalent);

c) a spacer of various flexibility connects both parts.

The fragments of quinoline[9,11–13], 2,4-dihydroxy-3-propylacetophenone[14–16] or biphenyl[10,17] are frequently used as the "western" moieties. It was found out in quinoline antileukotrienics that the distance between the quinoline moiety and the acidic function is important for leukotriene receptor affinity. For example, the insertion of a methoxyphenyl spacer between quinoline and the carboxyl carrier led to the chromone derivative **1** with almost 10^5-fold LTD_4 receptor affinity in comparison with an original compound[18]. A similar result, concerning the distance between the lipophilic region and carboxyl, was obtained from the QSAR analysis of antileukotrienic activities[19,20] in the series of 2,4-dihydroxy-3-propylacetophenone derivatives **2**. This conclusion is in agreement with the hypothesis[10,21,22] concerning the binding sites on LTB_4 and LTD_4 receptors.



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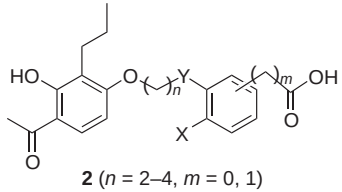


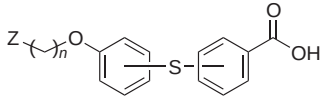
2 (*n* = 2–4, *m* = 0, 1)

This work was aimed at the preparation of derivatives, carrying the above-mentioned moieties, that would exhibit a broader spectrum of antileukotrienic activities and could be used in the treatment of asthma.

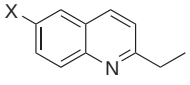
We have also tried to elucidate the role of lipophilicity in the antileukotrienic activities of the compounds studied with regard to the considerable extent of their lipophilicities.

RESULTS

The series of compounds **3**–**5** were synthesized using the fragments of quinoline, 2,4-dihydroxy-3-propylacetophenone and 2,4-difluorobiphenyl as the lipophilic moieties. The use of phenylsulfanylbenzoic acids as the carboxyl carriers offers a similar distance (corresponding to a number of atoms) between the quinoline moiety and carboxyl in comparison with compound **1**. The sulfur atom at the proximity of the carboxyl was described in LTB_4 antagonists[23] and LTD_4 antagonists[12,24]. Three different "western" moieties were used to change their lipophilicity and consequently the total lipophilicity.



3, Z =



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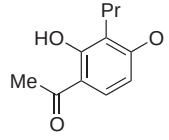
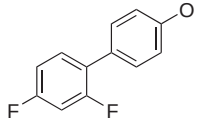
4, Z =



n = 2–4

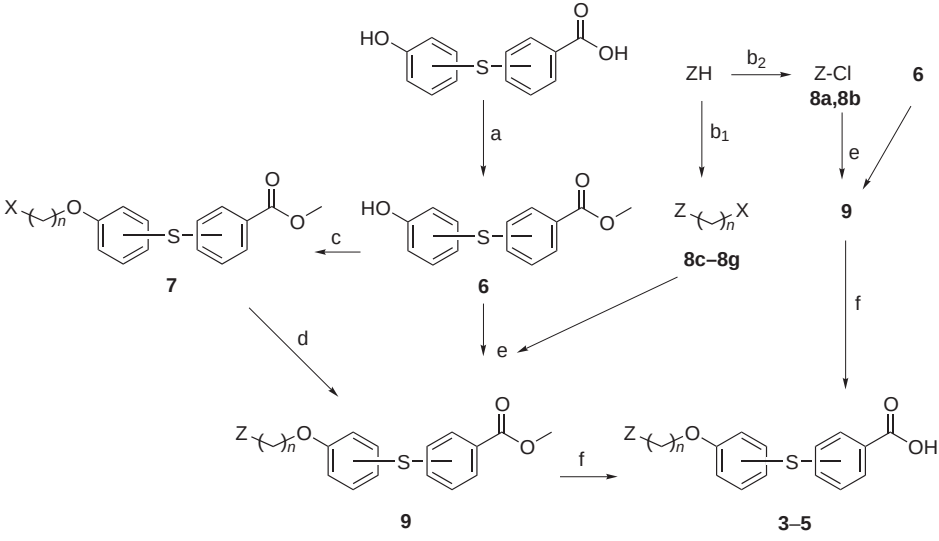
5, Z =



n = 3,4

3	X	Position of S to		**5**	*n*	Position of S to		**4**	*n*	Position of S to	
		O	COOH			O	COOH			O	COOH
a	H	*p*	*p*	**a**	3	*p*	*p*	**a**	2	*p*	*p*
b	H	*p*	*o*	**b**	4	*p*	*p*	**b**	3	*p*	*p*
c	H	*m*	*p*	**c**	3	*p*	*o*	**c**	4	*p*	*p*
d	H	*m*	*o*	**d**	4	*p*	*o*	**d**	2	*m*	*p*
e	Cl	*p*	*p*	**e**	3	*m*	*o*	**e**	3	*m*	*p*
f	Cl	*p*	*o*	**f**	4	*m*	*o*	**f**	4	*m*	*p*
g	Cl	*m*	*o*	**g**	4	*m*	*p*	**g**	3	*m*	*o*
								h	4	*m*	*o*
								i	3	*p*	*o*
								j	4	*p*	*o*

Synthesis of compounds **3**–**5** was accomplished using two methods, described in Scheme 1. In the first method, methyl [(hydroxyphenyl)-sulfanyl]benzoates **6** were treated with substituted alkyl halides **8** in the presence of potassium carbonate and esters **9** were then hydrolyzed to afford the desired acids. In the second method, esters **6** were treated with dihaloalkanes to obtain haloalkoxy derivatives **7**, used for the alkylation of phenols ZH to give esters **9**. Esters **6** were obtained from [(methoxyphenyl)sulfanyl]benzoic acids through O-demethylation with pyridine hydrochloride and subsequent esterification with H_2SO_4/MeOH.



a) boiling methanol, H_2SO_4, 16 h; b_1) ω,ω'-dihaloalkane, K_2CO_3, boiling 2-butanone, 10 h; b_2) K_2CO_3, tetrachloromethane, Cl_2; c) ω,ω'-dihaloalkane, K_2CO_3, boiling 4-methylpentan-2-one, $_{10}$ h; d) ZH, K_2CO_3, KI, boiling 4-methylpentan-2-one, 24 h; e) K_2CO_3, KI, boiling 5-methylpentan-2-one or $_2$-butanone; f) 1. KOH, boiling ethanol/water, 0.5 h, 2. dilute HCl or acetic acid

SCHEME 1

2-(Chloromethyl)quinoline was prepared[25] from 2-methylquinoline by treatment with chlorine. The same method was used for the preparation of 6-chloro-2-(chloromethyl)quinoline from 6-chloro-2-methylquinoline.

All compounds were subjected to the 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, necessary for antagonistic activities toward those LT. The compounds were also tested for their antiinflammatory activities *in vivo* in three models of inflammation.

Selected derivatives were subjected to the evaluation of antiasthmatic activity by the inhibition of bronchospasms induced by ovalbumin and LTD_4. Two antiasthmatics, 5-LO inhibitor zileuton and LTD_4 antagonist zafirlukast, were used as standards. The results of antileukotrienic and anti-inflammatory activities are summarized in Tables I and II, respectively; the values of bronchospasm inhibition are shown in Table III.

The log P_{calc} and log P_{frg} values (see Experimental) were used for the evaluation of total lipophilicity and lipophilicity of the "western" fragments. The retention characteristics measured by HPLC (log k) and TLC (R_M) methods were used as the experimental lipophilic parameters. The relationships between the experimental and calculated lipophilic variables were used for the evaluation of possible intramolecular hydrophobic interactions of the aromatic rings in compounds **3**–**5**. All values are summarized in Table I.

DISCUSSION

The regression equations representing the relationships between log P_{calc} and log k (Eq. (*1*)) and R_M (Eq. (*2*)) values did not show any important systematic deviations from linearity. This fact indicates the absence of intramolecular hydrophobic interactions in the chromatographic separation. The results of X-ray analysis of quinoline derivatives **3a** and **3c** also confirm the unfolded structure of both molecules. The aromatic rings are not coplanar and their distance is probably too large for π–π interactions. The structural arrangements of both compounds are shown in Figs 1, 3 and 2, 4, respectively. Statistically significant relationship between both experimental variables (Eq. (*3*)) confirms the similarity of the separation mechanisms in both chromatographic systems.

$$\log P_{calc} = 2.237(\pm 0.360) \log k + 4.841(\pm 0.473)$$

$$n = 20,\ r = 0.971,\ s = 0.243,\ F = 319.2 \qquad (1)$$

$$\log P_{calc} = 2.765(\pm 0.346) R_M + 6.933(\pm 0.149)$$

$$n = 20,\ r = 0.982,\ s = 0.191,\ F = 529.6 \qquad (2)$$

$$\log k = 1.214(\pm 0.114) R_M + 0.940(\pm 0.049)$$

$$n = 20,\ r = 0.992,\ s = 0.057,\ F = 1155.8 \qquad (3)$$

TABLE I
Antileukotrienic activities of compounds **3**–**5**

Compound	Inhibition of LTB_4 biosynthesis		Inhibition of LTB_4 binding		Inhibition of LTD_4 binding		log P_{calc}	R_M	log k'
	IC_{50} [a]	log $(1/IC_{50})+6$	IC_{50} [a]	log $(1/IC_{50})+6$	IC_{50} [a]	log $(1/IC_{50})+6$			
Quinoline derivatives									
3a	0.01	8.000	16.7	4.777	0.07	7.155	6.11	–0.16	0.769
3b	0.33	6.481	70.3	4.153	1.7	5.770	5.77	–0.50	0.354
3c	0.05	7.301	32.9	4.482	1.6	5.796	6.11	–0.28	0.627
3d	0.20	6.699	44.2	4.355	0.63	6.201	5.77	nd	nd
3e	0.17	6.770	5.0	5.301	3.8	5.420	6.75	0	0.971
3f	0.19	6.721	30.1	4.521	1.7	5.770	6.41	–0.22	0.653
3g	0.08	7.097	31.3	4.504	0.27	6.569	6.41	–0.26	0.564
2,4-Dihydroxyacetophenone derivatives									
4a	7.5	5.125	8.5	5.071	10.8	4.967	7.49	0.35	1.310
4b	1.0	6.000	5.0	5.301	19.0	4.721	7.98	0.48	1.563
4c	3.6	5.444	9.6	5.018	32.4	4.489	8.47	0.55	1.664
4d	1.7	5.770	5.2	5.284	26.1	4.583	7.49	0.18	1.172
4e	0.10	7.000	4.0	5.398	15.1	4.821	7.98	0.39	1.402
4f	1.2	5.921	3.7	5.432	3.9	5.409	8.47	0.50	1.602
4g	2.1	5.678	2.6	5.585	4.1	5.387	7.64	0.23	1.285
4h	0.82	6.086	8.1	5.092	7.0	5.155	8.13	0.43	1.535
4i	0.66	6.180	5.0	5.301	10.4	4.983	7.64	0.25	1.208
4j	0.65	6.187	15.8	4.801	13.6	4.866	8.13	0.41	1.395
2,4-Difluorobiphenyl derivatives									
5a	12.0	4.921	>100	ni	>100	ni	8.64	0.62	1.629
5b	74.6	4.127	>100	ni	>100	ni	9.13	0.72	1.859
5c	1.7	5.770	8.1	5.092	98.3	4.007	8.30	nd	nd
5d	6.9	5.161	>100	ni	>100	ni	8.79	nd	nd
5e	0.87	6.060	12.0	4.921	22.7	4.644	8.30	0.41	1.292
5f	4.6	5.337	>100	ni	>100	ni	8.79	nd	nd
5g	7.3	5.137	50.0	4.301	>100	ni	9.13	0.79	1.890
Standards									
Zileuton	0.17		>100		>100		3.06	nd	nd
Zafirlukast	1.12		>100		0.07		7.24	nd	nd

[a] In μM concentration.
nd, not determined; ni, not included in regression analysis.

TABLE II
Antiinflammatory activities of compounds **3**–**5**

Compound	CE[a] % of inhibition	Experimental pleuritis, % of inhibition[b]			Ear edema, % of inhibition[c]	
		A	B	C	D	E
3a	47	26	33	11(s)	27	46
3b	13	17	23	6[n]	20	5[n]
3c	10	28	29	1[n]	13	8[n]
3d	19	5[n]	20	15	16	3[n]
3e	14	10	25	15	1[n]	9[n]
3f	18	15	12	4(s)	7	3[n]
3g	25	15	19	4[n]	12	0
4a	31	8[n]	17	9[n]	13	8[n]
4b	32	2[n]	27	28	8	5[n]
4c	54	11	27(s)	38(s)	8[n]	2[n]
4d	30	2[n]	43(s)	46(s)	18	2[n]
4e	14	10	46(s)	61(s)	1[n]	0
4f	24	7[n]	18	11[n]	1[n]	9(s)
4g	22	26	29	6[n]	9	8[n]
4h	23	7[n]	9[n]	4[n]	17	5(s)
4i	35	10[n]	35	30	6[n]	2[n]
4j	41	14	35	26	16	5[n]
5a	17	10(s)	17(s)	5(s)	8	8[n]
5b	12	2(s)	0	7(s)	6[n]	5[n]
5c	4[n]	14(s)	7(s)	5(s)	15	0
5d	22	10	2(s)	6[n]	18	8
5e	12	11	10	6(s)	11	32
5f	12	15(s)	47(s)	26(s)	9[n]	6[n]
5g	9	38(s)	10(s)	17	8[n]	8[n]
Zileuton	46	36	49	20	9[n]	13
Zafirlukast	43[d]	nd	nd	nd	23	43

[a] Inhibition of carrageenan edema. [b] Inhibition of: A, volume of exudate in pleural cavity; B, number of cells; C, cellularity in a cell unit. [c] Inhibition of: D, edema of ear lobe; E, hyperemia of ear lobe. [d] After the dose of 10 mg/kg.
nd, not determined; s, % of stimulation; [n], the level of statistical significance $p > 0.05$.

Given the small number of compounds in individual subgroups, the relationships of antileukotrienic activities were studied in the whole series of compounds **3**–**5**. Reverse dependences on lipophilicity were found for the inhibition of LTB_4 biosynthesis (Eq. (*4*)) and for binding to LTD_4 receptors (Eq. (*5*)). Unfortunately, the dependence on lipophilicity accounts for only 62–71% of the dependences of these activities on physico-chemical parameters. The lipophilic parameters log P_{frg}, characterizing the lipophilicity of the "western" moieties, were also used in the regression analysis. Their insertion instead of log P_{calc} did not improve the statistical significance of Eqs (*4*)–(*6*). The outliers from the regression were studied, but no systematic deviations were found that would enable us to improve the regression by the use of other physico-chemical parameters. Several indicator variables characterizing the position of the substituents in the acidic part and the moieties in the lipophilic part of compounds **3**, **4** and **5** were also involved in the regression analysis. Minor improvement of the statistical significance was observed only in Eq. (*7*), where the indicator variable I_{ortho}, characterizing the relative position of carboxyl to sulfur, was used.

TABLE III
Inhibition of bronchospasm induced by ovalbumin or LTD_4 (dose: 100 mg/kg; % of inhibition at 2, 4, and 10 min intervals)

Compound	Mediator	
	Ovalbumin	LTD_4
3a	41, 45, 63	69, 70, 75
3b	21, 27, 31	14, 33, 43
3d	23, 36, 50	11, 28, 23
3e	3, 15, 30	14, 33, 43
3g	66, 72, 85	6, 38, 54
4e	nd	nd, 16, nd
4f	nd	nd, 98, nd
Zileuton	23, 28, 50	10, 54, 75

Inhibition of LTB_4 biosynthesis:

$$\log (1/C) = -0.643(\pm 0.300) \log P_{calc} + 10.964(\pm 2.323)$$

$$n = 24,\ r = 0.779,\ s = 0.549,\ F = 36.37 \qquad (4)$$

Binding to LTD_4 receptors:

$$\log (1/C) = -0.643(\pm 0.341) \log P_{calc} + 10.019(\pm 2.518)$$

$$n = 19,\ r = 0.785,\ s = 0.480,\ F = 30.00 \qquad (5)$$

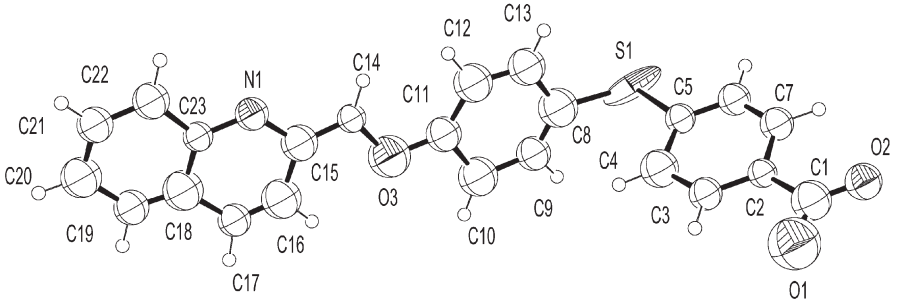


FIG. 1
ORTEP view of **3a**, showing the numbering scheme. Thermal ellipsoids are drawn at 50% probability

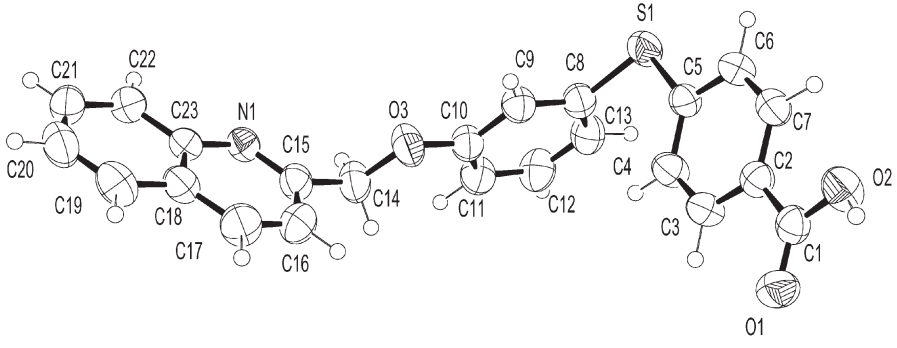


FIG. 2
ORTEP view of **3c**, showing the numbering scheme. Thermal ellipsoids are drawn at 50% probability

Binding to LTB_4 receptors:

$$\log (1/C) = 5.222(\pm 2.550) \log P_{calc} - 0.345(\pm 0.174) (\log P_{calc})^2 - \\ - 14.461 (\pm 10.138)$$

$$n = 20,\ r = 0.842,\ s = 0.229,\ F = 24.19 \qquad (6)$$

$$\log (1/C) = 5.254(\pm 2.465) \log P_{calc} - 0.348(\pm 0.169) (\log P_{calc})^2 - \\ - 0.157(\pm 0.149) I_{ortho} - 14.442(\pm 8.832)$$

$$n = 20,\ r = 0.856,\ s = 0.220,\ F = 18.36 \qquad (7)$$

Apparently, it can be concluded from the results of the regression analysis that the inhibition of LTB_4 biosynthesis and binding on LTD_4 receptors decrease with increasing lipophilicity. Probably, the compounds are situated, according to their lipophilicity, on the descending part of the nonlin-

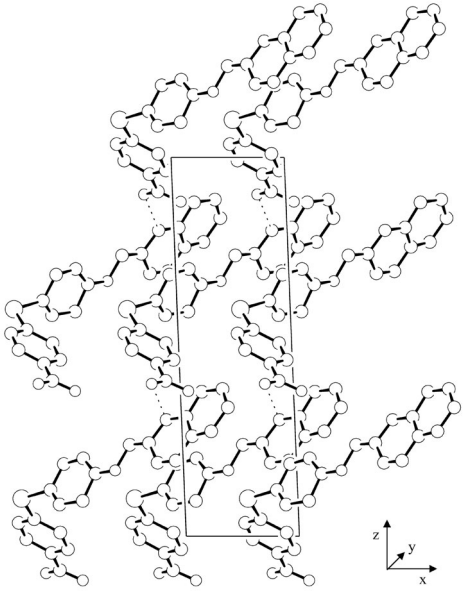


FIG. 3
Packing scheme of **3a**; dashed lines indicate hydrogen bonds (a view in the 0 → Y direction)

ear dependence of these activities on total lipophilicity. It is therefore not surprising that the most active compounds with regard to both activities belong to the group of quinoline derivatives **3** with the lowest lipophilicity. The most active compound **3a** manifested higher activities in both instances than the standards (Table I). In the case of LTB_4 receptor binding, a parabolic dependence facilitated the calculation of the optimum of lipophilicity, i.e. log P_{opt} –7.6, close to the series of compounds **4**, with the highest LTB_4 receptor binding. The dependences of the antileukotrienic activities on lipophilicity reflect in all three instances the influence of lipophilicity on their transport through the biological system. As regards the inhibition of bronchospasm induced either by albumin or LTD_4 (Table III), the most active compounds belong to the quinoline derivatives **3**. It can be assumed that the combination of the inhibition of LTB_4 biosynthesis and LTD_4 receptor antagonism *in vitro* is decisive for the inhibition of bronchospasm induced by both mediators *in vivo*. The location of the compounds, according to their lipophilicity, on the descending parts of the activity–lipophilicity dependences (Eqs (*4*), (*5*)) offers the possibility of increasing the antileukotrienic activities by shifting the total lipophilicity to a lower value; further work in that direction is in progress.

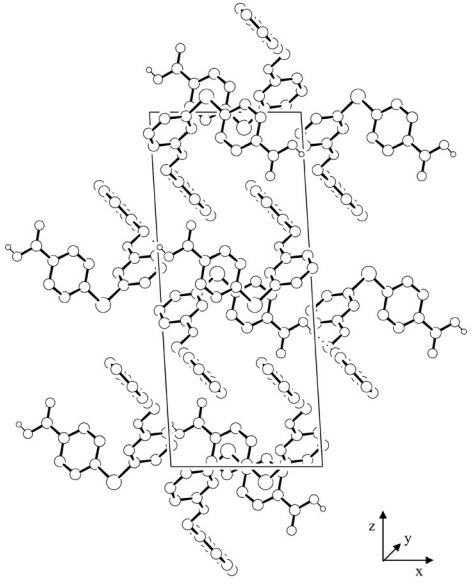
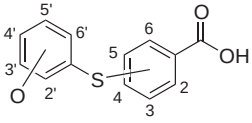


FIG. 4
Packing scheme of **3c**; dashed lines indicate hydrogen bonds (a view in the 0 → Y direction)

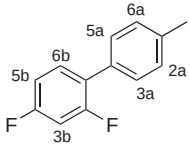
EXPERIMENTAL

The melting points were determined on a Boetius-type Kofler block and are not corrected. The ^{1}H NMR spectra (δ, ppm; *J*, Hz) of 6% solutions of the compounds in $CDCl_3$ (or in DMSO-d_6) containing TMS or 3-(trimethylsilyl)propanoic acid-d_5 as the internal standard were measured on a Bruker-250-DPX instrument, working at 250 MHz for ^{1}H. The following numbering was used for the aromatic rings:

a) (arylsulfanyl)benzoic acids



b) 2,4-difluorobiphenyl



The purity of compounds **3**–**5** 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 range. Cromasil C18 100 A (300 × 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.

Values of log P_{calc} were calculated using the KOWWIN Program, Version 1.63 (Syracuse Research Corp., U.S.A.); as log P_{frg} values were used: 3.89 for 2-hydroxy-3-propylacetophenone, 2.59 for 2-methylquinoline and 4.28 for 2,4-difluorobiphenyl.

The coefficients in the regression equations were calculated from the experimental results by multiple regression analysis and their statistical significance was tested by the Student *t*-test. The statistical significances of the regression equations were tested by the standard deviation (*s*), coefficient of multiple correlation (*r*) and Fisher–Snedecor criterion (*F*). The level of statistical significance *p* was better than 0.01 of the whole equations and individual variables (with the exception of I_{ortho} in Eq. (*7*), where $p < 0.1$).

Evaluation of Lipophilicity by Chromatographic Methods

TLC: silanized silica gel FPKG60F_{254} (Merck, Darmstadt) impregnated with a silicon oil Lukoil 100 (Synthesia, Kolín, Czech Republic) was used as a stationary phase and acetone with 40% of buffer (McIlvaine, pH 3.4) was used as a mobile phase. Each chromatogram contained ten compounds, two acids serving as reference samples. In the individual chromatograms, the R_F values of the standards did not differ by more than 0.02. The experimental details have been described elsewhere[26]. R_M values were calculated from the experimental R_F values according to the relationship $R_M = \log [(1/R_F) - 1]$.

HPLC: experiments were carried out using a liquid chromatograph with a LCP 4100 pump (ECOM, Prague, Czech Republic), an autosampler Waters 717 plus, a UV detector Waters 486 (Waters Assoc., Milford) and a data module CSW (DataApex, Czech Republic). Thermoquest Hypersil ODS 5 μm (Thermo Hypersil-Keystone, Asmoor Runcorn, U.K.) in a 250 × 4.6 mm I.D. column was used as a stationary phase and the mixture of acetonitrile–buffer pH 5.75 (50:50) was used as a mobile phase. The detection was performed by UV absorption at 233 nm. The retention time of sodium nitrate (0.02% solution) was taken as a t_0 and the capacity factor k was evaluated from the retention time of the solute, t_R, by the relationship: $k = (t_R - t_0)/t_0$.

Crystal Structure Determination

Data and refinement parameters are listed in Table IV. International Tables for X-Ray Crystallography[27], and programs SDP [28], CRYSTALS [29], SHELXS86 [30] and Ortep3 [31] were used. CCDC 208971 and 208972 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Crystal data for **3a**. M_r = 386.45, space group *Pc* (No. 7), a = 5.582(5), b = 9.081(5), c = 18.701(5) Å, V = 947(1) Å^3; λ = 1.54184 Å, D = 1.35 g cm^{-3}, Z = 2, F(000) = 404, colorless blocks, crystal fragment of dimensions 0.07 × 0.07 × 0.48 mm, μ(CuKα) = 17.17 cm^{-1}. The structure was solved by direct methods and due to the lack of observed reflections isotropically refined, except for S, which was refined anisotropically, by full-matrix least-squares. Hydrogen atoms were located on the basis of the expected geometry and their positions refined.

Crystal data for **3c**. M_r = 387.46, space group *P*21/*c* (No. 14), a = 8.7959(6), b = 10.6195(7), c = 20.557(1) Å, V = 1916.7(2) Å^3; λ = 1.54184 Å, D = 1.343 g cm^{-3}, Z = 4, F(000) = 808, colorless blocks, single crystal of dimensions 0.21 × 0.21 × 0.25 mm, μ(CuKα) = 16.97 cm^{-1}. The structure was solved by direct methods[32] and refined anisotropically, by full-matrix least-squares. Hydrogen atoms were located based on the expected geometry and Δρ maps and their positions refined.

Methyl 4-[(4-Hydroxyphenyl)sulfanyl]benzoate (**6a**)

A solution of 4-[(4-hydroxyphenyl)sulfanyl]benzoic acid (46.9 g, 0.19 mol) in methanol (480 ml) and sulfuric acid (5 ml) was heated under reflux for 16 h. Methanol was evaporated and the rest was poured into ice water (600 ml). Ester **6a** was obtained in a yield of 39.0 g (78.9%), m.p. 184–186 °C without purification. For $C_{14}H_{12}O_3S$ (260.3) calculated: 64.59% C, 4.65% H, 12.32% S; found: 64.52% C, 4.72% H, 11.99% S.

Methyl Esters **6b**, **6c** and **6d**

These esters were prepared similarly:

Methyl 4-[(3-hydroxyphenyl)sulfanyl]benzoate (**6b**). The compound was prepared in 82.9% yield with m.p. 86–87 °C (benzene–hexane). For $C_{14}H_{12}O_3S{\cdot}0.5C_6H_6$ (299.3) calculated: 68.22% C, 5.05% H, 10.69% S; found: 68.49% C, 4.96% H, 10.94% S.

Methyl 2-[(3-hydroxyphenyl)sulfanyl]benzoate (**6c**). The compound was prepared in 78.8% yield with m.p. 77–78.5 °C without purification. For $C_{14}H_{12}O_3S$ (260.3) calculated: 64.59% C, 4.65% H, 12.32% S; found: 64.73% C, 4.75% H, 11.98% S.

Methyl 2-[(4-hydroxyphenyl)sulfanyl]benzoate (**6d**). The compound was prepared in 77.1% yield with m.p. 140–142 °C (chloroform). For $C_{14}H_{12}O_3S$ (260.3) calculated: 64.59% C, 4.65% H, 12.32% S; found: 64.53% C, 4.81% H, 11.96% S.

2-(Chloromethyl)quinoline (**8a**)

The compound was prepared by a modified chlorination[15] of quinaldine in tetrachloromethane in the presence of anhydrous potassium carbonate. The crude product **8a** was purified by crystallization from hexane in the total yield of 65.0%, m.p. 54–56 °C (lit.[25] m.p. 56.5–57.5 °C).

TABLE IV
Data collection and refinement parameters

Parameter	**3a**	**3c**
Crystal dimensions, mm	0.07 × 0.07 × 0.48	0.21 × 0.21 × 0.25
Diffractometer and radiation used, Å	Enraf-Nonius CAD4, CuKα, λ = 1.54184	
Scan technique	ω/2θ	
Temperature, K	293	
No. and θ range of reflections for lattice parameter refinement, °	20; 28–31	20; 36–40
Range of *h*, *k* and *l*	0→5, –9→9, –18→18	–10→10, –12→12, 0→24
Standard reflections monitored in the interval; intensity fluctuation	60 min; 0.7%	60 min, 1.9%
Total number of reflections measured; 2θ range	2216; 4–100°	7219; 4–136°
No. of observed reflections	681	2480
Criterion for observed reflections	$I \geq 1.96\sigma(I)$	
Function minimized	$w(\|F_0\| - (\|F_c\|)^2$	
Weighting scheme	Chebyshev polynomial[21]	
Parameters refined	118	305
Value of *R*, *wR*, and *S*	0.1175, 0.1142 and 1.0589	0.0047, 0.036 and 1.168
Ratio of the maximum least-squares shift to e.s.d. in the last cycle	0.00007	0.0007
Maximum and minimum heights in final Δρ map, e Å^{-3}	0.58, –0.51	0.27, –0.36

6-Chloro-2-(chloromethyl)quinoline (**8b**)

A mixture of 6-chloroquinaldine (8.9 g, 50.0 mmol) (prepared according to[33] from 4-chloroaniline and crotonaldehyde in the presence of sulfuric acid and sodium 4-nitrobenzene-1-sulfonate) and anhydrous potassium carbonate in tetrachloromethane (40 ml) was heated to 50–55 °C and chlorine (4.7 g, 67.0 mmol) was continuously being introduced over 2 h. The mixture was cooled to 20 °C, the solid was filtered off and the filtrate extracted twice with 100 ml of 2 M HCl. The combined extracts were neutralized with sodium carbonate and the precipitated crude **8b** separated after cooling to 5 °C. Pure **8b** was prepared in 63.9% yield, m.p. 118–120 °C (70% ethanol). For $C_{10}H_7Cl_2N$ (212.1) calculated: 56.63% C, 3.33% H, 33.44% Cl, 6.60% N; found: 56.60% C, 3.48% H, 33.46% Cl, 6.35% N.

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

A mixture of **6a** (6.5 g, 25.0 mmol), **8a** (4.4 g, 25.0 mmol), anhydrous potassium carbonate (10.0 g) and potassium iodide (0.4 g) in butan-2-one (80 ml) was heated at reflux for 8 h. The hot suspension was filtered, the filtrate evaporated to dryness and the solid boiled with methanol (150 ml) to give, after cooling and filtration, 8.2 g (82.1%) of the methyl ester of **3a**, m.p. 125–127 °C. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 71.38% C, 4.81% H, 3.23% N, 7.99% S. This ester (5.7 g, 14.2 mmol) was suspended in ethanol (40 ml), a solution of potassium hydroxide (2.3 g) in water (15 ml) was added and the mixture heated at reflux for 15 min. The clear solution was evaporated and the residue dissolved in boiling water (250 ml). After filtration, the filtrate was acidified with acetic acid and the precipitated crude product purified by crystallization from propan-2-ol (100 ml) and water (5 ml). The precipitated product was filtered off at 40 °C to give **3a** (5.2 g, 94.4%), m.p. 204–206 °C (propan-2-ol). For $C_{23}H_{17}NO_3S$ (387.5) calculated: 71.30% C, 4.42% H, 3.61% N, 8.28% S; found: 71.15% C, 4.55% H, 3.38% N, 8.29% S. ^{1}H NMR (DMSO-d_6): 5.43 s (CH_2O); 7.19 m (H-3,5,3′,5′); 7.49 d, J = 9.0 (H-2′,6′); 7.83 d, J = 8.7 (H-2,6); 8.43 d, J = 8.2 (H-4 quin).

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

These acids were prepared similarly:

2-{[4-(Quinolin-2-ylmethoxy)phenyl]sulfanyl}benzoic acid (**3b**). The crude methyl ester of **3b** was obtained from **8a** and **6d** in 92.1% yield, m.p. 134–136 °C. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 71.53% C, 4.80% H, 3.46% N, 8.30% S. The ester was hydrolyzed and acid **3b** was obtained in 52.3% yield, m.p. 208–210 °C (butan-2-one). For $C_{23}H_{17}NO_3S$ (387.5) calculated: 71.30% C, 4.42% H, 3.61% N, 8.28% S; found: 71.08% C, 4.61% H, 3.89% N, 8.06% S. ^{1}H NMR (DMSO-d_6): 5.41 s (CH_2O); 8.02 m (H-3,4,5,6,2′,3′,5′,6′); 8.38 d, J = 8.5 (H-4 quin).

4-{[3-(Quinolin-2-ylmethoxy)phenyl]sulfanyl}benzoic acid (**3c**). The methyl ester of **3c** was prepared from **8a** and **6b**, after crystallization from methanol the ester was obtained in 75.5% yield, m.p. 95–97 °C. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 71.58% C, 4.81% H, 3.40% N, 7.81% S. The ester was hydrolyzed and acid **3c** was obtained in 71.4% yield, m.p. 190–192 °C (propan-2-ol). For $C_{23}H_{17}NO_3S{\cdot}H_2O$ (405.5) calculated: 68.12% C, 4.72% H, 3.45% N, 7.91% S; found: 68.45% C, 4.61% H, 3.61% N, 7.83% S. ^{1}H NMR (DMSO-d_6): 5.37 s (CH_2O); 6.97–7.87 m (H-3,5,2′,4′,5′,6′); 7.95 d, J = 8.2 (H-4 quin).

2-{[3-(Quinolin-2-ylmethoxy)phenyl]sulfanyl}benzoic acid (**3d**). The crude methyl ester of **3d** was prepared in nearly quantitative yield from **8a** and **6c**, m.p. 52–55 °C; the analytical sample was prepared by crystallization from methanol–ether, m.p. 70–72 °C. For $C_{24}H_{19}NO_3S$ (401.5) calculated: 71.80% C, 4.77% H, 3.49% N, 7.99% S; found: 71.83% C, 4.76% H, 3.18% N, 7.75% S. Acid **3d** was prepared in 60.9% yield from the crude ester by hydrolysis, purified by crystallization from butan-2-one–hexane, m.p. 169–171 °C. For $C_{23}H_{17}NO_3S$ (387.5) calculated: 71.30% C, 4.42% H, 3.61% N, 8.28% S; found: 71.06% C, 4.50% H, 3.38% N, 8.13% S. ^{1}H NMR (DMSO-d_6): 5.37 s (CH_2O); 6.84–7.85 m (H-3,4,5,6,2′,4′,5′,6′); 8.35 d, J = 9.0 (H-4 quin).

4-({4-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)benzoic acid (**3e**). The methyl ester of **3e** was obtained from **8b** and **6a** in 91.3% yield, m.p. 130–132 °C (methanol). For $C_{24}H_{18}ClNO_3S$ (435.9) calculated: 66.13% C, 4.16% H, 8.13% Cl, 3.21% N, 7.36% S; found: 65.84% C, 4.14% H, 8.29% Cl, 3.60% N, 7.16% S. The ester was hydrolyzed and after crystallization from dimethylformamide the acid **3e** was obtained in 93.0% yield, m.p. 232–235 °C. For $C_{23}H_{16}ClNO_3S$ (421.9) calculated: 65.48% C, 3.82% H, 8.40% Cl, 3.32% N, 7.60% S; found: 65.31% C, 3.91% H, 8.34% Cl, 3.60% N, 7.52% S. ^{1}H NMR (DMSO-d_6): 5.37 s (CH_2O); 7.10 d, J = 9.0 (H-3′,5′); 7.16 d, J = 8.2 (H-3,5); 7.37 d, J = 9.0 (H-2′,6′); 8.32 d, J = 8.5 (H-4 quin).

2-({4-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)benzoic acid (**3f**). The crude methyl ester of **3f** was prepared from **8b** and **6d** in 85.4% yield, m.p. 158–160 °C. For $C_{24}H_{18}ClNO_3S$ (435.9) calculated: 66.13% C, 4.16% H, 8.13% Cl, 3.21% N, 7.36% S; found: 65.77% C, 4.21% H, 8.30% Cl, 3.05% N, 7.32% S. Acid **3f** was obtained by hydrolysis, purified by repeated precipitation as the sodium salt in 86.9% yield, m.p. 238–240 °C. For $C_{23}H_{16}ClNO_3S$ (421.9) calculated: 65.48% C, 3.82% H, 8.40% Cl, 3.32% N, 7.60% S; found: 65.53% C, 3.91% H, 8.43% Cl, 3.37% N, 7.62% S. ^{1}H NMR (DMSO-d_6): 5.37 s (CH_2O); 7.22 m (H-3′,5′); 7.50 d, J = 8.8 (H-2′,6′); 7.82 m (H-3,4,5); 8.07 m (H-4 quin); 8.42 d, J = 8.5 (H-6).

2-({3-[(6-Chloroquinolin-2-yl)methoxy]phenyl}sulfanyl)benzoic acid (**3g**). The methyl ester of **3g** was obtained from **8b** and **6c** in 91.9% yield, m.p. 98–100 °C (methanol). For $C_{24}H_{15}ClNO_3S$ (435.9) calculated: 66.13% C, 4.16% H, 8.13% Cl, 3.21% N, 7.36% S; found: 65.93% C, 4.27% H, 8.30% Cl, 3.09% N, 7.17% S. Acid **3g** was obtained by hydrolysis and purification through the ammonium salt in 37.7% yield, m.p. 209–211 °C (water). For $C_{23}H_{16}ClNO_3S$ (421.9) calculated: 65.48% C, 3.82% H, 8.40% Cl, 3.32% N, 7.60% S; found: 65.56% C, 3.98% H, 8.62% Cl, 3.35% N, 7.56% S. ^{1}H NMR (DMSO-d_6): 5.40 s (CH_2O); 6.89 dd, J = 1.3, 7.9 (H-3); 7.17 m (H-4,5,2′,4′,6′); 7.41 t, J = 7.9 (H-5′); 7.88 dd, J = 1.9, 7.5 (H-6); 8,37 d, J = 8.8 (H-4 quin).

Methyl 4-{[3-(3-Chloropropoxy)phenyl]sulfanyl}benzoate (**7a**)

A mixture of **6b** (11.7 g, 44.5 mmol), 1-bromo-3-chloropropane (23.6 g, 0.15 mol) and anhydrous potassium carbonate (14.0 g) in 4-methylpentan-2-one (200 ml) was heated to reflux for 10 h. After cooling to 20 °C, the precipitate was filtered off and the filtrate evaporated. The oil was dissolved in ether (20 ml), diluted with hexane (20 ml) and the crystalline product was filtered off after cooling to 0 °C. The yield was 78.0%, m.p. 47–49 °C without purification. For $C_{17}H_{17}ClO_3S$ (336.8) calculated: 60.62% C, 5.09% H, 10.52% Cl, 9.52% S; found: 60.65% C, 5.12% H, 10.35% Cl, 9.42% S.

Intermediates **7b**, **7c** and **7d**

These compounds were prepared similarly:

Methyl 4-{[4-(3-chloropropoxy)phenyl]sulfanyl}benzoate (**7b**). Prepared from **6a** and 1-bromo-3-chloropropane in 92.8% yield, m.p. 65–67 °C without purification. For $C_{17}H_{17}ClO_3S$ (336.8) calculated: 60.62% C, 5.09% H, 10.52% Cl, 9.52% S; found: 60.46% C, 5.09% H, 10.35% Cl, 9.42% S.

Methyl 4-{[3-(4-bromobutoxy)phenyl]sulfanyl}benzoate (**7c**). Prepared from **6b** and 1,4-dibromobutane. The crude product was purified by column chromatography on silica gel using dichloromethane–hexane (1:1) as a mobile phase. Pure **7c** was obtained in 76.9% yield, m.p. 43–45 °C without recrystallization. For $C_{18}H_{19}BrO_3S$ (395.3) calculated: 54.69% C, 4.84% H, 20.22% Br, 8.11% S; found: 54.71% C, 4.80% H, 20.09% Br, 8.07% S.

Methyl 2-{[4-(4-bromobutoxy)phenyl]sulfanyl}benzoate (**7d**). Prepared from **6d** and 1,4-dibromobutane in 67.8% yield, m.p. 100–102 °C (benzene–hexane). For $C_{18}H_{19}BrO_3S$ (395.3) calculated: 54.69% C, 4.84% H, 20.22% Br, 8.11% S; found: 54.23% C, 4.83% H, 20.16% Br, 7.51% S.

4-{4-[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)ethoxy]phenylsulfanyl}benzoic Acid (**4a**)

A mixture of 4-(2-chloroethoxy)-2-hydroxy-3-propylacetophenone (**8c**; 7.7 g, 30.0 mmol) prepared from 2,4-dihydroxy-3-propylacetophenone and 2-chloroethyl tosylate according to[19], **6a** (7.8 g, 30.0 mmol), anhydrous potassium carbonate (13.8 g) and potassium iodide (0.6 g) in 4-methylpentan-2-one (160 ml) were heated to reflux for 45 h. The precipitate was filtered off, the filtrate evaporated to dryness and the solid dissolved in dichloromethane (20 ml) and purified on silica gel with dichloromethane as the eluent. The methyl ester of the title acid was isolated in the yield of 8.4 g (58.2%), m.p. 117–119 °C (without recrystallization). For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.31% C, 5.89% H, 6.67% S. A mixture of the methyl ester (8.0 g, 17.0 mmol) in ethanol (40 ml) and potassium hydroxide (3.3 g) in water (10 ml) was heated to reflux for 30 min. The residue after evaporation was diluted with water (20 ml), the solution was filtered with charcoal and acidified to pH 1 with dilute hydrochloric acid at 5 °C. The precipitated crude product (7.7. g, m.p. 134–137 °C) was crystallized from methanol in the total yield of 5.5 g (69.9%) with m.p. 146–148 °C (methanol). For $C_{26}H_{26}O_6S$ (466.6) calculated: 66.93% C, 5.61% H, 6.87% S; found: 66.74% C, 5.61% H, 6.99% S. ^{1}H NMR ($CDCl_3$): 2.58 s (CH_3CO); 4.41 s (CH_2CH_2); 7.01 d, J = 8.9 (H-3,5); 7.21 d, J = 9.2 (H-3′,5′); 7.50 d, J = 9.2 (H-2′,6′); 7.93 d, J = 8.9 (H-2,6); 12.75 s (HO).

Acids **4c**, **4d**, **4g**, **4h** and **4i**

These acids were prepared similarly:

4-{4-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butoxy]phenylsulfanyl}benzoic acid (**4c**). The corresponding methyl ester was prepared from 4-(4-bromobutoxy)-2-hydroxy-3-propylacetophenone[19] (**8d**) and **6a** in 62.0% yield. The title acid was prepared by subsequent hydrolysis in 59.9% yield, m.p.160–162 °C (90% ethanol). For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 67.89% C, 6.26% H, 6.36% S. ^{1}H NMR ($CDCl_3$): 2.04 bs (CH_2CH_2); 2.57 s (CH_3CO); 4.11 m (OCH_2 2×); 6.94 d, J = 8.9 (H-3′,5′); 7.07 d, J = 8.9 (H-3,5); 7.46 d, J = 8.9 (H-2′,6′); 7.87 d, J = 8.9 (H-2,6); 12.74 s (HO).

4-{3-[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)ethyloxy]phenylsulfanyl}benzoic acid (**4d**). The corresponding methyl ester was prepared from **8c** and **6b**, m.p. 46–48 °C (after purification by chromatography on silica gel, using toluene–ethyl acetate as the mobile phase) in 36.1% yield. For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.05% C, 5.88% H, 6.34% S. The title acid was prepared by subsequent hydrolysis in 67.0% yield, m.p. 146–148 °C (ethanol). For $C_{26}H_{26}O_6S$ (466.6) calculated: 66.93% C, 5.61% H, 6.87% S; found: 66.88% C, 5.83% H, 6.68% S. ^{1}H NMR (DMSO-d_6): 2.57 s (CH_3CO); 4.39 s (CH_2CH_2); 7.05 m (H-2′,4′,6′); 7.33 m (H-3,5,5′); 7.83 m (H-2,6); 12.77 s (HO).

2-{3-[3-(4-Acetyl-2-hydroxy-3-propylphenoxy)propoxy]phenylsulfanyl}benzoic acid (**4g**). The corresponding methyl ester was prepared from 4-(3-chloropropoxy)-2-hydroxy-3-propylacetophenone[19] (**8e**) and **6c** in 59.0% yield, m.p. 73–75 °C (methanol). The title acid was prepared by subsequent hydrolysis in 78.2% yield, m.p. 142–144 °C. For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.26% C, 5.94% H, 6.51% S. ^{1}H NMR (DMSO-d_6): 2.22 quintet, J = 6.1 (CH_2); 2.58 s (CH_3CO); 4.20 t, J = 6.2, 4.26 t, J = 6.1 (OCH_2 2×); 6.80 dd, J = 1.1, 8.1 (H-3); 7.04–7.48 m (H-4,5,2′,4′,5′,6′); 7.92 dd, J = 1.1, 8.1 (H-6); 12.83 s (HO).

2-{3-[4-(4-Acetyl-2-hydroxy-3-propylphenoxy)butoxy]phenylsulfanyl}benzoic acid (**4h**). The corresponding methyl ester was prepared from **8d** and **6c** in 76% yield, m.p. 60–62 °C (methanol). The title acid was prepared by subsequent hydrolysis in 66.5% yield, m.p. 66–68 °C (90% methanol). For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 68.04% C, 6.36% H, 6.10% S. ^{1}H NMR (DMSO-d_6): 1.91 m (CH_2CH_2); 2.58 s (CH_3CO); 4.07 m (OCH_2 2×); 7.01–7.47 m (H-4,5,2′,4′,5′,6′); 7.78 d, J = 9.1 (H-3); 7.92 dd, J = 1.5, 7.7 (H-6); 12.83 s (HO).

2-{4-[3-(4-Acetyl-2-hydroxy-3-propylphenoxy)propoxy]phenylsulfanyl}benzoic acid (**4i**). The corresponding methyl ester was prepared from **8e** and **6d** and isolated in 42.0% yield as an oil after chromatography on silica gel with toluene–ethyl acetate as the mobile phase. For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 68.27% C, 6.30% H, 6.18% S. Subsequent hydrolysis led to acid **4i** in 81.0% yield, m.p. 141–143 °C (methanol). For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.27% C, 6.00% H, 6.42% S. ^{1}H NMR (DMSO-d_6): 2.26 quintet, J = 6.1 (CH_2); 2.59 s (CH_3CO); 4.25 t, J = 6.1 (CH_2O); 4.29 t, J = 6.1 (CH_2O); 6.67 dd, J = 1.2, 7.6 (H-6); 7.10 m (H-3′,5′); 7.18 dt, J = 1.2, 7.6 (H-4); 7.34 ddd, J = 1.8, 7.3, 8.8 (H-5); 7.48 m (H-2′,6′); 7.93 dd, J = 1.5, 7.6 (H-3).

4-{4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenylsulfanyl}benzoic Acid (**4b**)

A mixture of **7b** (9.0 g, 26.5 mmol), 2,4-dihydroxy-3-propylacetophenone (5.2 g, 26.5 mmol), anhydrous potassium carbonate (18.0 g) and potassium iodide (0.8 g) in 4-methylpentan-2-one (160 ml) was heated at reflux for 24 h. The hot suspension was filtered, the filtrate evaporated and the precipitate washed with ether and crystallized from methanol to give the methyl ester of **4b** (6.6 g, 50.4%), m.p. 58–61 °C. For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 67.65% C, 6.14% H, 6.38% S. A mixture of the ester (6.2 g, 12.5 mmol) in ethanol (30 ml) and potassium hydroxide (2.25 g, 40.0 mmol) in water (10 ml) was stirred under reflux for 30 min. The solution was evaporated, the solid dissolved in water, filtered with charcoal and the filtrate acidified with acetic acid. The crude product was collected by filtration and crystallized from methanol (150 ml) to give **4b** (3.5 g, 50.8%), m.p. 177–179 °C (methanol). For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.35% C, 5.85% H, 6.40% S. ^{1}H NMR ($CDCl_3$): 2.30 m (CH_2); 2.55 s (CH_3CO); 4.21 m

(CH_2O 2×); 6.94 d, *J* = 8.20 (H-3′,5′); 7.04 d, *J* = 8.40 (H-3,5); 7.43 d, *J* = 8.20 (H-2′,6′); 7.83 d, *J* = 8.40 (H-2,6); 12.72 s (HO).

Acids **4e**, **4f** and **4j**

These acids were prepared similarly:

4-{3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy)phenylsulfanyl}benzoic acid (**4e**). The crude methyl ester of **4e** obtained from **7a** and 2,4-dihydroxy-3-propylacetophenone was purified by chromatography on silica gel using dichloromethane and chloroform as eluents to give the pure ester (71.8%), m.p. 99–101 °C. For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 67.68% C, 6.16% H, 6.49% S. Hydrolysis led to **4e** in 94.6% yield, m.p. 104–106 °C (80% methanol). For $C_{27}H_{28}O_6S$ (480.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.42% C, 5.95% H, 6.71% S. ^{1}H NMR ($CDCl_3$): 2.20 m (CH_2); 2.57 s (CH_3CO); 4.21 m (CH_2O 2×); 6.82–7.38 m (H-3,5,2′,4′,5′,6′); 7.87 d, *J* = 8.7 (H-2,6); 12.76 bs (HO).

4-{3-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butoxy]phenylsulfanyl}benzoic acid (**4f**). The crude methyl ester of **4f** was obtained from **7c** and 2,4-dihydroxy-3-propylacetophenone as an oily product in 74.2% yield. For $C_{29}H_{32}O_6S$ (508.6) calculated: 68.48% C, 6.34% H, 6.30% S; found: 67.65% C, 6.23% H, 6.62% S. Hydrolysis led to crude **4f**, which was purified by chromatography on silica gel to give the title acid in 75.0% yield, m.p. 100–102 °C (without recrystallization). For $C_{28}H_{30}O_6S$ (494.6) calculated: 68.00% C, 6.11% H, 6.48% S; found: 67.18% C, 6.10% H, 6.50% S. ^{1}H NMR (DMSO-d_6): 1.89 m (CH_2 2×); 2.56 s (CH_3CO); 4.10 m (CH_2O 2×); 7.00 m (H-2′,4′,5′); 7.31 m (H-6′); 7.29 d, *J* = 8.00 (H-3,5); 7.88 d, *J* = 8.00 (H-2,6); 12.78 bs (HO).

2-{4-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy]butoxy}phenylsulfanyl)benzoic acid (**4j**). The crude methyl ester of **4j** was obtained from **7d** and 2,4-dihydroxy-3-propylacetophenone as an oily product in 65.0% yield. The hydrolysis led to **4j** after chromatography on silica gel in 69.5% yield, m.p. 155–157 °C (without recrystallization). For $C_{28}H_{30}O_6S$ (494.6) calculated: 67.48% C, 5.87% H, 6.67% S; found: 67.57% C, 5.68% H, 6.45% S. ^{1}H NMR (DMSO-d_6): 1.95 m (CH_2O 2×); 2.59 s (CH_3CO); 4.15 m (CH_2CH_2); 6.69 d, *J* = 8.2 (H-6); 7.08 m (H-3′,5′); 7.17 dt, *J* = 1.2, 7.6 (H-4); 7.33 ddd, *J* = 1.8, 7.3, 8.8 (H-5); 7.45 m (H-2′,6′); 7.95 dd, *J* = 1.5, 7.6 (H-3).

1-Bromo-3-[(2′,4′-difluorobiphenyl-4-yl)oxy]propane (**8f**)

A mixture of 4-(2′,4′-difluorophenyl)phenol (13.0 g, 63.0 mmol), 1,3-dibromopropane (45.6 g, 0.226 mol) and anhydrous potassium carbonate (21.0 g) in butan-2-one (180 ml) was heated at reflux for 10 h. The hot mixture was filtered and the filtrate evaporated to dryness. The crystalline solid was dissolved in acetone (20 ml), the solvent evaporated after filtration and the residue thoroughly washed by stirring with hexane (50 ml). The yield of pure **8f** was 12.7 g (61.7%), m.p. 59–60 °C (ethanol). For $C_{15}H_{13}BrF_2O$ (327.2) calculated: 55.07% C, 4.00% H, 24.42% Br, 11.61% F; found: 55.51% C, 3.95% H, 23.75% Br, 11.79% F. ^{1}H NMR ($CDCl_3$): 2.34 quintet, *J* = 6.2 (CH_2); 3.62 t, *J* = 6.5 (CH_2O); 4.15 t, *J* = 5.9 (CH_2Br); 6.89 m (H-5b,6b); 6.98 m (H-3a,5a); 7.35 m (H-3b); 7.42 m (H-2a,6a).

1-Bromo-4-[(2′,4′-difluorobiphenyl-4-yl)oxy]butane (**8g**)

The compound was prepared similarly from 4-(2′,4′-difluorophenyl)phenol and 1,4-dibromobutane in 65.6% yield, m.p. 60–61 °C (acetone–hexane). For $C_{16}H_{15}BrF_2O$ (341.2) calculated:

56.31% C, 4.43% H, 23.44% Br, 11.14% F; found: 56.71% C, 4.47% H, 23.25% Br, 11.36% F. ^{1}H NMR ($CDCl_3$): 1.90–2.15 m (CH_2CH_2); 3.50 t, *J* = 6.6 (CH_2O); 4.03 t, *J* = 5.9 (CH_2Br); 6.88 m (H-5b,6b); 6.95 m (H-3a,5a); 7.35 m (H-3b); 7.41 m (H-2a,6a).

4-[(4-{3-[(2′,4′-Difluorobiphenyl-4-yl)oxy]propoxy}phenyl)sulfanyl]benzoic Acid (**5a**)

A mixture of **6a** (2.6 g, 0.01 mol), **8f** (3.3 g, 0.01 mol), anhydrous potassium carbonate (4.6 g) and potassium iodide (0.2 g) in butan-2-one (80 ml) was heated at reflux for 8 h. The suspension was filtered while boiling, the filtrate evaporated to dryness and the crude, partially crystalline methyl ester of acid **5a** (3.9 g, 77.5%) was dissolved in methanol (45 ml). A solution of potassium hydroxide (1.5 g) in water (15 ml) was added and the mixture was heated at reflux for 2 h. The solvent was evaporated, water (30 ml) added, the resultant solution filtered with charcoal and the filtrate acidified with dilute hydrochloric acid. The crude acid was crystallized from ethanol–dimethylformamide and **5a** (2.7 g, 75.3%) was obtained, m.p. 173–174 °C (ethanol–dimethylformamide). For $C_{28}H_{22}F_2O_4S$ (492.5) calculated: 68.28% C, 4.50% H, 7.71% F, 6.51% S; found: 68.16% C, 4.37% H, 7.79% F, 6.27% S. ^{1}H NMR ((DMSO-d_6): 2.22 quintet, *J* = 6.3 (CH_2); 4.23 t, *J* = 6.3 (CH_2O 2×); 7.17 d, *J* = 8.5 (H-3,5); 7.43 m (H-3a,5a); 7.49 m (H-6b); 7.82 d, *J* = 8.5 (H-2,6).

Acids **5b**, **5c**, **5d**, **5e**, **5f** and **5g**

These acids were prepared similarly:

4-[(4-{4-[(2′,4′-Difluorobiphenyl-4-yl)oxy]butoxy}phenyl)sulfanyl]benzoic acid (**5b**). The methyl ester of **5b** was obtained from **6a** and **8f** in 52.5% yield, m.p. 117–118 °C (ethanol–dimethylformamide); hydrolysis gave acid **5b** in 93.0% yield, m.p. 197–200 °C (propan-2-ol). For $C_{29}H_{24}F_2O_4S$ (506.6) calculated: 68.76% C, 4.78% H, 7.50% F, 6.33% S; found: 68.51% C, 4.80% H, 7.28% F, 6.08% S. ^{1}H NMR (DMSO-d_6): 1.93 bs (CH_2 2×); 4.12 bs (CH_2O 2×); 7.05 d, *J* = 7.5 (H-3′,5′,2a,6a); 7.14 d, *J* = 8.5 (H-3,5); 7.45 m (H-2′,6′); 7.53 m (H-6b); 7.84 d, *J* = 8.5 (H-2,6).

2-[(4-{3-[(2′,4′-Difluorobiphenyl-4-yl)oxy]propoxy}phenyl)sulfanyl]benzoic acid (**5c**). The methyl ester of **5c** was prepared from **6d** and **8g** in 68.0% yield and the crude ester was hydrolyzed into acid **5c**, obtained after crystallization in 61.2% yield, m.p. 171–172 °C (propan-2-ol). For $C_{28}H_{22}F_2O_4S$ (492.5) calculated: 68.28% C, 4.50% H, 6.51% F, 7.71% S; found: 67.97% C, 4.50% H, 6.45% F, 7.56% S. ^{1}H NMR (DMSO-d_6): 2.24 quintet, *J* = 6.3 (CH_2); 4.24 m (CH_2O 2×); 6.73 dd, *J* = 0.9, 8.2 (H-3); 7.10 d, *J* = 7.08 (H-3′,5′,1a,6a); 7.33 m (H-4); 7.46 m (H-2′,6′,3a,5a); 7.53 m (H-6b); 7.89 dd, *J* = 1.6, 7.9 (H-6).

2-[(4-{4-[(2′,4′-Difluorobiphenyl-4-yl)oxy]propoxy}phenyl)sulfanyl]benzoic acid (**5d**). The methyl ester of **5d** was prepared from **6d** and **8g** in 75.4% yield, m.p. 155–157 °C (butan-2-one). Acid **5d** was obtained by hydrolysis in 91.3% yield, m.p. 193–195 °C (propan-2-ol). For $C_{29}H_{24}F_2O_4S$ (506.6) calculated: 68.76% C, 4.78% H, 6.33% F, 7.50% S; found: 68.69% C, 4.95% H, 6.33% F, 7.37% S. ^{1}H NMR ((DMSO-d_6): 1.94 m (CH_2 2×); 4.13 m (CH_2O 2×); 6.73 dd, *J* = 1.0, 8.2 (H-3); 7.08 d, *J* = 8.8 (H-3′,5′); 7.06 d, *J* = 8.8 (H-2a,6a); 7.16 bm (H-5,3b,5b); 7.33 m (H-4).

2-[(3-{3-[(2′,4′-Difluorobiphenyl-4-yl)oxy]propoxy}phenyl)sulfanyl]benzoic acid (**5e**). The methyl ester of **5e** was prepared from **6c** and **8f** in 96.5% yield and without purification hydrolyzed into acid **5e**, obtained in 87.4% yield after crystallization from ethanol–dimethylformamide, m.p. 210–212 °C. For $C_{28}H_{22}F_2O_4S$ (492.5) calculated: 68.28% C, 4.50% H, 7.71% F, 6.51% S;

found: 67.90% C, 4.67% H, 7.75% F, 6.80% S. ^{1}H NMR (DMSO-d_6): 2.19 quintet, J = 6.3 (CH_2); 4.21 t, J = 6.3, 4.18 t, J = 6.3 (CH_2O 2×); 6.80 m (H-4′); 7.04 m (H-3,5,2′,5′,6′,2a,6a); 7.28 t, J = 8.0 (H-4); 7.43 dd, J = 1.6, 8.8 (H-3a,5a); 7.50 m (H-6b); 7.71 m (H-6).

2-[(3-{4-[(2′,4′-Difluorobiphenyl-4-yl)oxy]butoxy}phenyl)sulfanyl]benzoic acid (**5f**). The methyl ester of **5f** was prepared from **6c** and **8g** in 98.0% yield and without purification hydrolyzed into acid **5f** obtained in 66.4% yield after crystallization from propan-2-ol–dimethylformamide, m.p. 175–177 °C. For $C_{29}H_{24}F_2O_4S$ (506.6) calculated: 68.76% C, 4.47% H, 7.50% F, 6.33% S; found: 68.59% C, 4.82% H, 7.22% F, 6.11% S. ^{1}H NMR ((DMSO-d_6): 1.89 m (CH_2 2×); 4.08 m (CH_2O 2×); 6.90 m (H-4′,3b); 7.07 m (H-3,5,2′,5′,6′,2a,6a,5b); 7.29 t, J = 8.2 (H-4); 7.41 dd, J = 1.6, 8.8 (H-3a,5a); 7.49 m (H-6b); 7.75 m (H-6).

4-[(3-{4-[(2′,4′-Difluorobiphenyl-4-yl)oxy]butoxy}phenyl)sulfanyl]benzoic acid (**5g**). The methyl ester of **5g** was prepared from **6b** and **8g** in almost quantitative yield and without purification hydrolyzed into acid **5g** obtained in 61.5% yield after crystallization from ethanol, m.p. 148–150 °C. For $C_{29}H_{24}F_2O_4S$ (506.6) calculated: 68.76% C, 4.48% H, 7.50% F, 6.33% S; found: 68.50% C, 4.99% H, 7.27% F, 6.21% S. ^{1}H NMR ((DMSO-d_6): 1.98 m (CH_2 2×); 4.03 m (CH_2O 2×); 6.94 m (H-2′,4′,6′,2a,6a,3b,5b); 7.23 d, J = 8.8 (H-3,5); 7.33 m (H-6b); 7.40 dd, J = 1.6, 8.8 (H-3a,5a); 7.90 d, J = 8.8 (H-2,6).

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[34]. The cells were stimulated with the Ca^{2+} ionophore A23187 (Sigma) and incubated with various concentrations of the tested drugs. LTB_4 was determined in the supernatants using a commercial RIA kit (Amersham). For the LTB_4 receptor binding study, a slightly modified method of Cheng et al.[35] was used. The membrane fraction was prepared from a male guinea pig spleen; 2 mg of the membranes were incubated with 0.3 nM ^{3}H-LTB_4 at 25 °C for 30 min in 100 μl of the incubated mixture. Nonspecific binding was determined in the presence of 0.1 μM 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.[36] The membrane fraction was prepared from male guinea-pig lungs. 4 mg of this fraction were incubated with 0.4 nM ^{3}H-LTD_4 at 25 °C for 60 min in 100 μl of the incubated mixture. Nonspecific binding was determined in the presence of 0.1 μM LTD_4. Filtration of the membranes, washing and the measurement of radioactivity were the same as in the previous instance. The activities *in vitro* were expressed in μM concentrations leading to a 50% inhibition.

The inhibition of carrageenan edema was evaluated by the method of Winter[37], the experimental conditions have been described elsewhere[38]. The effect was expressed as the percentage of inhibition after a dose of 100 mg/kg in comparison with an untreated control. Inhibition of experimental pleuritis was evaluated by the method of Hidaka[39] in a group of Wistar Han female rats pretreated with 1.0% carrageenan in saline by intrapleural injection. The tested compounds in suspension with gum arabic were applied orally in a single dose of 100 mg/kg 1 h before the application of carrageenan. The volume of the exudate from the pleural cavity and the number of cells in the exudate (determined with a Sysmex counter) were compared with those of untreated animals and the effect was expressed as the percentage of the inhibition. Arachidonic acid induced ear inflammation in mice was performed by

the method of Opas[40], the ear pinna inflammation was induced by the application of 20 µl of arachidonic acid solution in acetone. The compound was administered orally (200 mg/kg), 1 h before edema induction. The degree of ear hyperemia and the weight of the ear were evaluated 1 h after the application of arachidonic acid. The results were expressed as the percentage of the inhibition in comparison with an untreated control. The inhibition of bronchospasm was induced by the intravenous injection of 0.35 mg/kg of ovalbumin to a presentisized guinea pig following the modified method of Kreutner et al.[41] The method of Jones and Masson[42] 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 p.o. in the doses of 10, 30, 100 mg/kg, 60 min before the application of albumin or LTD_4. The effect was expressed as the percentage of the inhibition of bronchospasm in relation to the untreated control.

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REFERENCES

1. Taylor G. W., Clarke S. R.: *Trends Pharmacol. Sci.* **1986**, *7*, 100.
2. Samuelsson B.: *Science* **1983**, *220*, 568.
3. Dahlen S.-E., Hedquist P., Hammarstrom S., Samuelsson B.: *Nature* **1980**, *288*, 484.
4. Goldman D. W., Gifford L. A., Marotti T., Koo C. H., Goetzl E. J.: *Fed. Proc.* **1987**, *46*, 203.
5. Palmblad J., Malmster C., Uden A., Radmark O., Engstedt L., Samuelsson B.: *Blood* **1981**, *58*, 658.
6. Brooks C. D. W., Summers J. B.: *J. Med. Chem.* **1996**, *39*, 2629.
7. Carter G. W., Young P. R., Albert D. H., Bouska J., Dyer R., Bell R. L.: *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929.
8. Matassa V. G., Maduskaie 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.
9. Jones T. R., Labelle M., Belley M., Champion E., Charett L., Evans J., Ford-Hutchinson A. W., Gauthier J.-Y., Lord A.: *Can. J. Physiol. Pharmacol.* **1995**, *73*, 191.
10. 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.
11. Jones T. R., Zamboni R., Belley M., Champion E., Charette L., Ford-Hutchinson A. W., Gauthier J. Y., Leger S., Masson P.: *Can. J. Physiol. Pharmacol.* **1991**, *69*, 1847.
12. Palomer A., Pascual J., Cabré F., Garcia L., Mauleón D.: *J. Med. Chem.* **2000**, *43*, 392.
13. Kolasa T., Gunn D. E., Gunn D. E., Bhatia P., Basha A., Craig R. A., 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*, 3322.
14. von Sprecher A., Beck A., Sallmann A., Breitstein W., Wiestner H., Kimmel S., Anderson G. P., Subramanian N., Bray M. A.: *Drugs Fut.* **1991**, *16*, 827.

15. Penning G. T., Djuric S. W., Miyashiro J. M., Yu S., Snyder J. P., Spangler D., Anglin C. P., Fretland D. J., Kachur J. F., Keith R. S., Walsh R. E., Widomski D. L.: *J. Med. Chem.* **1995**, *38*, 858.
16. Tsai B. S., Keith R. H., Villani-Price D., Katchur J. F., Yang D.-C., Djuric S. W., Yu S.: *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1499.
17. Kuchař M., Poppová M., Jandera A., Panajotová V., Zůnová H., Buděšínský M., Tomková H., Jegorov A., Taimr J.: *Collect. Czech Chem. Commun.* **1997**, *62*, 498.
18. Huang F. C., Galemmo J. R. A., Poli G. B., Learn K. S., Morrisette M. M., Johnson J. W. H., Dankulich W. P., Campbell H. F., Carnathan G. W., van Invegen R. G.: *J. Med. Chem.* **1991**, *34*, 1704.
19. Kuchař M., Čulíková K., Panajotová V., Brůnová B., Jandera A., Kmoníček V.: *Collect. Czech. Chem. Commun.* **1998**, *63*, 103.
20. Kuchař M., Jandera A., Kmoníček V., Brůnová B., Schneider B. in: *Molecular Modeling and Prediction of Bioactivity* (K. Gundertofte and F. S. Jorgensen, Eds), p. 390. Kluwer Academic Plenum Press, Copenhagen 1999.
21. Harper R. W., Herron D. K., Bollinger N. G., Sawyer J. S., Baldwin R. F., Roman C. R., Rinkema L. E., Fleisch J. H.: *J. Med. Chem.* **1992**, *35*, 1191.
22. Zwaangstra M. E., Timmerman H., Tamura M., Tohma T., Wada Y., Onogi K., Zhang M.-Q.: *J. Med. Chem.* **1997**, *40*, 1075.
23. Daines R. A., Chambers P. A., Pendrak I., Jakas D. R., Sarau H. M., Foley J. J., Schmidt D. B., Griswold D. E., Martin L. D., Kingsbury W. D.: *J. Med. Chem.* **1993**, *36*, 2703.
24. Abram T. S., Boeshagen H., Butler J. E., Cuthbert N. J., Francis H. P., Gardiner P. J., Harwig W., Kluender H. C., Norman P., Meier H., Rosentreter U., Schlemmer K. H.: *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1993.
25. Mathes W., Schuely H.: *Angew. Chem.* **1963**, *75*, 235.
26. Kuchař M., Rejholec V., Kraus E., Miller V., Rabek V.: *J. Chromatogr.* **1983**, *280*, 279.
27. *International Tables for X-ray Crystallography*, Vol. IV. Kynoch Press, Birmingham 1974.
28. Frenz B. A. and Associates Inc. SDP: *Structure Determination Package*. Enraf–Nonius, Delft 1985.
29. Watkin D. J., Carruthers R. J., Betteridge P.: *CRYSTALS*, Issue 10. Chemical Crystallography Laboratory, Oxford (U.K.) 1998.
30. Sheldrick G. M.: *SHELXS86, Program for Crystal Structure Solution*. University of Göttingen, Göttingen 1986.
31. Farrugia L. J.: *J. Appl. Crystallogr.* **1997**, *30*, 565.
32. Carruthers J. R., Watkin D. J.: *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1979**, *35*, 698.
33. Utermohlen W. P., Jr.: *J. Org. Chem.* **1943**, *8*, 544.
34. Palmer R. M. J., Salmon J. A.: *Immunology* **1983**, *50*, 65.
35. Cheng J. B., Cheng E. I.-P., Kohi F., Townley R. G.: *J. Pharmacol. Exp. Ther.* **1986**, *236*, 126.
36. Bruns R. F.: *Life Sci.* **1983**, *33*, 645.
37. Winter J.: *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
38. Grimová J., Kuchař M., Pavlíková I., Němeček O.: *Cesk. Farm.* **1980**, *29*, 305.
39. Hidaka J.: *J. Pharm. Pharmacol.* **1986**, *38*, 242.
40. Opas E. E., Bonney E. Y., Homes J. L.: *J. Invest. Dermatol.* **1985**, *84*, 253.
41. Kreutner W., Sherwood J., Rizzo C.: *Agents Actions* **1989**, *28*, 173.
42. Jones T. R., Masson P.: *Prostaglandins* **1985**, *29*, 799.