ω-[(ω-Arylalkyl)aryl]alkanoic Acids: A New Class of Specific LTA_4 Hydrolase Inhibitors

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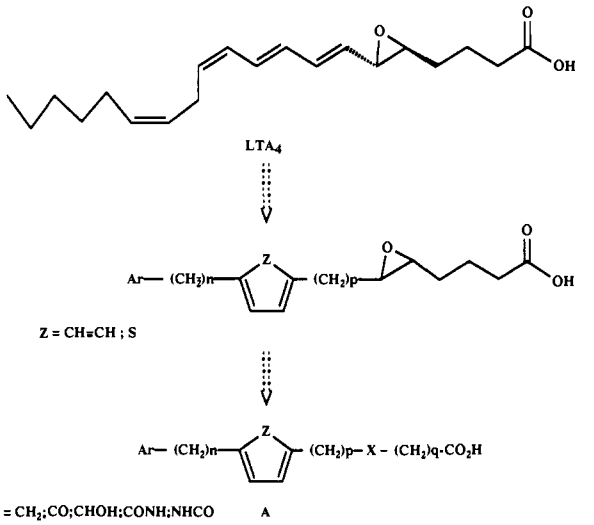
The synthesis and structure–activity profile of a new class of potent and specific LTA_4 hydrolase inhibitors are described. Many compounds of this series of ω-[5-(ω-arylalkyl)-2-thienyl]- and ω-[4-(ω-arylalkyl)phenyl]alkanoic acids were found to be potent in vitro inhibitors of the LTB_4 production by porcine leukocytes with IC_{50} ranging from 1 to 10 μM. The side-chain lengths were critical for an optimal activity. Substitutions on the terminal aromatic ring, in the benzene series, by lipophilic and electron-donating substituents substantially enhanced the LTA_4 hydrolase inhibition potency. On the other hand, in the thiophene series, the effect of such substitutions on the LTA_4 hydrolase inhibition was rather small. Functionalization within the carboxylic acid side chain by a carbonyl or by a hydroxyl group led to less potent compounds. A metabolically stable LTA_4 hydrolase inhibitor, RP64966, was obtained by insertion of an oxygen atom in the β-position on the carboxylic acid side chain. After oral administration of RP64966 to rats, a plasma extract was found to display potent inhibition of the LTB_4 biosynthesis (40% inhibition at 5 mg/kg, po).

Leukotriene B_4, 5(*S*),12(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatrienoic acid (LTB_4), is a product of arachidonic acid metabolism by the 5-lipoxygenase (5-LO) pathway. LTB_4 has been shown to be a potent neutrophil polymorphonuclear leukocyte (PMN) activator and has been proposed as an important mediator of inflammation. It stimulates aggregation[1] and degranulation[2] of human neutrophils, induces chemotaxis of leukocytes,[1,3] and is a promoter of superoxide generation.[4] In man, LTB_4 has been detected in rheumatoid synovial[5] and gouty arthritic[6] fluids, in inflammatory gastrointestinal mucosa,[7] and in psoriatic skin.[8] Therefore the inhibition of LTB_4 biosynthesis can be considered as a reasonable approach for the treatment of such inflammatory diseases or any condition where LTB_4 may play the role of a pathological mediator.

The inhibition of 5-LO has been considered the most attractive target since it results in reduced formation of all the leukotrienes. However a drawback of this approach is the enhanced formation of cyclooxygenase products and concomitant inhibition of cysteinyl leukotrienes production possibly causing undesirable side effects. In fact, to selectively inhibit LTB_4 biosynthesis, the key enzyme seems to be the specific epoxide hydrolase, LTA_4 hydrolase, that converts the unstable allylic epoxide leukotriene A_4 to LTB_4. This enzymatic epoxide hydrolysis is the rate-limiting step in the LTB_4 formation.[9] LTA_4 is also the intermediate of the leukotriene C_4 and D_4 pathway. However the inhibition of LTA_4 hydrolase would block only the production of LTB_4, leaving the synthesis of cysteinyl leukotrienes unaffected and leading to spontaneous nonenzymatic hydroxylation, converting LTA_4 into biologically inactive *trans*-LTB_4 isomers.[10,11a] Therefore, the selective inhibition of LTA_4 hydrolase could have applications in the treatment of certain inflammatory conditions such as psoriasis, ulcerative colitis, and rheumatoid arthritis, and could possibly avoid undesirable side effects that may arise from a total inhibition of the leukotriene synthesis.

Very little work has been reported in this field. In fact the only compounds described until very recently as selective LTA_4 hydrolase inhibitors were the LTA_4 analog LTA_3 and related compounds containing an allylic epoxide fragment.[11a,b] It has been postulated that inhibition of LTA_4 hydrolase by these compounds involves covalent coupling of the reactive epoxide moiety to the enzyme thus leading to irreversible inhibition.[11b] More recently Bestatin, Captopril,[11c-e] and zinc chelating agents[11f] were re-

Scheme I. Design Stategy of LTA_4 Hydrolase Inhibitors



† Rhône-Poulenc Rorer GMBH.

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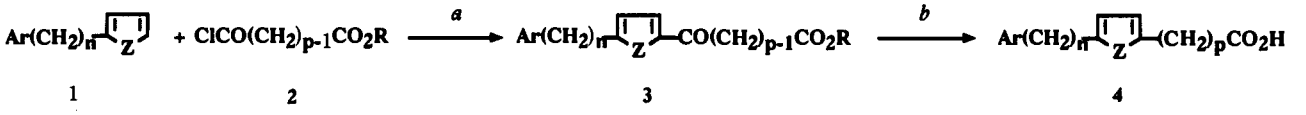
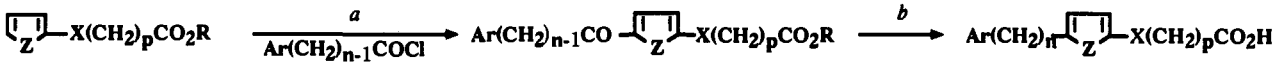
Scheme II[°]

Route A : (Z = CH=CH or S)



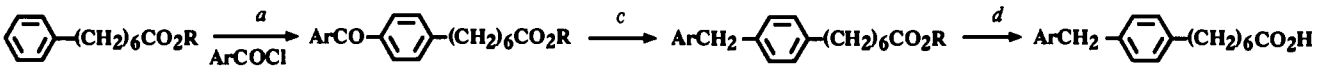
1 2 3 4

Route B : (Z = CH=CH or S and X = S or bond)



6 5 7 4 X=bond 8 X=S

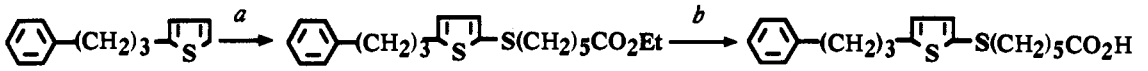
Route C :



10 9 11 12 13

°(a) $SnCl_4$ (Z = S) or $AlCl_3$ (Z = CH=CH); (b) H_2NNH_2, KOH, triethylene glycol; (c) Et_3SiH, CF_3CO_2H; (d) NaOH or 10 N HCl.

Scheme III[°]



14 15 16

°(a) (i) *n*-BuLi, THF, (ii) sulfur, (iii) $Br(CH_2)_5CO_2Et$; (b) NaOH, EtOH.

ported to inhibit LTA_4 hydrolase.

Chemical efforts in our laboratories have focused on the design and synthesis of selective LTA_4 hydrolase inhibitors with chemical and metabolic stability to investigate the significance of LTB_4 in inflammatory processes. Our initial attempts in this area concentrated on the structure of LTA_4. We reasoned that analogs of LTA_4, in which the planar unsaturated triene moiety is replaced by an aromatic ring such as benzene or thiophene and the terminal lipophilic tail by an ω-arylalkyl chain, might provide candidates for our biological studies on the selective inhibition of LTA_4 hydrolase. In order to obtain chemically stable inhibitors, the epoxide ring could be suppressed or simulated by less reactive functional groups X (Scheme I). We report herein the synthesis and structure–activity relationship studies of ω-arylalkanoic acid derivatives having the general structure A which are selective inhibitors of LTA_4 hydrolase.

Chemistry

Most of compounds A were prepared as shown in Scheme II. Friedel–Craft acylation of a diarylalkane **1** by an acyl chloride **2** in the presence of $SnCl_4$ (Z = S) or $AlCl_3$ (Z = CH=CH) afforded compound **3** which was reduced to **4** under the conditions of the Huang-Minlon modification of the Wolff-Kishner reaction[12] (route A). Another way to prepare compounds **4** (or **8** when X = S) involving a similar two-step procedure was to start from an ω-aryl- or ω-arylthioalkanoate **6** and an ω-arylalkanoyl chloride **5** (route B). For several compounds **11**, prepared as described for **7** by Friedel–Craft acylation of a 7-phenylheptanoate **10** by an aroyl chloride **9**, the Wolff–Kishner reduction was not adequate to prepare the desired acid **13**. Therefore an alternative method was developed.

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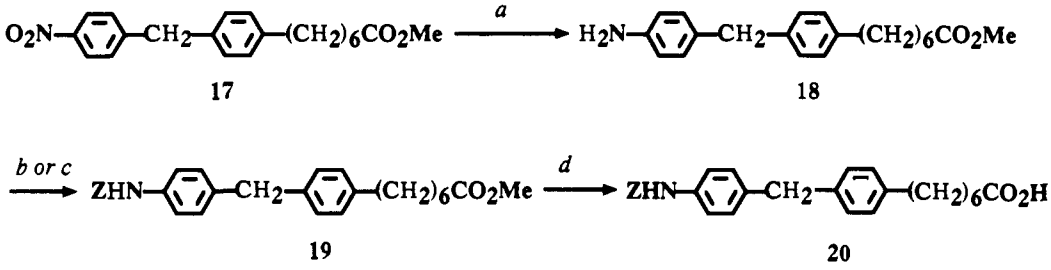
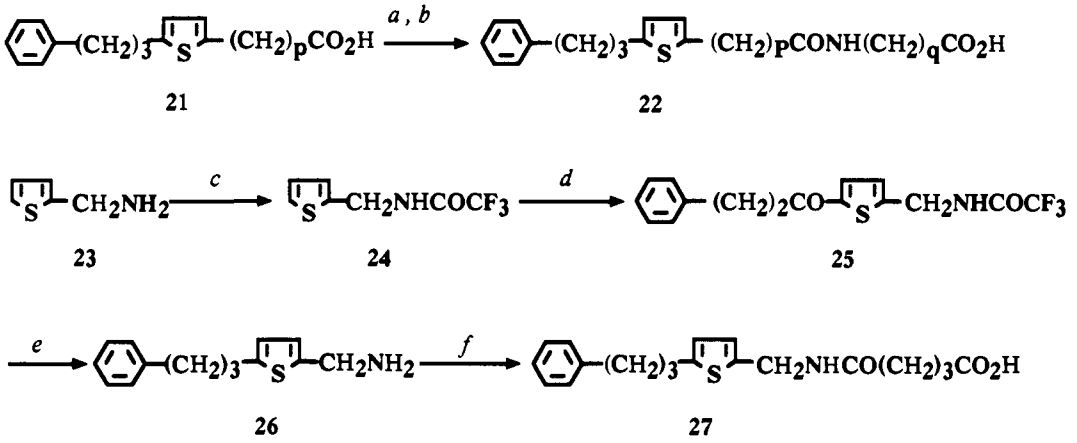
Scheme IV[a]



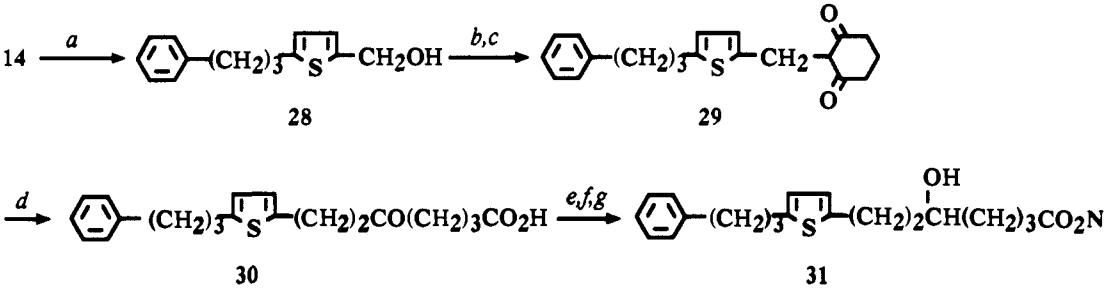
[a] (a) $SnCl_2$, MeOH; (b) Z = MeCO or $MeSO_2$: ZCl, $CHCl_3$, DMAP cat.; (c) Z = H_2NCO: KNCO, AcOH, H_2O; (d) NaOH, EtOH.

Scheme V[a]



[a] (a) (i) CDI, (ii) $H_2N(CH_2)_qCO_2R$; (b) NaOH, EtOH; (c) $(F_3CCO)_2O$, THF; (d) $Ph(CH_2)_2COCl$, $SnCl_4$, (e) H_2NNH_2, KOH, triethyleneglycol; (f) glutaric anhydride, THF.

Scheme VI[a]



[a] (a) (i) *n*-BuLi, Et_2O, (ii) $(CH_2O)_n$, 0 °C; (b) $SOCl_2$; (c) glutaric anhydride, KOH, KI; (d) $Ba(OH)_2$, H_2O; (e) EtOH, HCl; (f) $NaBH_4$, EtOH; (g) NaOH, EtOH.

When triethylsilane in trifluoroacetic acid[13] was used, the appropriate deoxygenation took place, giving rise to the desired ester **12** in good yields (route C). Base or acid hydrolysis of compound **12** afforded the desired acid **13**.

Compound **15** was prepared by lithiation of **14** with *n*-BuLi, followed by treatment with sulfur and subsequent alkylation of the resulting thiolate with ethyl 6-bromohexanoate in 43% overall yield. Saponification of **15** gave the expected product **16**, isolated as a sodium salt (Scheme III).

The *N*-acyl or sulfonyl analogs **20** were prepared in three steps from the nitro derivative **17** (Scheme IV), which was synthesized as described in Scheme II by reduction of the corresponding ketoester **11** with Et_3SiH in CF_3CO_2H (route C). Reduction of the nitro group by $SnCl_2$ in methanol[14] gave the corresponding amino derivative **18** in 60% yield. Reaction of **18** with acetyl chloride or methanesulfonyl chloride in chloroform in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) provided the *N*-acetyl or *N*-methylsulfonyl product **19** (Z = CH_3CO or CH_3SO_2), respectively. Likewise, compound **18** reacted with potassium isocyanate in aqueous acetic acid to give the ureido analog **19** (Z = H_2NCO) in 60% yield. Finally, base hydrolysis of compounds **19** afforded the desired acid **20**.

Several derivatives functionalized on the carboxylic acid side chain were also synthesized. Analogs possessing an amide function were prepared as described in Scheme V. A first route was to start from ω-(2-thienyl)alkanoic acids **21**, prepared by the standard method described in Scheme

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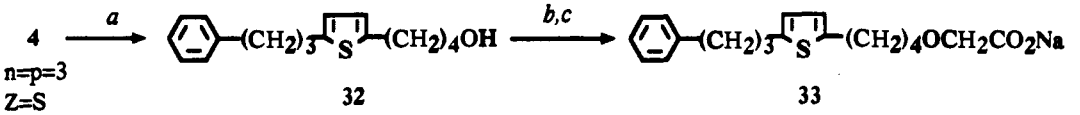
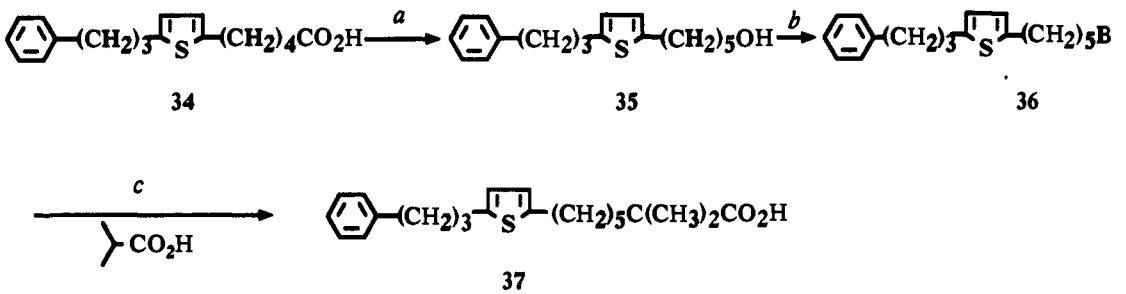
Scheme VII[a]



[a] $LiAlH_4$, THF; (b) $BrCH_2CO_2K$, *t*-BuOK, *t*-BuOH; (c) NaOH, MeCOMe.

Scheme VIII[a]



[a] (a) LiAlH, THF; (b) CDI, $BrCH_2CH{=}CH_2$, CH_3CN; (c) LDA, THF.

II (route A or B). Amidification of **21** with an ω-aminoalkanoate, promoted by *N,N'*-carbonyldiimidazole, and subsequent hydrolysis gave the corresponding acid **22**. Compound **27** with the reverse amide function was prepared from 2-thenylamine **23** (Scheme V). Protection of the amine function by a trifluoroacetyl group gave compound **24**. The latter was acylated with 3-phenylpropionyl chloride in the presence of $SnCl_4$ to give **25** in 94% yield. Reduction of **25** to the amine **26** took place under Wolff-Kishner conditions (Huang-Minlon modification) in 36% yield. The amine **26** was then acylated with glutaric anhydride to afford compound **27** in 74% yield.

Analogs with a carbonyl function or a hydroxyl group on the carboxylic acid side chain were prepared as shown in Scheme VI. The anion of 2-(3-phenylpropyl)thiophene **14**, generated by *n*-BuLi in ether, was reacted with paraformaldehyde to give the corresponding hydroxymethyl derivative **28** in 79% yield. Chlorination of **28** with $SOCl_2$ afforded the corresponding chloride, which, being unstable, was immediately treated with cyclohexane-1,3-dione in an aqueous potassium hydroxide solution to provide the alkylated product **29** in low yield (8% over the two steps). Reaction of **29** with barium hydroxide in hot water afforded the desired keto acid **30** (34%). After esterification of **30**, reduction of the resulting keto ester by sodium borohydride and subsequent base hydrolysis gave the corresponding hydroxyl compound **31** isolated as a sodium salt.

The β-oxa analog **33** was prepared from the corresponding ω-arylalkanoic acids **4** ($n = p = 3$ and Z = S) (Scheme VII). Reduction of the carboxylic acid function of **4** by lithium aluminum hydride in THF afforded, in 80% yield, the corresponding alcohol **32** which was then alkylated with the potassium salt of bromoacetic acid to yield **33** (54%), isolated as a sodium salt.

The α,α-dimethyl analog **37** was prepared from the pentanoic acid derivative **34** (Scheme VIII). After reduction of **34** with lithium aluminum hydride and bromination of the resulting alcohol **35** with 1,1'-carbonyldiimidazole and allyl bromide,[15] the resulting bromo derivative **36** was alkylated with the dianion of isobutyric acid[16] to yield the α,α-dimethyl carboxylic acid **37** (27%).

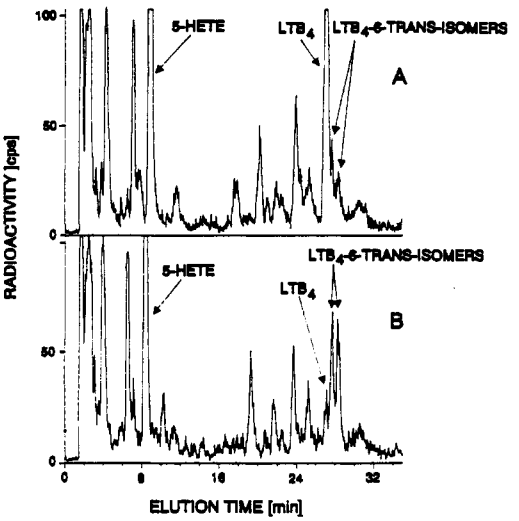


Figure 1. Selective inhibition of LTB_4 biosynthesis by LTA_4 hydrolase inhibitor **41**. SP-HPLC chromatograms of the products formed during a 5-min incubation of porcine leukocyte homogenate with [1-^{14}C]arachidonic acid (see biological methods) in the absence of (A) and in the presence (B) of 20 mmol/L of **41**. The identity of the various compounds was assessed by cochromatography of standard substances.

The synthesis of compounds not available through the general methods, along with commercially unavailable starting materials, are described in the Experimental Section.

Pharmacology

For the in vitro LTA_4 hydrolase inhibition studies, porcine leukocyte homogenates were incubated for 5 min at 37 °C with [1-^{14}C]arachidonic acid. After extraction, LTB_4, 5-HETE, and LTB_4 6-trans-isomers, formed from [1-^{14}C]arachidonic acid, were directly measured by HPLC (Figure 1).

In the presence of 5,8,11,14-eicosatetraynoic acid to suppress 12-lipoxygenase activity, arachidonic acid is principally metabolized by porcine leukocytes to 5-HETE and leukotriene A_4, whose hydrolysis by LTA_4 hydrolase leads to leukotriene B_4. Small amounts of biologically inactive LTB_4 6-trans-isomers are also detected, resulting

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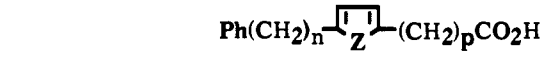
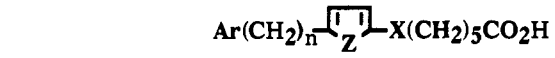
Table I. Variation of LTA_4 Hydrolase Inhibition with Side-Chain Lengths



compd	Z	n	p	mp, °C	formula	anal.°	route[b]	% inhibn[c] (20 μM)	IC_{50}[d] (μM)
34	S	3	4	224–6	$C_{18}H_{21}NaO_2S$	C,H,Na[e]	A	0	
38	CH=CH	3	4	223–5	$C_{20}H_{23}NaO_2$	C,H[e]	A	35	
39	CH=CH	3	5	41–42	$C_{21}H_{26}O_2$	C,H,O	A	43	
40	S	3	5	oil	$C_{19}H_{24}O_2S$	C,H,O,S	A	61	
41	CH=CH	3	6	35–36	$C_{22}H_{28}O_2$	C,H,O	A	76	3.4
42	S	3	6	31	$C_{20}H_{26}O_2S$	C,H,O,S	B	84	2.9
43	CH=CH	3	7	43–45	$C_{23}H_{30}O_2$	C,H,O	A	45	
44	S	3	7	208–10	$C_{21}H_{27}NaO_2S$	e	A	0	
45	CH=CH	0	6	102	$C_{19}H_{22}O_2$		A	41	
46	S	0	6	135	$C_{17}H_{20}O_2S$	C,H,O,S	A	67	
47	CH=CH	1	6	62	$C_{20}H_{24}O_2$	C,H,O	A	79	3.0
48	S	1	6	47–48	$C_{18}H_{22}O_2S$	C,H,O,S	B	51	15.0
49	CH=CH	2	6	90	$C_{21}H_{26}O_2$	C,H,O	B	43	30.0
50	S	2	6	57–59	$C_{19}H_{24}O_2S$	C,H,O,S	B	86	3.5
51	S	4	6	>230	$C_{21}H_{27}NaO_2S$	C,H,Na[e]	B	0	

° Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] Percentage of LTB_4 biosynthesis inhibition at 2×10^{-5} M. [d] IC_{50}. [e] Isolated as the sodium salt.

Table II. Variation of LTA_4 Hydrolase Inhibition with the Nature of the Terminal Aromatic Ring



compd	Ar	Z	n	X	mp, °C	formula	anal.[a]	route[b]	% inhibn[c] (20 μM)	IC_{50}[d] (μM)
52	4-ClC_6H_4	S	3	CH_2	49–50	$C_{20}H_{25}ClO_2S$	C,H,Cl,O,S	B	63	
53	4-ClC_6H_4	CH=CH	1	CH_2	58–59	$C_{20}H_{23}ClO_2$	C,H,Cl,O	B	73	7.2
54	3-ClC_6H_4	S	3	CH_2	42–44	$C_{20}H_{25}ClO_2S$	C,H,O,S	B	45	
55	2-ClC_6H_4	CH=CH	1	CH_2	68–69	$C_{20}H_{23}ClO_2$	H,Cl,O,C[e]	C	0	
56	4-$MeOC_6H_4$	CH=CH	1	CH_2	67–68	$C_{21}H_{26}O_3$	C,H,O	B	69	9.2
57	4-MeC_6H_4	CH=CH	1	CH_2	76–77	$C_{21}H_{26}O_2$	C,H,O	B	63	21.1
58	4-$O_2NC_6H_4$	CH=CH	1	CH_2	94–96	$C_{20}H_{23}NO_4$	C,H,N,O	C	53	72.5
59	4-$F_3CC_6H_4$	CH=CH	1	CH_2	63–65	$C_{21}H_{23}F_3O_2$	C,H,F	C	19	187.8
60	4-$tBuC_6H_4$	CH=CH	1	CH_2	61–63	$C_{24}H_{32}O_2$	C,H,O	B	0	
61	4-HOC_6H_4	CH=CH	1	CH_2	112–3	$C_{20}H_{24}O_3$	C,H,O	f	56	
62	4-$H_2NC_6H_4$	CH=CH	1	CH_2	127–8	$C_{20}H_{25}NO_2$	C,H,N,O	f	89	0.9
63	4-$Me_2NC_6H_4$	CH=CH	1	CH_2	95–96	$C_{22}H_{29}NO_2$	C,H,N,O	C	29	
64	4-$MeHNC_6H_4$	CH=CH	1	CH_2	74–75	$C_{21}H_{27}NO_2$	C,H,N,O	B	78	
65	4-$H_2NCOHNC_6H_4$	CH=CH	1	CH_2	186–7	$C_{21}H_{26}N_2O_3$	C,H,N,O	g	100	1.7
66	4-$MeO_2SHNC_6H_4$	CH=CH	1	CH_2	158–9	$C_{21}H_{27}NO_4S$	C,H,N,O,S	g	0	
67	4-$MeCOHNC_6H_4$	CH=CH	1	CH_2	116	$C_{22}H_{27}NO_3$	C,H,N	g	41	
68	4-$MeOC_6H_4$	S	3	CH_2	39–40	$C_{21}H_{28}O_3S$	C,H,O,S	B	80	9.7
69	4-$MeOC_6H_4$	CH=CH	3	S	64–65	$C_{22}H_{28}O_3S$	C,H,O,S	B	35	
70	4-HOC_6H_4	S	3	CH_2	82–84	$C_{20}H_{26}O_3S$	C,H,O,S	f	69	
71	2-quinolyl	CH=CH	1	CH_2	101–2	$C_{23}H_{25}NO_2$	C,H,N,O	B	48	
72	3-quinolyl	CH=CH	1	CH_2	110	$C_{23}H_{25}NO_2$	C,H,N,O	B	85	5.0
73	4-quinolyl	CH=CH	1	CH_2	137–8	$C_{23}H_{25}NO_2$	C,H,N,O	B	0	
74	2-pyridyl	CH=CH	1	CH_2	74–75	$C_{19}H_{23}NO_2$	C,H,N,O	A	76	7.7
75	3-pyridyl	CH=CH	1	CH_2	120–1	$C_{19}H_{23}NO_2$	C,H,N,O	B	65	
76	4-pyridyl	CH=CH	1	CH_2	119–10	$C_{19}H_{23}NO_2$	C,H,N,O	B	43	
77	1-naphthyl	CH=CH	1	CH_2	97	$C_{24}H_{26}O_2$	C,H,O	B	0	
78	2-naphthyl	CH=CH	1	CH_2	89	$C_{24}H_{26}O_2$	C,H,O	B	22	

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] Percentage of LTB_4 biosynthesis inhibition at 2×10^{-5} M. [d] IC_{50}. [e] C: calcd 72.61; found 72.1. [f] See Experimental Section. [g] See Scheme V.

from nonenzymatic hydrolysis of LTA_4 (Figure 1A). In the presence of a selective LTA_4 hydrolase inhibitor, as previously described by Evans with a semipurified enzyme,[11a] LTB_4 formation inhibition is associated with a concomitant increase in the nonenzymatically produced LTB_4 6-trans-isomers (Figure 1B), the sum of all 5-LO products remaining unchanged. Furthermore, the selectivity of LTB_4 biosynthesis inhibition is also demonstrated by the amount of produced 5-HETE as 5-LO inhibitors display a concomitant inhibition of 5-HETE and LTB_4 formation (for details of the method see ref 11g).

To assess the bioavailability and metabolic stability of the inhibitors, some in vitro LTA_4 hydrolase inhibition studies using plasma extracts were performed. Rats were first orally pretreated with the inhibitor. After 3 hours, the blood was taken. Plasma extracts were then studied in the in vitro LTA_4 hydrolase inhibition test.

Results and Discussion

All of the compounds (Table I, II, and III) were assayed for their ability to selectively inhibit the in vitro biosynthesis of leukotriene B_4 by porcine leukocytes at the level of LTA_4 hydrolase. In an attempt to define the structural parameters necessary for activity, our strategy was to systematically examine each portion of the structure A keeping the central aromatic ring constant and equal to 2,5-thiophene or 1,4-benzene. The potent inhibitory activities displayed by several ω-[5-(ω-arylalkyl)-2-thienyl]- and ω-[4-(ω-arylalkyl)phenyl]alkanoic acids (Table I) clearly demonstrated that an epoxide ring was not critical

Table III. Variation of LTA_4 Hydrolase Inhibition with Functionality on the Carboxylic Acid Side Chain

$$Ph(CH_2)_n\text{-}Z\text{-}(CH_2)_pX(CH_2)_qCO_2H$$

compd	Z	X	n	p	q	mp, °C	formula	anal.[a]	route[b]	% inhibn[c] (20 μM)	IC_{50}[d] (μM)
79	CH=CH	O	1	0	5	76	$C_{19}H_{22}O_3$	C,H,O	*e*	69	
80	CH=CH	S	1	0	5	96–97	$C_{19}H_{22}O_2S$	C,H,O,S	B	82	9.1
81	CH=CH	S	3	0	5	57	$C_{21}H_{26}O_2S$	C,H,O,S	B	74	6.2
16	S	S	3	0	5		$C_{19}H_{23}NaO_2S_2$	C,H[f]	*g*	79	2.8
82	S	SO	3	0	5	160–1	$C_{19}H_{23}NaO_3S_2$	C,H,Na[f]	*e*	0	
83	S	SO_2	3	0	5	oil	$C_{19}H_{24}O_4S_2$		*e*	0	
84	CH=CH	SO_2	1	0	5	103–5	$C_{19}H_{22}O_4S$	C,H,O,S	*e*	2	
85	CH=CH	CO	3	0	5	86	$C_{22}H_{26}O_3$	C,H,O[h]	*i*	27	
86	S	CO	3	0	5	69–70	$C_{20}H_{24}O_3S$	C,H,O,S	*i*	66	
30	S	CO	3	2	3	41	$C_{20}H_{24}O_3S$	C,H,O,S	*j*	82	6.3
31	S	CHOH	3	2	3		$C_{20}H_{25}NaO_3S$	C,H,Na,S[f]	*j*	73	6.2
87	S	CONH	3	1	3	75–76	$C_{19}H_{23}NO_3S$	C,H,N,O,S	*k*	12	
27	S	NHCO	3	1	3	88	$C_{19}H_{23}NO_3S$	C,H,N,O,S	*k*	38	
88	S	CONH	3	3	1	190–1	$C_{19}H_{22}NNaO_3S$	C,H,N,S[f]	*k*	53	
37	S	CMe_2	3	5	0	oil	$C_{22}H_{30}O_2S$	C,H,O,S	*e*	46	
33	S	O	3	4	1	192–4	$C_{19}H_{23}NaO_3S$	C,H,Na,S[f]	*l*	90	1.5

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] Percentage of LTB_4 biosynthesis inhibition at 2×10^{-5} M. [d] IC_{50}. [e] See Experimental Section. [f] Isolated as sodium salt. [g] See Scheme IV. [h] O: calcd 14.8; found 13.5. [i] Prepared by base hydrolysis of the corresponding ester **3** (Scheme III). [j] See Scheme VII. [k] See Scheme VI. [l] See Secheme VIII.

to obtain potent specific inhibitors of LTA_4 hydrolase. The length of the alkanoic acid side chain had a marked effect on inhibitor potency. The best inhibitory activities were displayed by 7-phenyl- and 7-(2-thienyl)heptanoic acid derivatives (**41** and **42**, Table I). The analogs with just slightly longer (**43** and **44**) or shorter chains (**34**, **38–40**) showed substantially reduced activities. This optimum chain length is consistent with the distance in LTA_4 between the carboxylic acid and the triene moiety.

The influence on potency of the chain length between the two aromatic rings was not so pronounced. Furthermore, the optimum lengths were conditioned by the nature of the central aromatic ring. For the 7-(2-thienyl)alkanoic acids an optimum chain or 2 or 3 atoms was determined (**42** and **50**). The analogs with shorter chains were around 5-fold less active (**46** and **48**) whereas a longer chain provided an entirely inactive compound (**51**). For the 7-phenylheptanoic acids there were two preferred spacings between the two aromatics, with three methylenes (**41**) as in the case of 7-(2-thienyl)heptanoic acid derivatives and with one methylene (**47**), the two methylenes analog (**49**), surprisingly, being 10-fold less active.

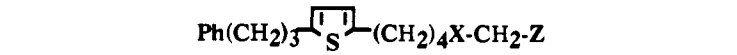
Modifications on the terminal aromatic ring were extensively examined (Table II). Ortho and meta substitution provided compounds with lower activities than para-substituted analogs (**52**, **53** > **54** ≫ **55**). The nature of the para-substituent had a marked effect on the inhibitory potency of the 7-[4-(arylmethyl)phenyl]heptanoic acid derivatives. The best activities were displayed by compounds with amino substituents exhibiting high electron-donating properties combined with a high hydrophilicity, such as NH_2 (**62**), $NHCONH_2$ (**65**), and $NHCH_3$ (**64**). Among the latter compounds, the *para*-amino derivative **62** showed the highest potency with an IC_{50} of 0.9 μM. Compounds with amino substituents exhibiting lower electron-donating properties such as $NHCOCH_3$ (**67**) and $NHSO_2CH_3$ (**66**) showed substantially reduced activities or no activity. Among the substituents displaying high electron-donating and hydrophilic properties, the best one were those possessing an NH function (NH_2 (**62**) > $NHCH_3$ (**64**) > OH (**61**) ≫ $N(CH_3)_2$ (**63**)). Compounds substituted by potent electron-withdrawing groups (**58**,**59**) or by a highly lipophilic fragment (**60**) clearly displayed the lowest inhibitor activities. The effect of para-substitution in analogs possessing a longer link than one methylene between the two aromatic rings was not so noticeable. In this case the para-substituted compounds **52** and **68–70** were uniformly less active than their unsubstituted counterparts (**41**,**42**).

The replacement of the terminal phenyl ring by another aromatic ring was also investigated (**71–78**, Table II). 2-Pyridyl and 3-quinolyl derivatives exhibited the best activities among the *N*-heteroaromatic analogs (**74** > **75**,**76** and **72** > **71**,**73**). However compounds **74** and **72** were less potent than the corresponding phenyl derivative **47**. The higher activity of the 2- and 3-quinolyl analogus (**71**,**72**) compared to the 2-naphthyl derivative **78** demonstrated in the case of fused-aromatic rings and positive effect of the incorporation of nitrogen within the terminal aromatic ring. Furthermore, the inactivity of the 4-quinolyl and 1-naphthyl derivatives **73** and **77** was consistent with the loss of potency observed in the case of ortho substitution (**55**), indicating bulk intolerance in this region of the molecule.

The effect of functionalities at various locations on the carboxylic acid side chain was investigated (Table III). With regard to the beginning of the chain, a comparison of compounds **41**, **42**, and **47** with **16** and **79–81** demonstrated that carbon, sulfur, and oxygen were suitable junctions, with carbon being generally superior to sulfur and oxygen showing the lowest potency (**79**). Oxidation of sulfur to sulfoxide or sulfone led to inactive compounds (**82–84**). Inclusion of a carbonyl function at the beginning of the carboxylic acid chain resulted in less active compounds (**85** and **86**). In order to mimic the epoxide moiety of the leukotriene A_4, compounds with a functionality such as carbonyl or hydroxyl groups on the carboxylic acid chain were synthesized (**27**,**30**,**31**,**87**, and **88**, Table III). Among these analogs, compounds **30** and **31**, respectively, with a carbonyl and a hydroxyl group in the 5-position, displayed the best activities, whereas inclusion of an amide function with the carbonyl group in position 3 (**88**), 5 (**27**) or 6 (**87**) led to clearly less potent inhibitors. This 5-position exactly corresponds to the position of the epoxide ring on the LTA_4 carboxylic acid side chain. However these functionalized analogs **30** and **31** were half as active as their unsubstituted counterpart **42**.

In an attempt to stabilize the fatty acid tail towards β-oxidation several compounds were designed (**33** and **37**, Table III). The α-ramified analog **37** showed substantially

Table IV. Variation of LTA_4 Hydrolase Inhibition with Terminal Functionality



compd	X	Z	mp, °C	formula	anal.[a]	route[b]	% inhibn[c] (20 μM)
89	O	CO_2Me	oil	$C_{20}H_{26}O_3S$	C,H,O	d	66
90	CH_2	$CONH_2$	76	$C_{20}H_{27}NOS$		e	0
91	CH_2	CN	oil	$C_{20}H_{25}NS$	C,H,N,S	e	0
92	CH_2	tetrazolyl	48	$C_{20}H_{26}N_4S$	C,H,N,S	e	29

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] Percentage of LTB_4 biosynthesis inhibition at 2×10^{-5} M. [d] See Scheme VIII. [e] See Experimental Section.

Table V. LTA_4 Hydrolase Inhibition Activities of Plasma Extracts

compd	IC_{50} (μM) in vitro	% inhibition (plasma) at 100 mg/kg po	30 mg/kg po	5 mg/kg po
42	2.8	82	44	0
41	3.4	–	15	–
33	1.5	73	54	40
81	6.2	12	20	–
16	2.8	19	19	4
72	5.0	27	19	27
53	7.2	7	–	22
62	0.9	31	–	29

reduced potency compared to the corresponding linear compound **42**, indicating bulk intolerance in this region of the molecule. However the introduction of an oxygen atom in the β-position on the carboxylic acid side chain substantially improved the inhibitor potency (**33** > **42**).

Variations on the terminal functionality were also studied (Table IV). Carboxylic acids displayed the best inhibitory activities. Replacement of the terminal carboxylic acid function by an ester (**89**), an amide (**90**), or a nitrile group (**91**) gave rise to less active or inactive compounds. Moreover, tetrazolyl analogue **92** showed substantially reduced activity (**42** ≫ **92**).

Our goal was to design metabolic stable and potent inhibitors of LTA_4 hydrolase in order to determine the importance of LTB_4 in the maintenance of inflammation. Thus plasma extracts of rats, orally pretreated with selected compounds, were tested for inhibition of LTA_4 hydrolase (Table V). The best inhibitor activity was displayed by the β-oxa derivative **33**, with a dose-related specific LTB_4 biosynthesis inhibition of 73%, 54%, and 40% at 100, 30, and 5 mg/kg, respectively. The corresponding β-methylene derivative **42** showed a lower potency with only 44% inhibition at 30 mg/kg and no inhibition at 5 mg/kg. The metabolic stabilization of the heptanoic acid side chain by insertion of an oxygen atom at β-position could explain in a large extent the best activity observed for **33**. The benzene analog of **42**, compound **41**, showed substantially reduced activity with only 15% inhibition at 30 mg/kg compared to 44% for **42** at the same doses. The other tested compounds, despite good in vitro inhibitor activities, displayed poor activities (plasma extract) at 100 mg/kg (<30%). It is worth noting the detrimental effect of the insertion of a sulfur atom at the beginning of the fatty acid side chain on inhibitory activity of the plasma extract (**42** ≫ 16). This result could reflect a greater metabolization of **16**, certainly by oxidation of sulfur, leading to inactive compounds (**82**,**83**).

In conclusion, we have designed, starting from the LTA_4 structure, 7-[5-(ω-arylalkyl)-2-thienyl]- and 7-[4-(ω-arylalkyl)phenyl]heptanoic acid derivatives which are potent specific inhibitors of LTA_4 hydrolase. The most potent inhibitor displayed an in vitro IC_{50} of 0.9 μM. By stabilization of the fatty acid side chain towards β-oxidation by insertion of an oxygen atom in β-position, potent in vitro activities were obtained in a plasma extract of pretreated rats. The most potent member of this series, compound **33**, specifically inhibits the LTB_4 biosynthesis after oral administration (plasma extract, 40% inhibition at 5 mg/kg). Compound **33**, RP64966, is to our knowledge the first specific LTA_4 hydrolase inhibitor displaying potential oral activity. On the basis of these results, RP64966 (**33**) appears to be a valuable tool for the evaluation of the importance of LTB_4 in the maintenance of inflammation in animal models and human diseases. Further pharmacological evaluations of RP64966 are now in progress.

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Brucker W 200 SY spectrometer, and proton chemical shifts are relative to tetramethylsilane as internal standard. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, qui = quintuplet, br = broad, m = multiplet. The infrared spectra were measured on a Nicolet Instrument NIC-3600 spectrophotometer. Melting points were measured on a Büchi 510 melting point apparatus in open capillary tubes and are uncorrected. Mass spectrum analyses were carried out on a Varian MAT 311A mass spectrometer, data recording with a Finnigan-Incos System 2300. Where elemental analyses are reported only by symbols of the elements, results were within ±0.4% of the theoretical values. All reactions as well as column chromatography were monitored routinely with the aid of thin-layer chromatography with precoated silica gel 60 F_{256} from Merck.

Route A: General Procedure in the Thiophene Series. 7-(5-Phenyl-2-thienyl)heptanoic Acid (46). Tin(IV) chloride (18.7 g, 71.8 mmol) was added dropwise to a cold mixture of 2-phenylthiophene[17] (8 g, 50 mmol) and ethyl 6-(chloroformyl)-hexanoate[18] (10.3 g, 53.6 mmol) in 1,2-dichloroethane (80 mL). During the addition, the reaction temperature was kept below 5 °C. The resulting mixture was stirred at room temperature for 1 h and then poured into cold H_2O (800 mL). The layers were then separated, and the aqueous layer was extracted three times with CH_2Cl_2. The organic extracts were then combined, washed with H_2O, dried over Na_2SO_4 and concentrated in vacuo. The residue was flash-chromatographed on silica gel (eluent: CH_2Cl_2) to yield the corresponding ethyl ester 3 as a light yellow oil (9.5 g, 57.5%). The ester (9.5 g, 28.8 mmol) was then directly mixed with hydrazine monohydrate (4.3 g, 85.9 mmol) and KOH (6.4 g, 114 mmol) in triethylene glycol (100 mL). The reaction mixture was heated to 210 °C for 4 h. Excess of hydrazine and water were then distilled off for 2 h under normal pressure. After cooling to 25 °C, H_2O (100 mL) was added. The aqueous layer was acidified to pH = 2 with HCl (concentrated) and extracted three times with CH_2Cl_2. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated. The resulting solid residue was purified by recrystallization from toluene, giving

(17) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M. Nickel-Phosphine Complex Catalyzed Grignard Coupling. II. Grignard Coupling of Heterocyclic Compounds. *Tetrahedron* **1982**, *38*, 3347–3354.

(18) Prout, F. S.; Cason, J.; Ingersoll, A. W. Branched-Chain Fatty Acids. V. The Synthesis of Optically Active 10-Methyloctadecanoic Acids. *J. Am. Chem. Soc.* **1948**, *70*, 298–305.

pure **46** as a white solid (4.95 g, 34.3%): mp 135 °C; NMR ($CDCl_3$ + CD_3OD) δ 7.55 (d, J = 7.5 Hz, 2 H), 7.45–7.14 (m, 3 H), 7.13 (d, J = 3.75 Hz, 1 H), 6.74 (d, J = 3.75 Hz, 1 H), 2.83 (t, J = 7.5 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.88–1.54 (m, 4 H), 1.51–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1693; MS m/z 288 (M^+). Anal. ($C_{17}H_{20}O_2S$) C, H, O.

The following compounds were prepared from the indicated starting materials by using the general procedure described above.

5-[5-(3-Phenylpropyl)-2-thienyl]pentanoic acid (34) was prepared from 2-(3-phenylpropyl)thiophene[19] and methyl 4-(chloroformyl)butyrate and isolated as the sodium salt (25.6%, over two steps): mp 224–6 °C; NMR (CD_3OD) δ 7.34–7.09 (m, 5 H), 6.56 (d, J = 2.5 Hz, 1 H), 6.53 (d, J = 2.5 Hz, 1 H), 2.87–2.55 (m, 6 H), 2.21 (t, J = 7.5 Hz, 2 H), 1.92 (qui, J = 7.5 Hz, 2 H), 1.78–1.54 (m, 4 H); IR (KBr, cm^{-1}) 1693. Anal. ($C_{18}H_{21}NaO_2S$) C, H, Na.

6-[5-(3-Phenylpropyl)-2-thienyl]hexanoic acid (40) was prepared from 2-(3-phenylpropyl)thiophene[19] and ethyl 5-(chloroformyl)pentanoate[20] (59.5%, over two steps): NMR ($CDCl_3$) δ 7.30–7.10 (m, 5 H), 6.54 (s, 2 H), 2.81–2.60 (m, 6 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.98 (qui, J = 7.5 Hz, 2 H), 1.75–1.55 (m, 4 H), 1.48–1.30 (m, 2 H); IR (film, cm^{-1}) 1708; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S.

8-[5-(3-Phenylpropyl)-2-thienyl]octanoic acid (44) was prepared from 2-(3-phenylpropyl)thiophene[19] and methyl 7-(chloroformyl)heptanoate[21] and isolated as the sodium salt (30.7%, over two steps): mp 208–210 °C. NMR (CD_3OD) δ 7.30–7.08 (m, 5 H), 6.54 (s, 2 H), 2.71 (t, J = 7.5 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.15 (t, J = 7.5 Hz, 2 H), 1.90 (qui, J = 7.5 Hz, 2 H), 1.70–1.45 (m, 4 H), 1.43–1.18 (m, 6 H); IR (KBr, cm^{-1}) 1693.

Route A: General Procedure in the Benzene Series. 7-(4-Benzylphenyl)heptanoic Acid (47). Aluminum chloride (7 g, 52.5 mmol) was added portionwise, over 90 min, to a cold mixture (−15 °C) of ethyl 6-(chloroformyl)hexanoate[18] (5 g, 26 mmol) and diphenylmethane (3.66 g, 21.75 mmol) in 1,2-dichloroethane (80 mL). During the addition, the reaction temperature was kept below −10 °C. The resulting mixture was then poured into cold water (300 mL). The aqueous layer was acidified to pH = 1 with HCl (concentrated). The layers were then separated, and the aqueous layer was extracted three times with diethyl ether. The organic extracts were then combined, washed with a saturated $NaHCO_3$ solution and then with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was flash-chromatographed on a silica gel column (eluent: hexane/ethyl acetate 85/15) to yield the corresponding ethyl ester **3** as a pale yellow oil (3.5 g, 46%). The title compound was directly obtained from the ester, by using the Wolff–Kishner procedure described above in the thiophene series, as a white solid (1.35 g, 56%): mp 57 °C; NMR ($CDCl_3$) δ 7.34–7.11 (m, 5 H), 7.09 (s, 4 H), 3.95 (s, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.70–1.46 (m, 4 H), 1.44–1.21 (m, 4 H); IR (KBr, cm^{-1}) 1712; MS m/z 296 (M^+). Anal. ($C_{20}H_{24}O_2$) C, H, O.

The following compounds were prepared from the indicated starting materials by using the general procedure described above.

5-[4-(3-Phenylpropyl)phenyl]pentanoic acid (38) was prepared from 1,3-diphenylpropane and methyl 4-(chloroformyl)butanoate and isolated as the sodium salt (23%, over two steps): mp 223–225 °C; NMR (CD_3OD) δ 7.27–6.33 (m, 9 H), 2.98–2.33 (m, 6 H), 2.16 (t, J = 7.5 Hz, 2 H), 2.63–1.20 (m, 6 H). Anal. ($C_{20}H_{23}NaO_2$) C, H.

6-[4-(3-Phenylpropyl)phenyl]hexanoic acid (39) was prepared from 1,3-diphenylpropane and ethyl 5-(chloroformyl)pentanoate[20] (33%, over two steps): mp 41–42 °C; NMR ($CDCl_3$) δ 7.33–7.11 (m, 5 H), 7.09 (s, 4 H), 2.72–2.50 (m, 6 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.65 (sext, J = 7.5 Hz, 4 H), 1.47–1.23 (m, 2 H); IR (KBr, cm^{-1}) 1693; MS m/z 310 (M^+). Anal. ($C_{21}H_{26}O_2$) C, H, O.

7-[4-(3-Phenylpropyl)phenyl]heptanoic acid (41) was prepared from 1,3-diphenylpropane and ethyl 6-(chloroformyl)-hexanoate[18] (49%, over two steps): mp 35–36 °C; NMR ($CDCl_3$) δ 7.33–7.13 (m, 5 H), 7.09 (s, 4 H), 2.70–2.50 (m, 6 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.73–1.50 (m, 4 H), 1.43–1.26 (m, 4 H); IR (KBr, cm^{-1}) 1704; MS m/z 324 (M^+). Anal. ($C_{22}H_{28}O_2$) C, H, O.

8-[4-(3-Phenylpropyl)phenyl]octanoic acid (43) was prepared from 1,3-diphenylpropane and ethyl 6-(chloroformyl)hexanoate[22] (29.5%, over two steps): mp 43–45 °C; NMR ($CDCl_3$) δ 7.33–7.11 (m, 5 H), 7.09 (s, 4 H), 2.71–2.51 (m, 6 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.73–1.48 (m, 4 H), 1.34 (br s, 6 H); IR (KBr, cm^{-1}) 1692; MS m/z 338 (M^+). Anal. ($C_{23}H_{30}O_2$) C, H, O.

7-(4-Biphenylyl)heptanoic acid (45) was prepared from biphenyl and ethyl 6-(chloroformyl)hexanoate[18] (11.3%, over two steps): mp 102 °C; NMR ($CDCl_3$) δ 7.65–7.10 (m, 9 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.80–1.25 (m, 8 H); IR (KBr, cm^{-1}) 1699; MS m/z 282 (M^+).

7-[4-(2-Pyridylmethyl)phenyl]heptanoic acid (74) was prepared from 2-benzylpyridine and ethyl 6-(chloroformyl)hexanoate[18] (8.9%, over two steps): mp 74–75 °C. NMR ($CDCl_3$) δ 8.64–8.52 (m, 1 H), 7.66–7.56 (m, 1 H), 7.18–7.05 (m, 6 H), 4.15 (s, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.74–1.50 (m, 4 H), 1.45–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1692; MS m/z 297 (M^+). Anal. ($C_{19}H_{23}NO_2$) C, H, N, O.

Route B: General Procedure in the Thiophene Series. 7-[5-(3-Phenylpropyl)-2-thienyl]heptanoic Acid (42). Ethyl 7-(2-thienyl)heptanoate[23] (30 g, 124.8 mmol), tin(IV) chloride (40 g, 153.5 mmol) were mixed together in 1,2-dichloroethane (600 mL) and cooled to 0 °C. 3-Phenylpropionyl chloride (22 g, 130.5 mmol) dissolved in 1,2-dichloroethane (200 mL) was then added dropwise. During the addition (1 h), the reaction temperature was kept below 5 °C. The resulting mixture was poured into cold water (500 mL). The layers were then separated, and the aqueous layer was extracted three times with CH_2Cl_2. The organic extracts were then combined, washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was flash-chromatographed on silica gel (eluent: hexane/ethyl acetate 9/1) to yield the corresponding ethyl ester **7** as a light yellow oil (36 g, 78%). The ester (36 g, 96.8 mmol) was then directly mixed with hydrazine monohydrate (14.5 g, 289.6 mmol) and KOH (21 g, 374.3 mmol) in triethylene glycol (500 mL). The reaction was heated to 210 °C for 4 h. Excess of hydrazine and water were then distilled off for 2 h under normal pressure. After cooling to 25 °C, H_2O (300 mL) was added. The aqueous layer was acidified to pH = 2 with HCl (concentrated) and extracted three times with CH_2Cl_2. The combined extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by flash-chromatography over silica gel (eluent: hexane/ethyl acetate 9/1) giving pure **42** as a white solid (23 g, 71.8%): mp 32–34 °C; NMR ($CDCl_3$) δ 7.36–7.09 (m, 5 H), 6.56 (br s, 2 H), 2.86–2.58 (m, 6 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.98 (qui, J = 7.5 Hz, 2 H), 1.78–1.50 (m, 4 H), 1.48–1.23 (m, 4 H); IR (KBr, cm^{-1}) 1700; MS m/z 330 (M^+). Anal. ($C_{20}H_{26}O_2S$) C, H, O, S.

The following were prepared from the indicated starting materials by using the general procedure described above.

7-(5-Benzyl-2-thienyl)heptanoic acid (48) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and benzoyl chloride (60.4%, over two steps): mp 47–48 °C. NMR ($CDCl_3$) δ 7.33–7.15 (m, 5 H), 6.58 (br s, 2 H), 4.07 (br s, 2 H), 2.73 (t, J = 7 Hz, 2 H), 2.34 (t, J = 7 Hz, 2 H), 1.85–1.13 (m, 8 H); IR (KBr, cm^{-1}) 1700; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S.

7-(5-Phenethyl-2-thienyl)heptanoic acid (50) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and phenylacetyl chloride (77.9%, over two steps): mp 57–59 °C; NMR ($CDCl_3$) δ 7.30–7.10 (m, 5 H), 6.56 (br s, 2 H), 3.12–2.87 (m, 4 H), 2.75 (t, J = 7 Hz, 2 H), 2.35 (t, J = 7 Hz, 2 H), 1.86–1.20 (m, 8 H); IR (KBr, cm^{-1}) 1707; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S.

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7-[5-(4-Phenylbutyl)-2-thienyl]heptanoic acid (51) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and 4-phenylbutanoyl chloride and isolated as the sodium salt (22%, over two steps): mp >230 °C, NMR (CD_3OD) δ 7.37–7.08 (m, 5 H), 6.52 (d, J = 2.5 Hz, 1 H), 6.47 (d, J = 2.5 Hz, 1 H), 2.82–2.65 (m, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.16 (t, J = 7.5 Hz, 2 H), 1.92 (t, J = 7.5 Hz, 2 H), 1.75–1.48 (m, 4 H), 1.46–1.15 (m, 8 H). Anal. ($C_{21}H_{27}NaO_2S$) C, H, Na.

7-[5-[3-(4-Chlorophenyl)propyl]-2-thienyl]heptanoic acid (52) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and 3-(4-chlorophenyl)propionyl chloride (57.1%, over two steps): mp 49–50 °C; NMR ($CDCl_3$) δ 7.24 (d, J = 7.5 Hz, 2 H), 7.11 (d, J = 7.5 Hz, 2 H), 6.56 (s, 2 H), 2.83–2.69 (m, 4 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.76–1.54 (m, 4 H), 1.48–1.30 (m, 4 H); IR (KBr, cm^{-1}) 1693; MS m/z 364 (M^+). Anal. ($C_{20}H_{25}ClO_2S$) C, H, Cl, O, S.

7-[5-[3-(3-Chlorophenyl)propyl]-2-thienyl]heptanoic acid (54) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and 3-(3-chlorophenyl)propionyl chloride (54.2%, over two steps): mp 42–44 °C; NMR ($CDCl_3$) δ 7.30–7.00 (m, 4 H), 6.57 (s, 2 H), 2.85–2.60 (m, 6 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.96 (qui, J = 7.5 Hz, 2 H), 1.78–1.53 (m, 4 H), 1.50–1.28 (m, 4 H); IR (KBr, cm^{-1}) 1700; MS m/z 364 (M^+). Anal. ($C_{20}H_{25}ClO_2S$) C, H, O, S.

7-[5-[3-(4-Methoxyphenyl)propyl]-2-thienyl]heptanoic acid (68) was prepared from ethyl 7-(2-thienyl)heptanoate[23] and 3-(4-methoxyphenyl)propionyl chloride (27.7%, over two steps): mp 39–40 °C; NMR ($CDCl_3$) δ 7.10 (d, J = 7.5 Hz, 2 H), 6.81 (d, J = 7.5 Hz, 2 H), 6.55 (s, 2 H), 3.80 (s, 3 H), 2.80–2.68 (m, 4 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.78–1.53 (m, 4 H), 1.48–1.23 (m, 4 H); IR (KBr, cm^{-1}) 1705; MS m/z 360 (M^+). Anal. ($C_{21}H_{28}O_3S$) C, H, O, S.

Route B: General Procedure in the Benzene Series. 7-[4-(4-Chlorobenzyl)phenyl]heptanoic Acid (53). Aluminum chloride (23 g, 172.5 mmol) and 4-chlorobenzoyl chloride (10 g, 57.1 mmol) were mixed together in 1,2-dichloroethane (180 mL), and the mixture was allowed to cool to −5 °C. Ethyl 7-phenylheptanoate[24] (13.4 g, 57.1 mmol) 1,2-dichloroethane was then added dropwise over 3 h. During the addition, the reaction temperature was kept below −5 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 3 h. The mixture was again cooled to 0 °C. Brine (12 mL) and H_2O (300 mL) were then added. After filtration, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were then combined, washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was flash-chromatographed on a silica gel column (eluent: hexane/ethyl acetate 9/1) to yield the corresponding ethyl ester **7** as a pale yellow oil (6.7 g, 31.3%). The title compound was directly obtained from the ester by using the Wolff–Kishner procedure described above, in the benzene series, as a white solid (1.75 g, 30%): mp 58–59 °C; NMR ($CDCl_3$) δ 7.23 (d, J = 8.75 Hz, 2 H), 7.09 (d, J = 8.75 Hz, 2 H), 7.07 (s, 4 H), 3.90 (s, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.48 (m, 4 H), 1.45–1.23 (m, 4 H); IR (KBr, cm^{-1}) 1697; MS m/z 330 (M^+). Anal. ($C_{20}H_{23}ClO_2$) C, H, Cl, O.

The following compounds were prepared from the indicated starting materials by using the general procedure described above.

7-[4-(2-Phenethyl)phenyl]heptanoic acid (49) was prepared from ethyl 7-phenylheptanoate[24] and 2-phenylacetyl chloride (10.1%, over two steps): mp 90 °C; NMR ($CDCl_3$) δ 7.34–7.04 (m, 9 H), 2.91 (br s, 4 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.73–1.49 (m, 4 H), 1.46–1.28 (m, 4 H); IR (KBr, cm^{-1}) 1706; MS m/z 310 (M^+). Anal. ($C_{21}H_{26}ClO_2$) C, H, O.

7-[4-(4-Methoxybenzyl)phenyl]heptanoic acid (56) was prepared from ethyl 7-phenylheptanoate[24] and 4-methoxybenzoyl chloride (6.75%, over two steps): mp 67–68 °C; NMR ($CDCl_3$) δ 7.10 (d, J = 8.75 Hz, 2 H), 7.08 (s, 4 H), 6.81 (d, J = 8.75 Hz, 2 H), 3.88 (s, 2 H), 3.78 (s, 3 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.73–1.49 (m, 4 H), 1.45–1.28 (m, 4 H); IR (KBr, cm^{-1}) 1696; MS m/z 326 (M^+). Anal. ($C_{21}H_{26}O_3$) C, H, O.

7-[4-(4-Methylbenzyl)phenyl]heptanoic acid (57) was prepared from ethyl 7-phenylheptanoate[24] and 4-methylbenzoyl chloride (12.4%, over two steps): mp 76–77 °C; NMR ($CDCl_3$) δ 7.09 (s, 8 H), 3.90 (s, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 2.31 (s, 3 H), 1.74–1.48 (m, 4 H), 1.44–1.24 (m, 4 H); IR (KBr, cm^{-1}) 1700; MS m/z 310 (M^+). Anal. ($C_{21}H_{26}O_2$) C, H, O.

7-[4-(4-*tert*-Butylbenzyl)phenyl]heptanoic acid (60) was prepared from ethyl 7-phenylheptanoate[24] and 4-*tert*-butylbenzoyl chloride (44.8%, over two steps): mp 61–63 °C; NMR ($CDCl_3$) δ 7.34 (d, J = 8.75 Hz, 2 H), 7.15 (d, J = 8.75 Hz, 2 H), 7.14 (s, 4 H), 3.94 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.74–1.49 (m, 4 H), 1.46–1.24 (m, 4 H), 1.30 (br s, 9 H); IR (KBr, cm^{-1}) 1705; MS m/z 352 (M^+). Anal. ($C_{24}H_{32}O_2$) C, H, O.

7-[4-[4-(Methylamino)benzyl]phenyl]heptanoic acid (64) was prepared from ethyl 7-phenylheptanoate[24] and *N*-methyl-4-(trifluoroacetamido)benzoyl chloride (15.8%, over two steps): mp 74–75 °C; NMR ($CDCl_3$) δ 7.09 (br s, 4 H), 7.04 (d, J = 8.75 Hz, 2 H), 6.59 (d, J = 8.75 Hz, 2 H), 6.45 (br s, 2 H), 3.86 (s, 2 H), 2.83 (s, 3 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.48 (m, 4 H), 1.46–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1698; MS m/z 325 (M^+). Anal. ($C_{21}H_{27}NO_2$) C, H, N, O.

6-[[4-[3-(4-Methoxyphenyl)propyl]phenyl]thio]hexanoic acid (69) was prepared from ethyl 6-(phenylthio)hexanoate (prepared by reaction of sodium thiophenolate with ethyl 6-bromohexanoate in DMF (96%)) and 3-(4-methoxyphenyl)-propionyl chloride (13.9%, over two steps): mp 64–65 °C; NMR ($CDCl_3$) δ 7.28 (d, J = 7.5 Hz, 2 H), 7.13 (d, J = 7.5 Hz, 4 H), 6.84 (d, J = 7.5 Hz, 2 H), 3.79 (s, 3 H), 2.89 (t, J = 7.5 Hz, 2 H), 2.59 (m, 4 H), 2.38 (t, J = 7.5 Hz, 2 H), 1.9 (qui, J = 7.5 Hz, 2 H), 1.78–1.33 (m, 6 H); IR (KBr, cm^{-1}) 1703; MS m/z 372 (M^+). Anal. ($C_{22}H_{28}O_3S$) C, H, O, S.

7-[4-(2-Quinolylmethyl)phenyl]heptanoic acid (71) was prepared from ethyl 7-phenylheptanoate[24] and 2-quinolinecarbonyl chloride (4.8%, over two steps): mp 101–102 °C; NMR ($CDCl_3$) δ 9.95 (br s, 1 H), 8.16 (d, J = 8.75 Hz, 1 H), 8.05 (d, J = 8.75 Hz, 1 H), 7.81–7.64 (m, 2 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.24 (d, J = 7.5 Hz, 1 H), 7.22 (d, J = 8.75 Hz, 2 H), 7.11 (d, J = 8.75 Hz, 2 H), 4.35 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.48–1.24 (m, 4 H); IR (KBr, cm^{-1}) 1703; MS m/z 347 (M^+). Anal. ($C_{23}H_{25}NO_2$) C, H, N, O.

7-[4-(3-Quinolylmethyl)phenyl]heptanoic acid (72) was prepared from ethyl 7-phenylheptanoate and 3-quinolinecarbonyl chloride (4.7%, over two steps): mp 110–111 °C; NMR ($CDCl_3$) δ 8.81 (d, J = 2.5 Hz, 1 H), 8.12 (d, J = 7.5 Hz, 1 H), 7.92 (d, J = 2.5 Hz, 1 H), 7.73 (dd, J = 1.25, 7.5 Hz, 1 H), 7.65 (dt, J = 1.25, 7.5 Hz, 1 H), 7.50 (dt, J = 1.25, 7.5 Hz, 1 H), 7.11 (s, 4 H), 4.13 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.78–1.50 (m, 4 H), 1.48–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1710; MS m/z 347 (M^+). Anal. ($C_{23}H_{25}NO_2$) C, H, N, O.

7-[4-(4-Quinolylmethyl)phenyl]heptanoic acid (73) was prepared from ethyl 7-phenylheptanoate[24] and 4-quinolinecarbonyl chloride (9.3%, over two steps): mp 137–138 °C; NMR ($CDCl_3$) δ 8.88 (d, J = 3.75 Hz, 1 H), 8.21 (d, J = 7.5 Hz, 1 H), 8.10 (d, 7.5 Hz, 1 H), 7.74 (dt, J = 1.25, 7.5 Hz, 1 H), 7.58 (dt, J = 1.25, 7.5 Hz, 1 H), 7.20 (d, J = 3.75 Hz, 1 H), 7.13 (br s, 4 H), 4.44 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.48–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1700; MS m/z 347 (M^+). Anal. ($C_{23}H_{25}NO_2$) C, H, N, O.

7-[4-(3-Pyridylmethyl)phenyl]heptanoic acid (75) was prepared from ethyl 7-phenylheptanoate[24] and 3-pyridinecarbonyl chloride (12.6%, over two steps): mp 120–121 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 8.53–8.40 (m, 2 H), 7.51–7.43 (m, 1 H), 7.25–7.16 (m, 1 H), 7.13–7.01 (m, 4 H), 3.94 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 1.73–1.48 (m, 4 H), 1.45–1.28 (m, 4 H); IR (KBr, cm^{-1}) 1709; MS m/z 297 (M^+). Anal. ($C_{19}H_{23}NO_2$) C, H, N, O.

7-[4-(4-Pyridylmethyl)phenyl]heptanoic acid (76) was prepared from ethyl 7-phenylheptanoate[24] and 4-pyridinecarbonyl chloride (27.6%, over two steps): mp 119–120 °C; NMR ($CDCl_3$) δ 9.10 (br s, 1 H), 8.48 (d, J = 5 Hz, 2 H), 7.14 (d, J = 5 Hz, 2 H), 7.17–7.00 (m, 4 H), 3.94 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.49 (m, 4 H), 1.47–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1702; MS m/z 297 (M^+). Anal. ($C_{19}H_{23}NO_2$) C, H, N, O.

7-[4-(1-Naphthylmethyl)phenyl]heptanoic acid (77) was prepared from ethyl 7-phenylheptanoate[24] and 1-naphthalene-

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carbonyl chloride (10.4%, over two steps): mp 97 °C; NMR ($CDCl_3$) δ 8.06–7.93 (m, 1 H), 7.90–7.79 (m, 1 H), 7.75 (d, J = 8.75 Hz, 1 H), 7.47–7.34 (m, 3 H), 7.27 (d, J = 8.75 Hz, 1 H), 7.14–6.97 (m, 4 H), 4.41 (s, 2 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.75–1.45 (m, 4 H), 1.45–1.20 (m, 4 H); IR (KBr, cm^{-1}) 1706; MS m/z 346 (M^+). Anal. ($C_{24}H_{26}O_2$) C, H, O.

7-[4-(2-Naphthylmethyl)phenyl]heptanoic acid (78) was prepared from ethyl 7-phenylheptanoate[24] and 2-naphthalenecarbonyl chloride (39.5%, over two steps): mp 92–94 °C; NMR ($CDCl_3$) δ 7.85–7.69 (m, 3 H), 7.64 (br s, 1 H), 7.50–7.38 (m, 2 H), 7.31 (dd, J = 1.5, 7.5 Hz, 1 H), 7.19–7.00 (m, 4 H), 4.10 (s, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.78–1.48 (m, 4 H), 1.45–1.21 (m, 4 H); IR (KBr, cm^{-1}) 1702; MS m/z 346 (M^+). Anal. ($C_{24}H_{26}O_2$) C, H, O.

6-[(4-Benzylphenyl)thio]hexanoic acid (80) was prepared from ethyl 6-(phenylthio)hexanoate[25] and benzoyl chloride (51.3%, over two steps): mp 96–97 °C; NMR ($CDCl_3$) δ 7.35–7.04 (m, 9 H), 3.94 (s, 2 H), 2.88 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.76–1.34 (m, 6 H); IR (KBr, cm^{-1}) 1703; MS m/z 314 (M^+). Anal. ($C_{19}H_{22}O_2S$) C, H, O, S.

6-[[4-(3-Phenylpropyl)phenyl]thio]hexanoic acid (81) was prepared from ethyl 6-(phenylthio)hexanoate[25] and 3-phenylpropionyl chloride (15.6%, over two steps): mp 57 °C; NMR ($CDCl_3$) δ 7.42–7.00 (m, 9 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.78–2.5 (m, 4 H), 2.36 (t, J = 7.5 Hz, 2 H), 2.95 (m, 2 H), 1.80–1.31 (m, 6 H); IR (KBr, cm^{-1}) 1710; MS m/z 342 (M^+). Anal. ($C_{21}H_{26}O_2S$) C, H, O, S.

Route C: General Procedure. 7-[4-(4-Nitrobenzyl)-phenyl]heptanoic Acid (58). To a mixture of ethyl 7-[4-(4-nitrobenzoyl)phenyl]heptanoate (5.1 g, 13.3 mmol) (obtained in 73.5% yield from ethyl 7-phenylheptanoate[24] and 4-nitrobenzoyl chloride) and trifluoroacetic acid (15 mL, 194.5 mmol) was added triethylsilane (5.1 mL, 31.9 mmol). The reaction mixture was stirred at room temperature for 80 h. After cooling to 0 °C, H_2O (30 mL) was added. The pH of the aqueous layer was carefully adjusted to 11 with a 2 N NaOH and was then extracted three times with diethyl ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was flash-chromatographed on silica gel (eluent: hexane/ethyl acetate 85/15) to yield the ethyl ester of the title compound as a yellow oil (4.2 g, 85.7%). The ester (4.2 g, 11.4 mmol) was mixed with concentrated HCl (10 N, 9 mL) and water (9 mL). The reaction mixture was then refluxed for 77 h. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The solid residue was recrystallized from a mixture of hexane and ethyl acetate to give pure **58** as a yellow solid (2.52 g, 64.9%): mp 94–96 °C; NMR ($CDCl_3$) δ 8.18 (d, J = 8.75 Hz, 2 H), 7.37 (d, J = 8.75 Hz, 2 H), 7.20–7.05 (m, 4 H), 4.06 (s, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.48–1.28 (m, 4 H); IR (KBr, cm^{-1}) 1708, 1512; MS m/z 341 (M^+). Anal. ($C_{20}H_{23}NO_4$) C, H, N, O.

The following compounds were prepared from the indicated starting materials by using the general procedure described above.

7-[4-(2-Chlorobenzyl)phenyl]heptanoic acid (55) was prepared from ethyl 7-phenylheptanoate[24] and 2-chlorobenzoyl chloride, the ethyl ester of the title compound being hydrolyzed, in this case, under basic conditions (NaOH, EtOH) (11%, over three steps): mp 68–69 °C; NMR ($CDCl_3$) δ 7.43–7.31 (m, 1 H), 7.23–7.10 (m, 3 H), 7.11 (s, 4 H), 4.10 (s, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.47–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1708; MS m/z 330 (M^+). Anal. ($C_{20}H_{23}ClO_2$) H, Cl, O; C: calcd 72.61, found 72.1.

7-[4-[4-(Trifluoromethyl)benzyl]phenyl]heptanoic acid (59) was prepared from ethyl 7-phenylheptanoate[24] and 4-(trifluoromethyl)benzoyl chloride, the ethyl ester of the title compound being hydrolyzed, in this case, under basic conditions (NaOH, EtOH) (8.8%, over three steps): mp 63–65 °C; NMR ($CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 7.5 Hz, 2 H), 7.13 (br s, 4 H), 4.01 (s, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.74–1.49 (m, 4 H), 1.46–1.24 (m, 4 H); IR (KBr, cm^{-1}) 1716; MS m/z 364 (M^+). Anal. ($C_{21}H_{23}F_3O_2$) C, H, F.

7-[4-[4-(Dimethylamino)benzyl]phenyl]heptanoic acid (63) was prepared from ethyl 7-phenylheptanoate[24] and 4-(dimethylamino)benzoyl chloride, the ethyl ester of the title compound being hydrolyzed, in this case, under basic conditions (NaOH, EtOH) (11.8%, over three steps): mp 95–96 °C; NMR ($CDCl_3$) δ 7.09 (s, 4 H), 7.08 (d, J = 8.75 Hz, 2 H), 6.71 (d, J = 8.75 Hz, 2 H), 3.86 (s, 2 H), 2.91 (s, 6 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.73–1.48 (m, 4 H), 1.45–1.23 (m, 4 H); IR (KBr, cm^{-1}) 1698; MS m/z 339 (M^+). Anal. ($C_{22}H_{29}NO_2$) C, H, N, O.

6-[[5-(3-Phenylpropyl)-2-thienyl]thio]hexanoic Acid (16). To a cooled solution (0 °C) of 2-(3-phenylpropyl)thiophene[19] (10.52 g, 52 mmol) in dry diethyl ether (200 mL) was added dropwise n-BuLi (33 mL, 1.60 M in hexane). After stirring for 15 min, sulfur (1.67 g, 52 mmol) was added portionwise at 0 °C. The mixture was allowed to warm to 25 °C and stirred for 15 min. Ethyl 6-bromohexanoate (11.6 g, 52 mmol) was then added dropwise, and the reaction mixture was stirred 12 h at 25 °C. The mixture was poured into cold water, the layers were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated, giving an oily residue. The ethyl ester of the title compound was isolated by chromatography over a silica gel column (eluant: hexane/ethyl acetate 9/1). The ester (8.5 g, 22.6 mmol) was dissolved in methanol/water 25/1 (52 mL), and NaOH (5.1 g, 127.5 mmol) was added. The reaction mixture was heated at reflux for 2 h. The solvent was then evaporated, and the solid residue was dissolved in H_2O. The aqueous layer was acidified to pH = 1 with HCl (concentrated) and extracted twice with CH_2Cl_2. The extracts were dried over Na_2SO_4 and evaporated giving an oily residue. The title compound was isolated as the sodium salt (3.35 g, 40%): NMR (CD_3OD) δ 7.33–7.10 (m, 5 H), 6.91 (d, J = 3.75 Hz, 1 H), 6.68 (d, J = 3.75 Hz, 1 H), 2.83–2.58 (m, 6 H), 2.15 (t, J = 7.5 Hz, 2 H), 1.95 (qui, J = 7.5 Hz, 2 H), 1.70–1.30 (m, 6 H); IR (KBr, cm^{-1}) 1563. Anal. ($C_{19}H_{23}NaO_2S_2$) C, H.

Methyl 7-[4-(4-Aminobenzyl)phenyl]heptanoate (18). A mixture of methyl 7-[4-(4-nitrobenzyl)phenyl]heptanoate (17) (19.9 g, 56 mmol) (prepared as described for compound **58**, route C) and tin(II) chloride (53.2 g, 280.6 mmol) in methanol (300 mL) was heated for 5 h at reflux and was then dropped into ice (200 g). The pH was adjusted to 5 with 2 N NaOH. After removing methanol under vacuo, the pH of the aqueous layer was adjusted to 11 with 6 N NaOH and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated giving, after flash-chromatography over silica gel (eluent: hexane/ethyl acetate 4/6), an oily residue (11 g, 60%): NMR ($CDCl_3$) δ 7.09 (s, 4 H), 6.99 (d, J = 8.75 Hz, 2 H), 6.64 (d, J = 8.75 Hz, 2 H), 4.14 (br s, 2 H), 3.85 (s, 2 H), 3.67 (s, 3 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 1.78–1.13 (m, 8 H); MS m/z 325 (M^+).

5-(3-Phenylpropyl)-2-thiophenemethanamine (26) was prepared according to Scheme V from N-(trifluoroacetyl)-2-thiophenemethanamine (24) (obtained by reacting 2-thiophenemethanamine (23) with trifluoroacetic anhydride) and 3-phenylpropionyl chloride (33.8%, over two steps). The amine obtained in this manner was used directly for the subsequent acylation step without further purification.

5-Oxo-5-[[[5-(3-phenylpropyl)-2-thienyl]methyl]amino]-pentanoic Acid (27). To a solution of **26** (1.7 g, 7.4 mmol) in THF (40 mL) was added dropwise glutaric anhydride (0.9 g, 7.9 mmol) dissolved in THF (10 mL). The reaction mixture was stirred for 20 min at 25 °C and then evaporated. The solid residue was recrystallized from ethyl acetate providing the title compound as a pale yellow solid (1.9 g, 74%): mp 88 °C; NMR ($CDCl_3$) δ 7.33–7.10 (m, 5 H), 6.75 (d, J = 3.75 Hz, 1 H), 6.60 (d, J = 3.75 Hz, 1 H), 5.90 (br s, 1 H), 4.52 (d, J = 6.25 Hz, 2 H), 2.79 (t, J = 7.5 Hz, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 2.29 (t, J = 7.5 Hz, 2 H), 2.08–1.88 (m, 4 H); IR (KBr, cm^{-1}) 1699, 1642; MS m/z 345 (M^+). Anal. ($C_{19}H_{23}NO_3S$) C, H, N, O, S.

2-(Hydroxymethyl)-5-(3-phenylpropyl)thiophene (28). To a cooled solution (15 °C) of 2-(3-phenylpropyl)thiophene[19] (15 g, 74.2 mmol) in dry diethyl ether (150 mL) was added dropwise n-BuLi (56 mL, 1.60 M in hexane). The mixture was then cooled

(25) Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R. S. Direct Synthesis of Carboxylic Acids from Organoboranes. *J. Org. Chem.* **1990**, *55*, 6356–6360.

to 0 °C, and paraformaldehyde (3.7 g) was then added in one portion. The reaction mixture was then heated to 32 °C for 90 min and then poured into a mixture of cold H_2O (200 mL) and concentrated HCl (20 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography over a silica gel column (eluent: diethyl ether/petroleum ether 6/4), yielding the title compound as a pale yellow oil (13.6 g, 79%).

2-[[5-(3-Phenylpropyl)-2-thienyl]methyl]cyclohexane-1,3-dione (29). To a cooled solution (5 °C) of **28** (12.6 g, 54.3 mmol) in diethyl ether (50 mL) was added dropwise a solution of thionyl chloride (12.9 g, 108 mmol) in diethyl ether (25 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 5 h. The solvent was then evaporated. The oily residue, containing the unstable chloro intermediate, was not further purified but immediately used for the next step. Thus, the crude chloro derivative (14.6 g) was added dropwise to a mixture of 1,3-cyclohexanedione (7.1 g, 63.3 mmol) and KI (0.65 g, 3.9 mmol) in an aqueous KOH solution (16.2 mL, 20% w/w). The reaction mixture was then heated at reflux for 4 h. After cooling, the mixture was poured into H_2O. The aqueous layer was acidified to pH = 5 with HCl (concentrated) and extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography over a silica gel column (eluent: dichloromethane/methanol 99/1), yielding the title compound as a white solid (1.4 g, 8%, over two steps), mp 103–105 °C.

5-Oxo-7-[5-(3-phenylpropyl)-2-thienyl]heptanoic Acid (30). Compound **29** (1.4 g, 4.3 mmol) and barium hydroxide octahydrate (9.5 g, 30.1 mmol) were mixed in H_2O (15 mL), and the mixture was heated at reflux for 48 h. H_2O (100 mL) was added. The aqueous layer was acidifed to pH = 1 with HCl (concentrated) and extracted twice with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over a silica gel column (eluent: dichloromethane/methanol 98/2), yielding the title compound as a white solid (0.5 g, 34%): mp 41 °C; NMR ($CDCl_3$) δ 7.32–7.10 (m, 5 H), 6.56 (br s, 2 H), 3.04 (t, J = 7.5 Hz, 2 H), 2.85–2.69 (m, 4 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.50 (t, J = 7.5 Hz, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.05–1.80 (m, 4 H); IR (KBr, cm^{-1}) 1705; MS m/z 344 (M^+). Anal. ($C_{20}H_{24}O_3S$) C, H, O, S.

5-Hydroxy-7-[5-(3-phenylpropyl)-2-thienyl]heptanoic Acid (31). A solution of **30** (1.85 g, 5.4 mmol) in ethanol (100 mL) was saturated with HCl for 2 h at 5 °C. After evaporation, the residue was purified by chromatography over a silica gel column (eluent: diethyl ether/petroleum ether 2/8) to give the ethyl ester of **30** as a colorless oil (1.7 g, 85%). To a cold solution (5 °C) of the ethyl ester of **30** (1.7 g, 4.6 mmol) in ethanol (50 mL) was added sodium borohydride (0.086 g, 2.23 mmol). After stirring for 15 min at 0 °C, the mixture was poured into cold H_2O (100 mL). The aqueous layer was acidified to pH = 5 with HCl (2 N) and extracted twice with diethyl ether. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by chromatography over a silica gel column (eluent: diethyl ether), yielding the ethyl ester of the title compound as a pale yellow oil (1.2 g, 69.75%). The ester (1.2 g, 3.2 mmol) was dissolved in ethanol (15 mL), and 1 N NaOH (3.2 mL) was added. The reaction mixture was then stirred for 4 h at room temperature. H_2O (200 mL) was added. The aqueous layer was extracted twice with diethyl ether and freeze-dried, yielding the sodium salt of the title compound as a white powder (0.8 g, 72.2%): NMR (CD_3OD) δ 7.30–7.09 (m, 5 H), 6.63–6.53 (m, 2 H), 3.66–3.50 (m, 1 H), 3.00–2.55 (m, 6 H), 2.18 (t, J = 7.5 Hz, 2 H), 1.93 (qui, J = 7.5 Hz, 2 H), 1.83–1.40 (m, 6 H); IR (KBr, cm^{-1}) 1562. Anal. ($C_{20}H_{25}NaO_3S$) C, H, Na, S.

4-[5-(3-Phenylpropyl)-2-thienyl]-1-butanol (32). To a suspension of lithium aluminum hydride (8.1 g, 213 mmol) in THF (600 mL) was added dropwise (over 2 h) 4-[5-(3-phenylpropyl)-2-thienyl]butanoic acid (29 g, 100 mmol) (prepared by the route B (78.8%)) in THF (50 mL). The reaction mixture was stirred at room temperature for 1 h. After cooling to 10 °C, H_2O (200 mL) and H_2SO_4 (10%, 410 mL) were carefully added. The layers were then separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with 6 N NaOH and finally with brine. After drying over Na_2SO_4, the organic layer was filtered and evaporated. The residue was purified by flash chromatography over silica gel (eluent: hexane/diethyl ether 7/3) to yield **32** as a pale yellow oil (22 g, 80%).

2-[[4-[5-(3-Phenylpropyl)-2-thienyl]butyl]oxy]acetic Acid (33). Compound **32** (5 g, 18.2 mmol) and potassium bromoacetate (4.8 g, 27.1 mmol) were mixed together in *tert*-butyl alcohol (80 mL) and heated to 80 °C. Potassium *tert*-butoxide (6.14 g, 50 mmol) dissolved in 100 mL of *tert*-butyl alcohol was then added dropwise. The reaction mixture was then heated at reflux for 16 h. After cooling to room temperature, brine (130 mL) was added and the aqueous layer was extracted three times with diethyl ether. The resulting aqueous layer was then acidified to pH = 5 with 1 N HCl and extracted three times with ethyl acetate. The combined ethyl acetate extracts were then washed with water, dried over Na_2SO_4, and evaporated, leaving a yellow oil (3.83 g). The crude acid **33** was transformed into its sodium salt by treatment with an equimolar amount of NaOH in acetone, yielding the sodium salt of **33** as a white solid (3.48 g, 54.4%): mp 192–193 °C; NMR (CD_3OD) δ 7.33–7.06 (m, 5 H), 6.57 (d, J = 2.5 Hz, 1 H), 6.53 (d, J = 2.5 Hz, 1 H), 3.81 (s, 2 H), 3.48 (t, J = 7.5 Hz, 2 H), 2.81–2.66 (m, 4 H), 2.62 (t, J = 7.5 Hz, 2 H), 1.91 (qui, J = 7.5 Hz, 2 H), 1.78–1.56 (m, 4 H); IR (KBr, cm^{-1}) 1598; MS m/z 377 ($M + Na^+$). Anal. ($C_{19}H_{23}NaO_3S$) C, H, Na, S.

5-[5-(3-Phenylpropyl)-2-thienyl]-1-pentanol (35) was prepared as described for compound **32** but starting from the ethyl ester of **34** (77%) and isolated as a yellow oil, used without purification in the next step.

1-Bromo-5-[5-(3-phenylpropyl)-2-thienyl]pentane (36). 1,1′-Carbonyldiimidazole (4.5 g, 27.7 mmol) was added in one portion to a solution of **35** (8 g, 27.7 mmol) in acetonitrile (40 mL). Allyl bromide (16.8 g, 138.8 mmol) was then added dropwise over 15 min. The reaction mixture was heated at reflux for 1 h. After cooling, the mixture was poured into a mixture of diethyl ether (200 mL) and H_2O (100 mL). The layers were then separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 1 N HCl, followed by $NaHCO_3$ (aqueous, saturated) and finally with H_2O. After drying over Na_2SO_4, the organic layer was filtered and evaporated, yielding **36** as a yellow oil (8.5 g, 87%), used without further purification in the next step.

2,2-Dimethyl-7-[5-(3-phenylpropyl)-2-thienyl]heptanoic Acid (37). To a solution of LDA in THF (prepared from *n*-BuLi (21.4 mL, 1.60 M in hexane), diisopropylamine (3.5 g, 34.6 mmol), and 20 mL THF) at 0 °C, was added dropwise isobutyric acid (1.35 g, 15.3 mmol) and HMPA (2.4 g, 13.4 mmol). The reaction mixture was then heated to 50 °C for 2 h. After cooling to 0 °C, **36** (6 g, 17.1 mmol) dissolved in THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and was stirred for 2 h. The mixture was then poured into cold H_2O. The aqueous layer was acidified to pH = 1 with 2 N HCl and extracted three times with diethyl ether. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography over silica gel (eluent: diethyl ether/hexane 1/1), yielding **37** as a pale yellow oil (1.64 g, 26.8%): NMR ($CDCl_3$) δ 7.30–7.10 (m, 5 H), 6.56–6.50 (m, 2 H), 2.84–2.61 (m, 6 H), 1.98 (qui, J = 7.5 Hz, 2 H), 1.72–1.24 (m, 8 H), 1.18 (br s, 6 H); IR (film, cm^{-1}) 1698; MS m/z 358 (M^+). Anal. ($C_{22}H_{30}O_2S$) C, H, O, S.

7-[4-(4-Hydroxybenzyl)phenyl]heptanoic Acid (61). The ethyl ester of **56** (2.6 g, 7.3 mmol) and pyridine hydrochloride (21.7 g, 56 mmol) were mixed together and heated to 180 °C for 5 h. After cooling, water (60 mL) was added and the aqueous layer was extracted five times with diethyl ether. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from a mixture of ethanol and water, giving **61** as a pale yellow solid (1.89 g, 83%): mp 112–113 °C; NMR ($CDCl_3$ + CD_3OD) δ 7.05–6.85 (m, 6 H), 6.70–6.60 (m, 2 H), 3.76 (s, 2 H), 2.48 (t, J = 7.5 Hz, 2 H), 2.20 (t, J = 7.5 Hz, 2 H), 1.65–1.40 (m, 4 H), 1.36–1.15 (m, 4 H); IR (KBr, cm^{-1}) 1701; MS m/z 312 (M^+). Anal. ($C_{20}H_{24}O_3$) C, H, O.

7-[4-(4-Aminobenzyl)phenyl]heptanoic acid (62) was prepared from ethyl 7-[4-(4-nitrobenzoyl)phenyl]heptanoate (see the preparation of **58** by the route C) by using the Wolff–Kishner procedure described above in the Route A and was obtained as a white solid (35%): mp 126–127 °C; NMR ($CDCl_3$ + DMSO-d_6)

δ 7.06 (br s, 4 H), 6.95 (d, J = 7.5 Hz, 2 H), 6.60 (d, J = 7.5 Hz, 2 H), 6.21 (br s, 3 H), 3.82 (s, 2 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.27 (t, J = 7.5 Hz, 2 H), 1.73–1.48 (m, 4 H), 1.45–1.22 (m, 4 H); IR (KBr, cm^{-1}) 1703; MS m/z 311 (M^+). Anal. ($C_{20}H_{25}NO_2$) C, H, N, O.

7-[4-(4-Ureidobenzyl)phenyl]heptanoic Acid (65). To a mixture of 18 (2 g, 6 mmol) was dropped potassium isocyanate (0.5 g, 6 mmol) dissolved in water (10 mL). The reaction mixture was stirred 30 min at room temperature. Cold H_2O was then added, and the resulting mixture was vigorously stirred 30 min. The obtained precipitate was filtrated and recrystallized in acetone to yield the methyl ester of the title compound as a whitish solid (1.3 g, 60%): mp: 155–160 °C. The title compound was obtained as a white solid by using the ester hydrolysis procedure described for compound 16 (0.22 g, 14.3%): mp 186–187 °C. NMR (DMSO d_6): δ 8.45 (s, 1 H), 7.29 (d, J = 7.5 Hz, 2 H), 7.09 (s, 4 H), 7.05 (d, J = 7.5 Hz, 2 H), 5.78 (s, 2 H), 3.79 (s, 2 H), 2.49 (t, J = 7.5 Hz, 2 H), 2.16 (t, J = 7.5 Hz, 2 H), 1.68–1.10 (m, 8 H); IR (KBr, cm^{-1}) 1713, 1670, 1595, 1543; MS m/z 311 (100%). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N, O.

7-[4-[4-(Methylsulfonamido)benzyl]phenyl]heptanoic Acid (66). Methanesulfonyl chloride (0.6 g, 5.2 mmol) dissolved in chloroform (10 mL) was added to a mixture of 18 (0.7 g, 2.2 mmol), triethylamine (0.6 mL, 4.4 mmol), and a catalytic amount of DMAP in chloroform (10 mL). The reaction mixture was stirred at room temperature for 30 h. H_2O was then added, and the layers were then separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was flash-chromatographed on a silica gel column (eluent: hexane/ethyl acetate 75/25), giving the methyl ester of the title compound as a white solid (0.4 g, 47%): mp 80–81 °C. The title compound was obtained as a white solid by using the ester hydrolysis procedure described for compound 16 (0.27 g, 70%): mp 158–159 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 9.04 (br s, 1 H), 7.29–7.03 (m, 8 H), 4.73 (br s, 1 H), 3.90 (s, 2 H), 2.93 (s, 3 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.26 (t, J = 7.5 Hz, 2 H), 1.73–1.49 (m, 4 H), 1.45–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1694, 1325, 1146; MS m/z 389 (M^+). Anal. ($C_{21}H_{27}NO_4S$) C, H, N, O, S.

7-[4-(4-Acetamidobenzyl)phenyl]heptanoic Acid (67). Acetyl chloride (0.44 g, 6 mmol) dissolved in $CHCl_3$ (10 mL) was added to a mixture of 18 (2 g, 6 mmol), triethylamine (0.8 mL, 6 mmol), and a catalytic amount of DMAP in chloroform (20 mL). The reaction mixture was stirred at room temperature for 50 h. H_2O was then added, and the layers were then separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was flash-chromatographed on a silica gel column (eluent: hexane/ethyl acetate 1/5), giving the ethyl ester of the title compound as a white solid (1.5 g, 67%): mp 78–80 °C. The title compound was obtained as a white solid by using the ester hydrolysis procedure described for compound 16 (0.83 g, 58.8%): mp 116 °C; NMR (DMSO-d_6) δ 11.8 (br s, 1 H), 9.73 (br s, 1 H), 7.43 (d, J = 7.5 Hz, 2 H), 7.10 (d, J = 7.5 Hz, 2 H), 7.07 (s, 4 H), 3.77 (s, 2 H), 2.45 (t, J = 7.5 Hz, 2 H), 2.13 (t, J = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.67–1.02 (m, 8 H); IR (KBr, cm^{-1}) 1703, 1658, 1534; MS m/z 353 (M^+). Anal. ($C_{22}H_{27}NO_3$) C, H, N.

7-[5-[3-(4-Hydroxyphenyl)propyl]-2-thienyl]heptanoic Acid (70). 7-[5-[3-(4-Methoxyphenyl)propyl]-2-thienyl]heptanoic acid (68) (2 g, 5.55 mmol) and pyridine hydrochloride (6.4 g, 56 mmol) were mixed together and heated to 180 °C for 3 h. After cooling, H_2O (100 mL) and ethyl acetate (100 mL) were added. The layers were separated, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from toluene/hexane 1/1, giving 70 as a white solid (33.7%): mp 82–84 °C; NMR ($CDCl_3$) δ 7.08 (d, J = 8.75 Hz, 2 H), 6.76 (d, J = 8.75 Hz, 2 H), 6.57 (s, 2 H), 2.95–2.68 (m, 4 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.94 (qui, J = 7.5 Hz, 2 H), 1.80–1.54 (m, 4 H), 1.50–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1707; MS m/z 346 (M^+). Anal. ($C_{20}H_{26}O_3S$) C, H, O, S.

6-(4-Benzylphenoxy)hexanoic Acid (79). A mixture of 4-benzylphenol (18.4 g, 99.8 mmol), ethyl 6-bromohexanoate (33.5 g, 150 mmol) and K_2CO_3 (41.5 g, 300 mmol) in 200 mL of DMF was heated at reflux for a week. Ice (2409 g) was then added. The aqueous layer was acidified to pH = 1 with concentrated HCl and extracted three times with ethyl acetate. The combined extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The solid residue was recrystallized in hexane to give 79 as a white solid (4.7 g, 14.3%): mp 76 °C; NMR ($CDCl_3$) δ 7.36–6.98 (m, 7 H), 6.80 (d, J = 7.5 Hz, 2 H), 4.04 (m, 4 H), 2.38 (t, J = 7.5 Hz, 2 H), 1.90–1.38 (m, 6 H); MS m/z 298 (M^+). Anal. ($C_{19}H_{22}O_3$) C, H, O.

6-[[5-(3-Phenylpropyl)-2-thienyl]sulfinyl]hexanoic Acid (82). To a cold (0 °C) solution of 6-[[5-(3-phenylpropyl)-2-thienyl]thio]hexanoic acid (16) (2 g, 5.75 mmol) in CH_2Cl_2 (15 mL) was added dropwise 3-chloroperbenzoic acid (1 g, 5.79 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h at 0 °C. The mixture was then allowed to warm to 25 °C and stirred overnight. After evaporation, the residue was flash-chromatographed on a silica gel column (eluent: ethyl acetate), giving an oily residue. The title compound was isolated as the sodium salt (1 g, 68%): mp 160–161 °C; NMR (CD_3OD) 7.46 (d, J = 3.5 Hz, 1 H), 7.36–7.10 (m, 5 H), 6.91 (d, J = 3.5 Hz, 1 H), 3.21–2.93 (m, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.69 (t, J = 7.5 Hz, 2 H), 2.30–1.23 (m, 10 H); IR (KBr, cm^{-1}) 1565. Anal. ($C_{19}H_{23}NaO_3S_2$) C, H, Na.

6-[[5-(3-Phenylpropyl)-2-thienyl]sulfonyl]hexanoic Acid (83). To a cold (0 °C) solution of 6-[[5-(3-phenylpropyl)-2-thienyl]sulfinyl]hexanoic acid (82) (2 g, 5.49 mmol) in CH_2Cl_2 (50 mL) was added dropwise 3-chloroperbenzoic acid (1.1 g, 6.37 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1 h at 0 °C. 3-Chloroperbenzoic acid (1 g, 5.79 mmol) in CH_2Cl_2 (20 mL) was again added. The mixture was then allowed to warm to 25 °C and stirred overnight. After evaporation, the residue was flash-chromatographed on a silica gel column (eluent: ethyl acetate/hexane 1/1), giving the title compound as an oily residue (1.6 g, 94%): NMR ($CDCl_3$) δ 7.55 (d, J = 3.5 Hz, 1 H, 7.40–7.10 (m, 5 H), 6.97 (d, J = 3.5 Hz, 1 H), 3.30–2.50 (m, 6 H), 2.34 (t, J = 7.5 Hz, 2 H), 2.23–1.12 (m, 8 H); IR (KBr, cm^{-1}) 1724; MS m/z 380 (M^+).

6-[(4-Benzylphenyl)sulfonyl]hexanoic Acid (84). To a solution of 80 (3 g, 9.5 mmol) in acetic acid (80 mL) was added 4 mL of a solution of hydrogen peroxide in H_2O (30% w/w). The reaction mixture was heated to 90 °C for 1 h and then was stirred for 16 h at room temperature. The mixture was then dropped into H_2O. The resulting precipitate was filtered and recrystallized from a mixture of hexane and ethyl acetate to give 84 as a white solid (2.1 g, 66%): mp 103–105 °C; NMR ($CDCl_3$) δ 11.2 (br s, 1 H), 7.86 (d, J = 8.75 Hz, 2 H), 7.56–7.07 (m, 7 H), 4.09 (s, 2 H), 3.09 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.91–1.26 (m, 6 H); MS m/z 346 (M^+). Anal. ($C_{19}H_{22}O_4S$) C, H, O, S.

7-Oxo-7-[4-(3-phenylpropyl)phenyl]heptanoic Acid (85). The ester of the title compound was prepared by using the Friedel–Crafts procedure described in the route A (benzene series), but starting from 1,3-diphenylpropane (5.8 g, 29.5 mmol), $AlCl_3$ (5 g, 37.5 mmol), and ethyl 6-(chloroformyl)hexanoate[18] (3.85 g, 18.7 mmol). The resulting ester (5 g, 13.7 mmol) was hydrolyzed by using the ester hydrolysis procedure described for compound 16 to yield 85 as a pale yellow solid (1.5 g, 23.7%, over two steps): mp 86 °C; NMR ($CDCl_3$) δ 7.88 (d, J = 8.75 Hz, 2 H), 7.33–7.11 (m, 5 H), 7.25 (d, J = 8.75 Hz, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 1.98 (qui, J = 7.5 Hz, 2 H), 1.85–1.60 (m, 4 H), 1.53–1.35 (m, 4 H); IR (KBr, cm^{-1}) 1706, 1683; MS m/z 338 (M^+). Anal. ($C_{22}H_{26}O_3$) C, H; O: calcd 14.8, found 13.5.

7-Oxo-7-[5-(3-phenylpropyl)-2-thienyl]heptanoic Acid (86). The ethyl ester of the title compound was prepared by using the Friedel–Crafts procedure described in the route A (thiophene series), but starting from 2-(3-phenylpropyl)thiophene[19] (6 g, 29.7 mmol), $SnCl_4$ (9.3 g, 45 mmol), and ethyl 6-(chloroformyl)hexanoate[18] (6.1 g, 29.5 mmol). The resulting ester (9.1 g, 9.1 mmol) was hydrolyzed by using the ester hydrolysis procedure described for compound 16, yielding 86 as a white solid (5.4 g, 53.1%, over two steps): mp 69–70 °C; NMR ($CDCl_3$) δ 11.3 (br s, 1 H), 7.94 (d, J = 3.75 Hz, 1 H), 7.35–7.13 (m, 5 H), 6.83 (d, J = 3.75 Hz, 1 H), 2.86 (t, J = 7.5 Hz, 4 H), 2.69 (t, J = 7.5 Hz, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.00 (qui, J = 7.5 Hz, 2 H), 1.85–1.58 (m, 4 H), 1.50–1.30 (m, 2 H); IR (KBr, cm^{-1}) 1705, 1654; MS m/z 344 (M^+). Anal. ($C_{20}H_{24}O_3S$) C, H, O, S.

***N*-[2-[5-(3-Phenylpropyl)-2-thienyl]acetyl]-4-aminobutyric Acid (87).** To a solution of 2-[5-(3-phenylpropyl)-2-thienyl]acetic acid (7 g, 26.7 mmol) (prepared according to the route A, thiophene

series, from ethyl 2-thiopheneacetate and 3-phenylpropionyl chloride (25.6%)) in dry THF (100 mL) was added portionwise 1,1'-carbonyldiimidazole (4.5 g, 27.75 mmol), and the mixture was stirred for 1 h at room temperature. Ethyl 4-aminobutyrate (3.5 g, 26.7 mmol) was then added. After stirring 2 h, the solvent was evaporated. Ethyl acetate (200 mL) was added to the residue, and the mixture was washed twice with water. The organic layer was dried over Na_2SO_4 and evaporated. After flash chromatography over a silica gel column (eluent: hexane/ethyl acetate 7/3), the ethyl ester of the title compound was obtained as a white solid (6.6 g, 66%): mp 55–57 °C. The ester was hydrolyzed by using the ester hydrolysis procedure described for compound **16**, providing **87** as a white solid (3.35 g, 48%): mp 75–76 °C; NMR ($CDCl_3$) δ 9.26 (br s, 1 H), 7.34–7.11 (m, 5 H), 6.71 (d, J = 2.5 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.00 (m, 1 H), 3.70 (s, 2 H), 3.29 (q, J = 7.5 Hz, 2 H), 2.79 (t, J = 7.5 Hz, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.99 (qui, J = 7.5 Hz, 2 H), 1.79 (qui, J = 7.5 Hz, 2 H); IR (KBr, cm^{-1}) 1698, 1645; MS m/z 345 (M^+). Anal. ($C_{19}H_{23}NO_3S$) C, H, N, O, S.

2-[[4-[5-(3-Phenylpropyl)-2-thienyl]butanoyl]amino]acetic acid (88) was prepared by using the same two-step procedure described for compound **87** but from 4-[5-(3-phenylpropyl)-2-thienyl]butyric acid (prepared according to the route A from ethyl 4-(2-thienyl)butyrate and 3-phenylpropionyl chloride (78.8%)) and ethyl glycinate and isolated as the sodium salt (32.4%, over two steps): mp 190–191 °C; NMR (DMSO-d_6) δ 7.34–7.06 (m, 6 H), 6.63 (s, 2 H), 3.3 (d, J = 3.75 Hz, 2 H), 2.79–2.54 (m, 6 H), 2.16 (t, J = 7.5 Hz, 2 H), 2.00–1.64 (m, 4 H); IR (KBr, cm^{-1}) 1614, 1567, 1551. Anal. ($C_{19}H_{22}NNaO_3S$) C, H, N, S.

Methyl 2-[[4-[5-(3-Phenylpropyl)-2-thienyl]butyl]oxy]-acetate (89). Compound 33 (4.2 g, 12.6 mmol) was dissolved in methanol (80 mL) containing H_2SO_4 (0.5 mL). The mixture was heated at reflux for 24 h. The solvent was then evaporated, and the residue was dissolved in ethyl acetate (15 mL). The organic layer was washed with 2 N NaOH and finally with H_2O. After drying over Na_2SO_4, the organic layer was filtered and evaporated. The residue was purified by flash chromatography over silica gel (eluent: hexane/ethyl acetate 95/5), yielding **89** as a colorless oil (4 g, 92%): NMR ($CDCl_3$) δ 7.42–7.15 (m, 5 H), 6.61 (s, 2 H), 4.07 (s, 2 H), 3.76 (s, 3 H), 3.55 (t, J = 7.5 Hz, 2 H), 2.95–2.60 (m, 6 H), 1.98 (qui, J = 7.5 Hz, 2 H), 1.85–1.57 (m, 4 H); IR (KBr, cm^{-1}) 1757, 1740. MS m/z 346 (M^+). Anal. ($C_{20}H_{26}O_3S$) C, H, O.

7-[5-(3-Phenylpropyl)-2-thienyl]heptanamide (90). The title compound was prepared by using the coupling procedure described for compound **87**, but starting from 7-[5-(3-phenylpropyl)-2-thienyl]heptanoic acid (**42**) (7.4 g, 22.4 mmol), 1,1'-carbonyldiimidazole (5.4 g, 33.3 mmol), and ammonia (1.14 g, 66.9 mmol) dissolved in 100 mL of THF, yielding **90** as a white solid (4.95 g, 67.5%): mp 76 °C; NMR ($CDCl_3$) δ 7.37–7.12 (m, 5 H), 6.56 (br s, 2 H), 5.58 (br s, 2 H), 2.86–2.59 (m, 6 H), 2.21 (t, J = 7.5 Hz, 2 H), 1.99 (qui, J = 7.5 Hz, 2 H), 1.76–1.52 (m, 4 H), 1.49–1.29 (m, 4 H); IR (KBr, cm^{-1}) 1647; MS m/z 329 (M^+).

7-[5-(3-Phenylpropyl)-2-thienyl]heptanenitrile (91). To a solution of 7-[5-(3-phenylpropyl)-2-thienyl]heptanohydroxamic acid **93** (10 g, 29 mmol) in benzene (200 mL) was added dropwise phosphorus tribromide (5.4 mL, 58 mmol). The resulting mixture was then heated to 80 °C for 3 h. After cooling to room temperature, the mixture was washed twice with $NaHCO_3$ (aqueous, saturated). The organic layer was then dried over Na_2SO_4 and evaporated. The oily residue was purified by chromatography over silica gel (eluent: ethyl acetate/hexane 5/95), giving **91** as a colorless oil (4 g, 44.3%): NMR ($CDCl_3$) δ 7.34–7.12 (m, 5 H), 6.56 (br s, 2 H), 2.83–2.61 (m, 6 H), 2.32 (t, J = 7.5 Hz, 2 H), 1.99 (qui, J = 7.5 Hz, 2 H), 1.75–1.56 (m, 4 H), 1.52–1.24 (m, 4 H); IR (KBr, cm^{-1}) 2245, 1455; MS m/z 311 (M^+). Anal. ($C_{20}H_{25}NS$) C, H, N, S.

5-[6-[5-(3-Phenylpropyl)-2-thienyl]hexyl]-1*H*-tetrazole (92). To a solution of **91** (6.8 g, 21.8 mmol) in 120 mL of 1,2-dimethoxyethane was added in one portion freshly prepared tri-*n*-butyltin azide (21.8 g, 65.5 mmol). The reaction mixture was then heated to 85 °C for 24 h. The mixture was then cooled to room temperature, and a 10:1 mixture of methanol and 1 N HCl (21 mL) was added. After stirring for 3 h, an equal volume of H_2O was then added and the resulting mixture was extracted with ethyl acetate. The aqueous layer was then acidified to pH = 1 with 1 N HCl and extracted twice with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and evaporated. The oily residue was purified by chromatography over silica gel (eluent: ethyl acetate/hexane 60/40 then 80/20), yielding **92** as a white solid (0.95 g, 12.3%): mp 48 °C; NMR ($CDCl_3$) δ 7.35–7.09 (m, 5 H), 6.56 (d, J = 2.5 Hz, 1 H), 6.52 (d, J = 2.5 Hz, 1 H), 3.06 (t, J = 7.5 Hz, 2 H), 2.85–2.57 (m, 6 H), 2.06–1.75 (m, 4 H), 1.72–1.52 (m, 2 H), 1.51–1.24 (m, 4 H); IR (KBr, cm^{-1}) 2855, 2932; MS m/z 354 (M^+). Anal. ($C_{20}H_{26}N_4S$) C, H, N, S.

7-[5-(3-Phenylpropyl)-2-thienyl]heptanohydroxamic Acid (93). To a solution of the ethyl ester of **42** (26.7 g, 75.5 mmol) in ethanol (80 mL) was added a solution of hydroxylamine hydrochloride (20.7 g, 298 mmol) in methanol (180 mL) and NaCN (0.37 g, 7.5 mmol). To the resulting suspension was added dropwise, over 35 min, a 5 M solution of KOH in methanol (74.5 mL). The temperature rase to 30 °C. The resulting white suspension was allowed to warm to 45 °C and was stirred for 4 h. The mixture was then evaporated. H_2O was added, and the resulting aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and evaporated. The solid residue was recrystallized from a mixture of hexane and ethyl acetate, giving **93** as a white solid (12.2 g, 47.6%): mp 59–60 °C.

Biological Methods. Preparation of the Rat Plasma Extracts for Use in the in Vitro Assays. Male Wistar rats were fasted during one night prior to use. The tested compound, suspended in tylose, was orally administrated. After 3 h, blood was taken from the vena cava and rapidly put into a 0.1 volume of Liquemin (from Hoffmann-La Roche). After centrifugation at 6000*g* for 10 min at room temperature, the plasma was separated from the sedimented blood cells. A plasma sample (1.5 mL), diluted with Tris/HCl buffer (17 mmol/L, pH = 7.2) containing NH_4Cl (0.17% w/w) (0.5 mL), was chromatographed on a C18 column, pretreated with methanol (2 mL) and water (2 mL). The eluate was collected (fraction 1). The column was then washed with water (3 mL) and with methanol (2 mL), giving fraction 2. Fraction 1 was acidified by 1 N HCl (300 μL) and chromatographed once more on a C18 column, pretreated with methanol (2 mL) and acidic water (2 mL, pH 2). The column was washed with acidic water (6 mL) and methanol (6 mL), giving fraction 3. The combined fractions 2 and 3 were evaporated. The residue was taken into ethanol (25 μL) and tested directly in the in vitro LTA_4 hydrolase inhibition assay.

Preparation of Porcine Leukocyte Homogenates. Porcine leukocytes were isolated from peripheral blood collected with one-ninth volume of an isotonic saline solution containing sodium citrate (3.8% w/w) and Liquemin (50 000 units/L) (from Hoffmann-La Roche). This solution was set in a 0.2 volume of an isotonic saline solution containing Dextran T-500 (6% w/w) (from Pharmacia Fine Chemicals). The cells were allowed to sediment at 4 °C causing the majority of red cells to separate from the white ones. After centrifugation at 500*g* for 10 min, the pellet was resuspended in HBSS buffer containing 0.38% of sodium citrate. The centrifugation was repeated once more. The pellet was resuspended in a Tris/HCl buffer (17 mmol/L, pH = 7.2) containing NH_4Cl (0.17% w/w) and incubated at 25 °C for 5 min to induce the lysis of the remaining red cells. After centrifugation, the cells were resuspended in a phosphate buffered (10 mmol/L, pH = 7.4) isotonic saline. The cell concentration was obtained by using a Coulter Counter (Coulter Electronics Ltd.) and was adjusted to 10^8 cells/mL with the phosphate buffered saline. The viability of the cell, as checked by the trypan blue exclusion test (Boehringer Mannheim), was higher than 95%.

LTA_4 Hydrolase Inhibition Assay: Incubation and Extraction. The porcine leukocytes were sonicated (Branson Sonifier, 1 min, 40 W, 4 °C) before incubation. The cell homogenate (500 μmol) was kept at 25 °C, and then calcium chloride and ATP were added to a final concentration of 2 mmol/L. For the inhibition experiment, the cell suspensions were preincubated with the inhibitor (in ethanol or phosphate buffered saline) or with the plasma extract for 3 min at 25 °C in the presence of 5,8,11,14-eicosatetraynoic acid (from Hoffmann-La Roche) (final concentration 4 μmol/L), in order to suppress the 12-LO activity of porcine leukocytes. The reaction was initiated by addition of [1-^{14}C]arachidonic acid (from NEN) (54.5 Ci/mol, 0.2 μCi totally). The incubation was then performed at 37 °C for 5 additional min

and terminated by the addition of 0.2 volume of 1% formic acid. The mixture was then extracted with 2 volumes of chloroform/methanol 1:1 (w/w) and then with 0.8 volume of chloroform. The chloroform extracts were combined and evaporated to be directly analyzed by HPLC.

High Pressure Liquid Chromatography Analysis. Analytical HPLC (Hewlett Packard 1084 B) was performed using a prepacked column (Lichrosorb 60, 7 μm, 250 mm × 4 mm) from Merck (Darmstadt). The compounds were eluted using first a 85:15 mixture of two elution systems, hexane/methanol/2-propanol 972:18:10 (vol/vol/vol) and hexane/methanol/2-propanol 972:18:70 (vol/vol/vol), containing 0.1% of acetic acid and 0.02% of water. After 12 min, the elution was performed by using a gradient, ranging from 15 to 95%, of the second eluting system in the first one. The flow rate was 2 mL/min. The labeled arachidonic acid metabolites, 5-HETE, LTB_4, and LTB_4-isomers were separated under these HPLC analysis conditions and quantitatively evaluated by detecting the radioactivity with an HPLC-Monitor (LB 505, Berthold, Wilbad). The inhibition of the LTA_4 hydrolase activity was calculated from the diminution of the LTB_4 production, resulting in the concomitant increase in nonenzymatic LTB_4 6-trans-isomers production. Values for inhibition of LTA_4 hydrolase represent the mean value obtained from at least three individual experiments with values within a range of ±10% of the mean. IC_{50} values were calculated by log-probit analysis of values from at least six different inhibitor concentrations.

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Registry No. **3** (Ar = Ph, n = 0, Z = S, p = 6, R = Et), 142259-74-3; 3 (Ar = Ph, n = 1, Z = CH=CH, p = 6, R = Et), 142259-75-4; **7** (Ar = Ph, n = 3, Z = S, X = bond, p = 6, R = Et), 142259-76-5; **7** (Ar = 4-ClC_6H_4, n = 1, Z = CH=CH, X = CH_2, p = 5, R = Et), 142259-77-6; 14, 29908-27-8; **15**, 142259-78-7; **16**, 142259-79-8; **16** free base, 142259-80-1; **17**, 142259-81-2; **18**, 142259-82-3; **23**, 27757-85-3; **24**, 142259-83-4; **26**, 142259-84-5; **27**, 142259-85-6; **28**, 142259-86-7; **29**, 142259-87-8; **30**, 142259-88-9; **30** ethyl ester, 142259-89-0; 31, 142259-90-3; **31** ethyl ester, 142259-91-4; **31** free base, 142259-92-5; **32**, 142259-93-6; **33**, 142259-94-7; **33** free base, 142259-95-8; **34**, 101336-01-0; **34** ethyl ester, 101336-13-4; **34** free base, 101335-99-3; **35**, 142259-96-9; **36**, 142259-97-0; **37**, 142259-98-1; **38**, 142259-99-2; **38** free base, 142260-00-2; **39**, 142260-01-3; **40**, 142260-02-4; **41**, 142260-03-5; **42**, 142260-04-6; **42** ethyl ester, 142260-05-7; **43**, 142260-06-8; **44**, 142260-07-9; **44** free base, 142260-08-0; **45**, 59324-68-4; **46**, 142260-09-1; **47**, 142260-10-4; **48**, 142260-11-5; **49**, 142260-12-6; **50**, 142260-13-7; **51**, 142260-14-8; **51** free base, 142260-15-9; **52**, 142260-16-0; **53**, 142260-17-1; **54**, 142260-18-2; **55**, 142260-19-3; **56**, 142260-20-6; **56** ethyl ester, 142260-21-7; **57**, 142260-22-8; **58**, 142260-23-9; **58** ethyl ester, 142260-24-0; **59**, 142260-25-1; **60**, 142260-26-2; **61**, 142260-27-3; **62**, 142260-28-4; **63**, 142260-29-5; **64**, 142260-30-8; **65**, 142260-31-9; **65** methyl ester, 142260-32-0; **66**, 142260-33-1; **66** methyl ester, 142260-34-2; **67**, 142260-35-3; **67** ethyl ester, 142260-36-4; **68**, 142260-37-5; **69**, 142260-38-6; **70**, 142260-39-7; **71**, 142260-40-0; **72**, 142260-41-1; **73**, 142260-42-2; **74**, 142260-43-3; **75**, 142260-44-4; **76**, 142260-45-5; **77**, 142260-46-6; **78**, 142260-47-7; **79**, 142260-48-8; **80**, 142260-49-9; **81**, 142260-50-2; **82**, 142260-51-3; **82** free base, 142260-52-4; **83**, 142260-53-5; **84**, 142260-54-6; **85**, 142260-55-7; **86**, 142260-56-8; **87**, 142260-57-9; **87** ethyl ester, 142260-58-0; **88**, 142260-59-1; **88** free base, 142260-60-4; **89**, 142260-61-5; **90**, 142260-62-6; **91**, 142260-63-7; **92**, 142260-64-8; **93**, 142260-65-9; LTA_4 hydrolase, 90119-07-6; $Ph(CH_2)_2COCl$, 645-45-4; $(F_3CCO)_2O$, 407-25-0; 4-[5-(3-phenylpropyl)-2-thienyl]butanoic acid, 142260-66-0; methyl 4-(chloroformyl)butyrate, 1501-26-4; ethyl 5-(chloroformyl)pentanoate, 1071-71-2; methyl 7-(chloroformyl)heptanoate, 41624-92-4; ethyl 6-(chloroformyl)hexanoate, 14794-32-2; 2-phenylthiophene, 825-55-8; diphenylmethane, 101-81-5; 1,3-diphenylpropane, 1081-75-0; biphenyl, 92-52-4; 2-benzylpyridine, 101-82-6; ethyl 7-(2-thienyl)heptanoate, 142293-82-1; benzoyl chloride, 98-88-4; phenylacetyl chloride, 103-80-0; 4-phenylbutanoyl chloride, 18496-54-3; 3-(4-chlorophenyl)propionyl chloride, 52085-96-8; 3-(3-chlorophenyl)propionyl chloride, 40478-50-0; 3-(4-methoxyphenyl)-propionyl chloride, 15893-42-2; 4-chlorobenzoyl chloride, 122-01-0; ethyl 7-phenylheptanoate, 134511-26-5; 4-methoxybenzoyl chloride, 100-07-2; 4-methylbenzoyl chloride, 874-60-2; 4-*tert*-butylbenzoyl chloride, 1710-98-1; *N*-methyl-4-(trifluoroacetamido)-benzoyl chloride, 95063-86-8; ethyl 6-(phenylthio)hexanoate, 142260-67-1; sodium thiophenolate, 930-69-8; ethyl 6-bromohexanoate, 25542-62-5; 2-quinolinecarbonyl chloride, 50342-01-3; 3-quinolinecarbonyl chloride, 84741-86-6; 4-quinolinecarbonyl chloride, 50821-72-2; 3-pyridinecarbonyl chloride, 10400-19-8; 4-pyridinecarbonyl chloride, 14254-57-0; 1-naphthalenecarbonyl chloride, 879-18-5; 2-naphthalenecarbonyl chloride, 2243-83-6; 4-nitrobenzoyl chloride, 122-04-3; 2-chlorobenzoyl chloride, 609-65-4; 4-(trifluoromethyl)benzoyl chloride, 329-15-7; 4-(dimethylamino)benzoyl chloride, 4755-50-4; ethyl 7-[4-(1-nitrobenzoyl)phenyl]heptanoate, 142260-68-2; 4-benzylphenol, 101-53-1; ethyl 2-thiopheneacetate, 57382-97-5; ethyl 4-aminobutyrate, 5959-36-4; ethyl 4-(2-thienyl)butyrate, 91950-17-3; ethyl glycinate, 459-73-4; glutaric anhydride, 108-55-4; 2-[5-(3-phenylpropyl)-2-thienyl]acetic acid, 142260-69-3.