ω-[(ω-Arylalkyl)thienyl]alkanoic Acids: From Specific LTA_4 Hydrolase Inhibitors to LTB_4 Receptor Antagonists

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A series of ω-[(ω-arylalkyl)thienyl]alkanoic acid isomers was prepared and a structure–activity relationship was investigated. These compounds have displayed either LTA_4 hydrolase inhibition activities or LTB_4 receptor binding activities, or both, depending on the relative orientation of the two side chains on the thiophene ring. Whereas the 2,5-isomers specifically exhibited LTA_4 hydrolase inhibition, 3,5-isomers displayed both activities. On the other hand, the "ortho-isomers" specifically inhibited the binding of the LTB_4 to its receptor. The side-chain lengths were also important for an optimal inhibition or binding activity. Substitutions on the terminal aromatic ring or on the thiophene nucleus led to small changes in both activities. The most dramatic effect was obtained by substituting the carboxylic acid side chain in the α-position with one or two methyl groups, which substantially enhanced the LTB_4 receptor binding activity. In the most favorable case, the α,α-dimethyl derivative RP66153 was found 20-fold more potent than its linear counterpart.

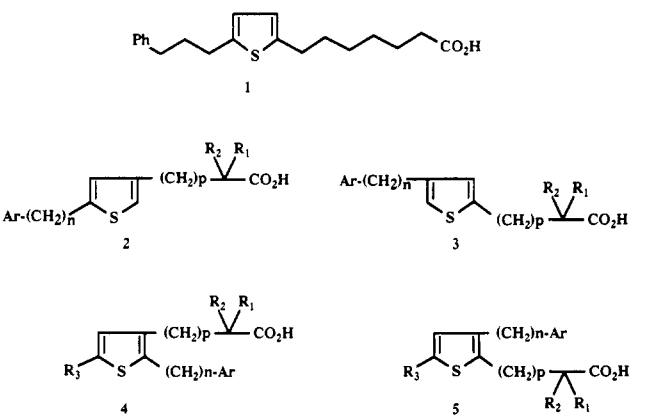
Leukotriene B_4, 5(*S*),12(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatrienoic acid (LTB_4), is a product of arachidonic acid metabolism by the 5-lipoxygenase (5-LO) pathway. LTB_4 has been shown to be a potent polymorphonuclear leukocyte (PMN) activator and has been proposed as an important mediator of inflammation.[1-4] Therefore reducing LTB_4 concentration by using specific LTA_4 hydrolase inhibitors and/or inhibiting the LTB_4 receptor-mediated functional responses to LTB_4 by using LTB_4 receptor antagonists could be useful in the treatment of certain inflammatory conditions.

We have described in a previous paper the design of selective and potent LTA_4 hydrolase inhibitors and more particularly 7-[5-(3-arylpropyl)-2-thienyl]heptanoic acid derivatives.[5] During the course of our structure–activity relationship (SAR) studies in this series, some isomers of the 7-[5-(3-phenylpropyl)-2-thienyl]heptanoic acid (**1**) have been synthesized (Scheme I). Some of them have retained potent LTA_4 hydrolase inhibition activities whereas others have displayed specific LTB_4 receptor binding activities.

Some research groups have already reported synthetic LTB_4 receptor antagonists. Structurally, these compounds fall into three principal categories: leukotriene analogs, based on the natural product, such as SM-9064[6] or U-75302,[7] hydroxyacetophenone derivatives, related to the prototype LTD_4 antagonist FPL55712, such as LY255283[8] or SC-41930,[9] and dicarboxylic acids such as LY223982[10] and ONO LB457.[11]

We report herein the synthesis and structure–activity relationship studies of the thienylalkanoic acid derivatives **2**, **3**, **4**, and **5** (Scheme I) which are selective inhibitors of LTA_4 hydrolase and/or specific LTB_4 receptor antagonists.

Scheme I



Chemistry

All the compounds **2** and **4** were prepared by the routes A, B, or C as shown in Scheme II. The Friedel–Crafts acylation of a ω-3-thienylalkanoate **6** by an acyl chloride **7**, in the presence of $SnCl_4$, afforded two acylation products **8** and **9**, which were separated by chromatography. Reduction of **8** and **9** under the Huang–Minlon modification of the Wolff–Kishner reaction[12] yielded the corresponding alkanoic acids **2** and **4**, respectively (route A). In the particular case of the reduction of the derivative with a *p*-methoxy group on the terminal aromatic ring, the desired compound **2e** was isolated as the minor product of the reaction, the major product of the Wolff–Kishner reduction being the corresponding hydroxy analog **2f**. The

† Rhône-Poulenc Rorer, GMBH.

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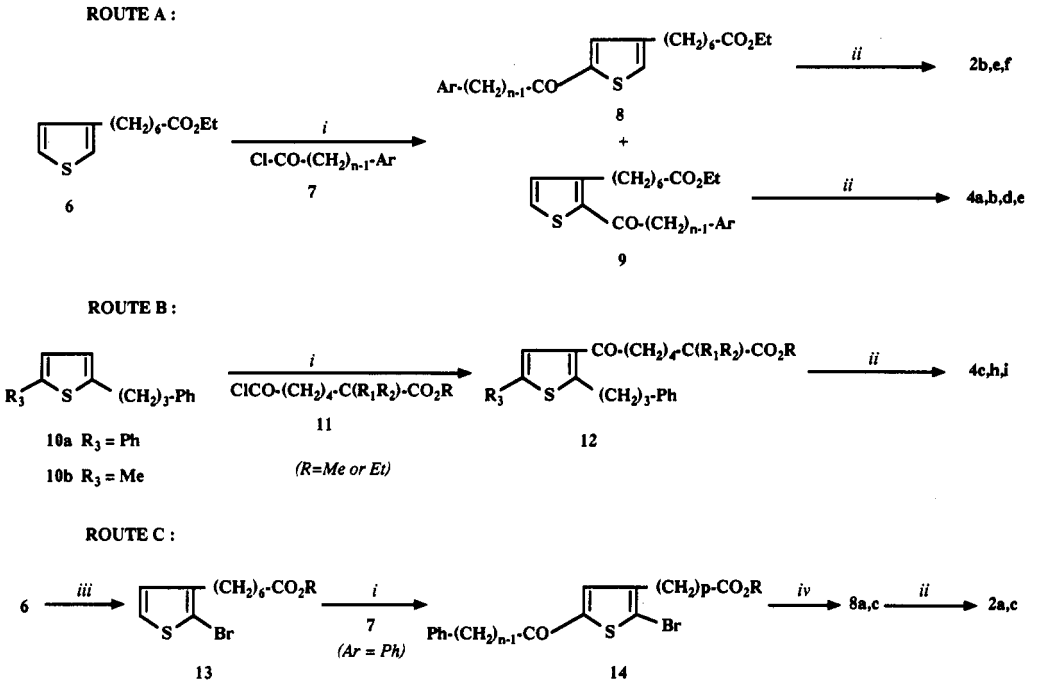
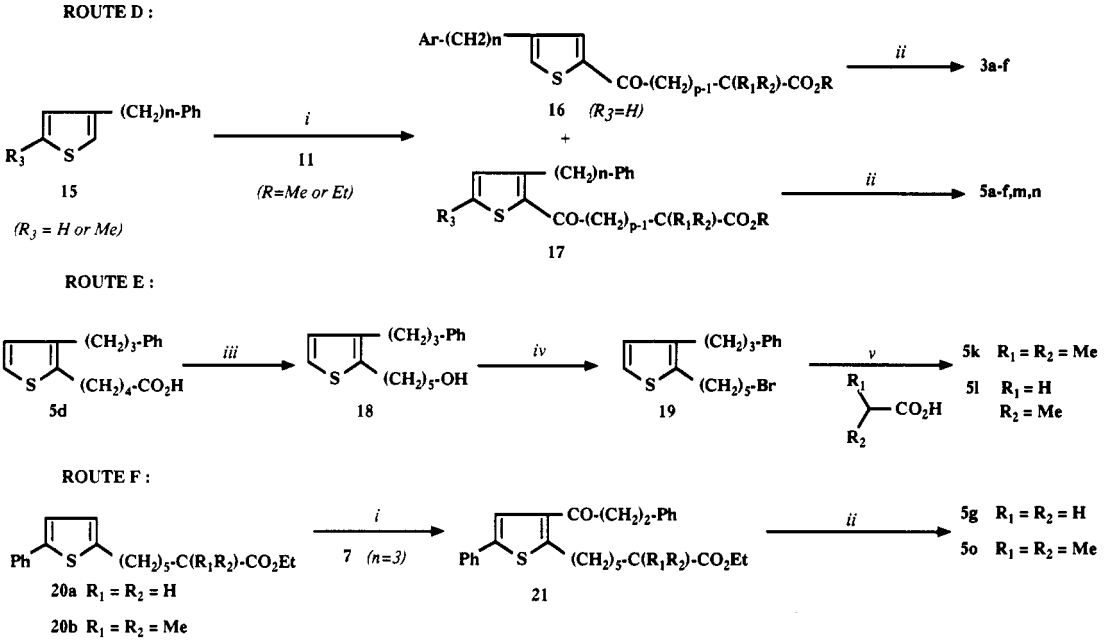
Scheme II.[a] Synthesis of Compounds 2 and 4



[a] (i) $SnCl_4$, $Cl(CH_2)_2Cl$; (ii) H_2NNH_2, KOH, diethylene glycol; (iii) NBS, MeOH; (iv) Zn(pulverized)AcOH.

Scheme III.[a] Synthesis of Compounds 3 and 5



[a] (i) $SnCl_4$, $Cl(CH_2)_2Cl$; (ii) H_2NNH_2, KOH, diethylene glycol; (iii) $LiAlH_4$, THF; (iv) CDI, $BrCH_2CH{=}CH$, MeCN; (v) LDA, THF, 0 °C.

same two-step procedure, but starting from a 2,5-disubstituted thiophene derivative **10** and using a ω-(chloroformyl)alkanoate **11** as acylating agent, afforded compounds **4**, substituted in the 5-position on the thiophene ring (route B). In the particular case of 3-(5-phenyl-2-thienyl)-1-phenylpropane (**10a**) only the acylation product **12** was obtained by the Friedel–Crafts reaction. On the contrary, starting from 3-(5-methyl-2-thienyl)-1-phenyl-

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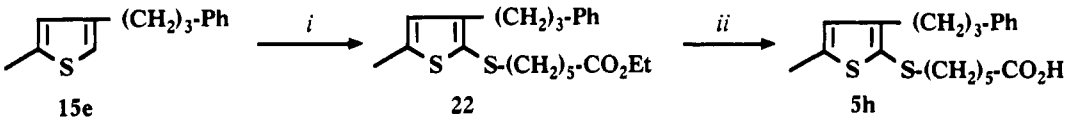
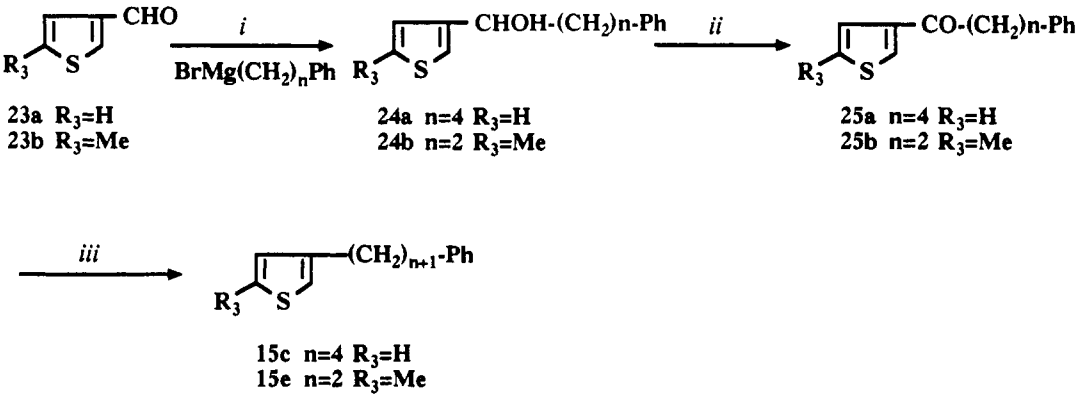
Scheme IV[a]



15e 22 5h

[a] (i) (1) *n*-BuLi, THF, (2) sulfur, (3) $Br(CH_2)_5CO_2Et$; (ii) NaOH, EtOH.

Scheme V[a]



23a R_3=H
23b R_3=Me

24a n=4 R_3=H
24b n=2 R_3=Me

25a n=4 R_3=H
25b n=2 R_3=Me

15c n=4 R_3=H
15e n=2 R_3=Me

[a] (i) THF, 1 h, reflux; (ii) PCC, NaOAc, CH_2Cl_2, 1 h, room temperature; (iii) H_2NNH_2, KOH, triethylene glycol, 200 °C.

propane (**10b**), the first acylation step afforded the two attempted products which were separated by flash chromatography. An alternative way to regiospecifically prepare compounds **2** was to apply the same two-step procedure to compound **13**, in which only the 5-position was able to be acylated, the 2-position being protected by the bromine substitution (route C). Compound **13** was obtained from **6** by bromination with *N*-bromosuccinimide in methanol.[13] Friedel–Crafts acylation of **13** with **7** exclusively afforded the 5-acylation product **14**. From **14**, direct Wolff–Kishner reduction afforded the corresponding compound **2**, but with rather low yields. The best results were obtained after a preliminary debromination step, converting **14** into **8**, by reaction with zinc in acetic acid.[14] As described in the route A, reduction of **8** under the Huang–Minlon modification of the Wolff–Kishner reaction[12] yielded the corresponding alkanoic acid **2**.

Most of compounds **3** and **5** were prepared by the routes D, E, or F, as described in Scheme III. Starting from **15**, when R_3 was a hydrogen atom, the same two-step procedure as described in the route A afforded the corresponding compounds **3** and **5** (route D). On the other hand, when R_3 was a methyl group, the first acylation step yielded only the 2,3-isomer **17**, which was directly reduced to compound **5**. Another way to synthesize the α-substituted compounds **5k** and **5l** was to start from compound **5d** (route E). After reduction of **5d** (prepared by the route D) with lithium aluminum hydride and bromination of the resulting alcohol **18** with 1,1′-carbonylimidazole and allylbromide,[15] the resulting bromo derivative **19** was alkylated with the dianion of either isobutyric acid or propionic[16] acid to yield, respectively, the α,α-dimethyl- or the α-methylheptanoic acid analog **5k** or **5l**. Compounds **5g** and **5o** were synthesized by the same pathway as the route B, described for compounds **4**, but starting from compounds **20a,b**[11] (route F). As in the case of the Friedel–Crafts acylation of compound **10a** (route B), acylation of **20** by **7** led to only one acylation product, **21**. The presence of a phenyl ring in the 5-position on the thiophene ring avoids acylation in the 4-position. The sulfur analog **22** was prepared by lithiation of **15e** with *n*-BuLi, treatment with sulfur and subsequent alkylation of the resulting thiolate with ethyl 6-bromohexanoate in 40% yield. Base hydrolysis of **22** gave the expected product **5h** (Scheme IV).

The starting compounds **15c** and **15e** were prepared in three steps from **23a** and **23b**, respectively, (Scheme V). Reaction of the appropriated Grignard reagent with the carboxaldehyde **23** yielded the corresponding alcohol **24** which were oxidized by PCC to the corresponding ketone **25**. Reduction of **25** under the Huang–Minlon modification of the Wolff–Kishner reaction[12] gave the corresponding thiophene derivatives **15**.

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

Biological Investigations

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, as described previously.[5] For the LTB_4 receptor binding assay, the activity of a compound was determined by measuring the percent inhibition of specific binding of [^{3}H]LTB_4 in the presence of the tested compound. The guinea pig spleen membranes were incubated with 1 nM [^{3}H]LTB_4 for 1 h at 4 °C (see Experimental Section).

Results and Discussion

All of the compounds (Tables I–IV) were assayed for their ability to inhibit the biosynthesis of leukotriene B_4 by specific inhibition of the LTA_4 hydrolase and their capability to inhibit the binding of [^{3}H]LTB_4 to guinea pig

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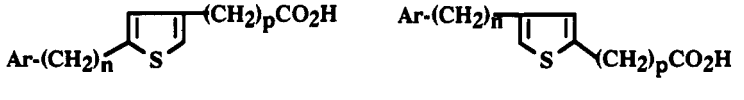
Table I. Influence of Side-Chain Lengths and Relative Position on Activity



2a-c **3a-f** **4a,b** **5a-e**

compd	*n*	*p*	mp, °C	formula	anal.[a]	route[b]	LTA$_4$ hydrol. IC$_{50}$, μM (% inhibn)[c]	LTB$_4$ bind. IC$_{50}$, μM (% inhibn)[d]
1	3	6					2.9 (84)	(18)
2a	3	6	oil	$C_{20}H_{26}O_2S$	C,H,O,S	C	1.5 (100)	10
2b	2	6	57	$C_{19}H_{24}O_2S$	C,H,O,S	A	(49)	10
2c	1	6	63–64	$C_{18}H_{22}O_2S$	C,H,O,S	C	(68)	10
3a	3	6	oil	$C_{20}H_{26}O_2S$	C,H,O,S	D	(42)	(38)
3b	1	6	39	$C_{18}H_{22}OS$	C,H,O,S	D	9.6 (70)	(33)
3c	5	6	oil	$C_{22}H_{30}O_2S$	C,H,O,S	D	(49)	(31)
3d	3	4	oil	$C_{18}H_{22}O_2S$	C,H,O,S	D	(0)	(35)
3e	3	5	oil	$C_{19}H_{24}O_2S$	C,H,O,S	D	(32)	(36)
3f	0	6	98	$C_{17}H_{20}O_2S$	H,O,C[e]	D	(25)	(0)
4a	3	6	34	$C_{20}H_{26}O_2S$	C,H,O,S	A	(0)	1
4b	2	6	oil	$C_{19}H_{24}O_2S$	C,H,O,S	A	(0)	(38)
5a	3	6	oil	$C_{20}H_{26}O_2S$	C,O,S,H[f]	D	(0)	1
5b	1	6	65	$C_{18}H_{22}O_2S$	C,H,O,S	D	(0)	(15)
5c	5	6	oil	$C_{22}H_{30}O_2S$	C,H,O,S	D	(9)	(39)
5d	3	4	oil	$C_{18}H_{22}O_2S$	C,H,O,S	D	(0)	3.5
5e	3	5	oil	$C_{19}H_{24}O_2S$	C,H,O,S	D	(0)	4.5

[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] Percentage of [^{3}H]LTB$_4$ binding inhibition at 10^{-5} M. [e] C: calcd 70.80, found 70.0. [f] H: calcd 7.93, found 7.4.

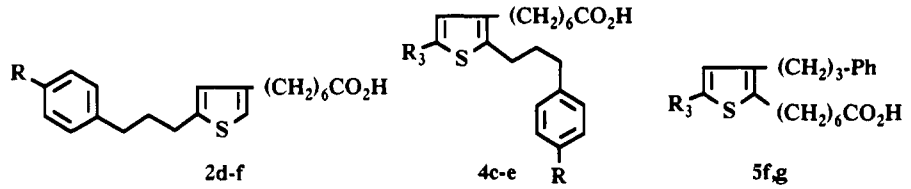
spleen LTB$_4$ receptors. Compound **1** was found to be a potent and specific LTA$_4$ hydrolase inhibitor (IC$_{50}$ = 2.8 μM)[5] but was without binding significant affinity for LTB$_4$ receptors (18% at 10 μmol). Nevertheless, during our SAR studies, we found that the relative position of the two side-chains on the thiophene ring was critical for both the LTB$_4$ biosynthesis inhibition and the LTB$_4$ receptor recognition. Compounds **4a** and **5a**, isomeric analogs of **1** with the two side chains in an ortho position with respect to one another displayed good LTB$_4$ receptor binding affinities (IC$_{50}$ = 1 μM) but were totally inactive in the LTA$_4$ hydrolase inhibition assay (Table I). Compound **2a**, an analog of **1** with the two side chains in a meta position with respect to one another, displayed both activities with IC$_{50}$ values of 1.5 and 10 μM, respectively, in the LTB$_4$ biosynthesis inhibition and the [^{3}H]LTB$_4$ binding inhibition assays. On the other hand, compound **3a**, the other meta-isomer analog of **1**, was notably less active in both assays (Table I).

Starting from these initial results, we have examined each portion of compounds **2**, **3**, **4**, and **5** to define the structural parameters essential for the both activities. All the "ortho-isomers" **4** and **5** were found to be inactive in the LTA$_4$ hydrolase inhibition assay, some of them displaying good affinities for the LTB$_4$ binding sites (**4a,b** and **5a–g**, Table I). A general requirement for optimal activity in both screens was the presence of a heptanoic acid side chain, consistent with the results obtained for the 2,5-isomers, analogs of **1**.[5] On the other hand, the optimal length of the chain linking the two aromatic rings was conditioned by the nature of the isomer. For the "meta-isomers" **2** and **3**, the optimum side-chain length between the two aromatic rings was conditioned by the position of the chain on the thiophene ring. For compounds **2**, an optimum chain of three atoms was determined for the LTA$_4$ hydrolase inhibition (**2a** > **2c** > **2b**, Table I). For compounds **3**, the best LTA$_4$ hydrolase inhibitory activity was obtained with the one-membered chain (**3b** > **3a,d** > **3f**, Table I). On the other hand, the influence of the chain lengths on the LTB$_4$ binding potency was negligible (Table I). Nevertheless, in the "meta series", the best activities in both assays were obtained with the 3,5-isomers **2**, possessing the ω-arylalkyl side chain in the 2-position on the thiophene ring (Table I).

For the "ortho-isomers" **4** and **5**, the best LTB$_4$ binding activities were also obtained with derivatives **4a** and **5a** having a three-membered chain between the two aromatic rings (Table I). Shorter or longer ω-arylalkyl side chains gave rise to substantially less active compounds (**4b**, **5b,c** ≪ **4a**, **5a**, Table I). Substitutions have been studied on the terminal aromatic ring (Table II). For the 3,5-isomers **2**, only the *p*-hydroxy derivative **2f** has retained a LTA$_4$ hydrolase inhibition activity comparable to the unsubstituted analog **2a** (Table II). The corresponding *p*-chloro- and *p*-methoxy analogs were somewhat less potent (**2d** and **2e**, Table II). On the contrary, the LTB$_4$ binding activity of compounds **2** was substantially increased by some para-substitutions on the terminal phenyl ring (Table II). The *p*-chloro analog of **2a**, **2d** was found 10-fold more active than the unsubstituted compound **2a**, the *p*-hydroxy derivative being slightly more potent. For the "ortho-isomers" **4**, the *p*-chloro derivative **4d** has retained the LTB$_4$ binding activity of the unsubstituted analog **4a**, the *p*-methoxy derivative being 3-fold less active (**4d** ≅ **4a** > **4e**, Table II).

Further structural variations on the "ortho-isomers" **4** and **5** have been studied to determine other structural requirements necessary for the LTB$_4$ binding activity (Tables II–IV). The presence of a methyl or a phenyl group in the 5-position on the thiophene ring gave rise to compounds equipotent to the unsubstituted analogs **4a** and **5a** (**4c**, **5f,g** ≅ **4a**, **5a**, Table II), suggesting some steric tolerance in this position. Some variations on the side-chain junctions have been studied on compounds **4** and **5** (Table III). All the attempts to change the nature of the side-chain junctions on the thiophene ring have led to less active or inactive compounds. The insertion within the ω-phenylalkyl side chain of a carbonyl function led to a practically inactive compound (**4f**, Table III). The same effect was observed on the carboxylic acid side chain, the insertion of a carbonyl function at the beginning of the side chain leading to substantially less active compounds (**4g** and **5i**, Table III). The corresponding alcohol **5j** displayed a slightly better activity than the keto derivative but was

Table II. Influence of Substitutions on the Terminal Aromatic Ring and on the Thiophene Ring



compd	R	R_3	mp, °C	formula	anal.[a]	route[b]	LTA_4 hydrol. % inhibn at 20 μM[c]	LTB_4 bind. IC_{50}, μM[d]
2d	Cl	H	54	$C_{20}H_{25}ClO_2S$	C,H,Cl,O,S	A	73	1
2e	OMe	H	52	$C_{21}H_{28}O_3S$	C,H,O,S	A	68	
2f	OH	H	75	$C_{20}H_{26}O_3S$	C,H,O,S	A[e]	100	5
4c	H	Me	oil	$C_{21}H_{28}O_2S$	C,H,O,S	B	0	0.7
4d	Cl	H	37	$C_{20}H_{25}ClO_2S$	C,H,Cl,O,S	A	24	1
4e	OMe	H	38	$C_{21}H_{28}O_3S$	H,O,S,C[f]	A	0	3
5f	H	Me	oil	$C_{21}H_{28}O_2S$	H,O,S,C[g]	D	0	1.5
5g	H	Ph	oil	$C_{26}H_{30}O_2S$	C,H,O,S	F	0	1.0

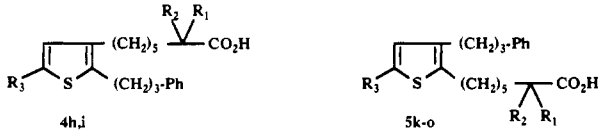
[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] Percentage of LTB_4 biosynthesis inhibition at 2×10^{-5} M. [d] [^{3}H]LTB_4 binding inhibition. [e] Obtained with **2f** by Wolff–Kishner reduction of **8f**. [f] C: calcd 69.96, found 70.6. [g] C: calcd 73.21, found 73.9.

Table III. Variation of LTB_4 Binding Activity with the Side-Chain Junctions

compd	X	Y	R_3	mp, °C	formula	anal.[a]	route[b]	LTB_4 bind.: IC_{50}, μM[c] (% inhibn)[d]
4f	CO	CH_2	H	61–62	$C_{20}H_{24}O_3S$	C,H,O,S	*e*	(17)
4g	CH_2	CO	Me	72	$C_{21}H_{26}O_3S$	C,H,O,S	*f*	(51)
5h	–	S	Me	oil	$C_{20}H_{26}O_2S_2$	H,S,C[g]	*h*	3.0
5i	–	CO	H	56	$C_{20}H_{24}O_3S$	C,H,O,S	*i*	(59)
5j	–	CHOH	H	94–95	$C_{20}H_{26}O_3S$	C,H,S	*j*	6.0

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] [^{3}H]LTB_4 binding inhibition. [d] Percentage of [^{3}H]LTB_4 binding inhibition at 10^{-5} M. [e] Obtained by saponification of **9a**. [f] Obtained by saponification of **12c**. [g] C: calcd 66.26, found 67.0. [h] See Scheme V. [i] Obtained by saponification of **17a**. [j] See Experimental Section.

Table IV. Effect of the α-Substitution on the LTB_4 Binding Activity



compd	R_1	R_2	R_3	mp, °C	formula	anal.[a]	route[b]	LTB_4 bind.: IC_{50}, μM[c]
4h	H	Me	Me	oil	$C_{22}H_{30}O_2S$	C,H,O,S	B	0.3
4i	Me	Me	Ph	58–59	$C_{28}H_{34}O_2S$	H,O,S,C[e]	B	1.2
5k	Me	Me	H	oil	$C_{22}H_{30}O_2S$	C,H,O,S	E	0.06
5l	H	Me	H	oil	$C_{21}H_{28}O_2S$	C,H,O,S	E	0.11
5m	H	Me	Me	oil	$C_{22}H_{30}O_2S$	C,H,O,S	D	0.3
5n	Me	Me	Me	oil	$C_{23}H_{32}O_2S$	C,H,O,S	D	0.2
5o	Me	Me	Ph	54	$C_{28}H_{34}O_2S$	C,H,O,S	F	0.8
LY223982								0.002

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] [^{3}H]LTB_4 binding inhibition. [d] C: calcd 73.21, found 73.9. [e] C: calcd 77.38, found 76.7.

found 6-fold less potent than compound **5a**. The insertion of a sulfur atom at the beginning of the carboxylic acid side chain gave rise to 3-fold less potent compounds (**5h**, Table III). In order to stabilize the carboxylic acid side chain towards β-oxidation, α-alkylheptanoic acid derivatives have been designed (**4h,i**, **5k–o**, Table IV). The introduction of one or two methyl groups in the α-position on the carboxylic acid side chain in compounds **4** and **5** greatly increased the LTB_4 binding activity. The α,α-dimethyl- and α-methyl analogs of **5a** (respectively, **5k** and **5l**, Table IV) were found 20-fold and 10-fold more potent than the linear parent compound. The α,α-dimethyl derivative **5k** has displayed the best LTB_4 binding activity in this series with an IC_{50} of 60 nM. The same dramatic effect has also been observed in the 2,5-thiophene series,[5] the α,α-dimethyl analog of **1** displaying a substantially more potent LTB_4 binding activity with an IC_{50} of 3.5 μM (data not shown). However the latter compound is an exception as more than 30 molecules of the 2,5-thiophene series were screened in the LTB_4 receptor assay and were found either inactive or of marginal activity (data not shown). This dramatic effect could indicate the presence of a lipophilic

pocket, near the carboxylic acid binding site on LTB_4 receptors, acting as a positive binding interaction and able to position the carboxylic acid in the optimal position on the LTB_4 receptor. This α-substitution effect was also observed in the 5-substituted analogs of **4** and **5** but with a smaller amplitude (**4h,i** and **5m–o**, Table IV). α-Substituted compounds **5m** and **5n**, with a methyl group in the 5-position on the thiophene ring, were found only around 5-fold more active than their linear counterpart **5f**, the α-substituted-5-phenyl derivative **5o** being equipotent to its linear analog **5g** (Tables II and IV). The same results were obtained with compounds **4**, the α-substituted 5-substituted derivatives **4h** and **4i** displaying a slightly better or the same activity than the linear derivative **4c** (Tables II and IV).

In conclusion, these results have demonstrated the possibility in the 7-[(ω-arylalkyl)thienyl]heptanoic acid series, starting from specific LTA_4 hydrolase inhibitors, to design potent LTB_4 receptor antagonists simply by modifying the relative position of the two side chains on the thiophene ring. The 3,5- or 2,4-derivatives (**2** and **3**, respectively) have displayed both activities, the 3,5-isomers **2** being substantially more potent with IC_{50} in the micromolar range in the two assays. The "ortho-isomers" have exhibited specific LTB_4 receptor binding activities (compounds **4** and **5**). The SAR studies in the "ortho series" have demonstrated the dramatic effect of the α-substitution on the heptanoic acid side chain for the LTB_4 binding activity. In the most favorable case, the α,α-dimethyl derivative was 20-fold more potent than the linear one, the more potent compound, **5k** (RP66153), displaying an IC_{50} of 60 nM on the guinea pig spleen LTB_4 receptors.

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.

General Procedures for the Preparation of Compounds 2 and 4. Route A: 7-[5-(2-Phenylethyl)-3-thienyl]heptanoic Acid (2b) and 7-[2-(2-Phenylethyl)-3-thienyl]heptanoic Acid (4b). Friedel–Crafts Acylation. Tin(IV) chloride (10.2 g, 39.2 mmol) in 1,2-dichloroethane (40 mL) was added dropwise to a cold (5 °C) solution of ethyl 7-(3-thienyl)heptanoate[17] (8 g, 33 mmol) in 1,2-dichloroethane (40 mL). During the addition, the reaction temperature was kept below 5 °C. A solution of 3-phenylacetyl chloride (5.1 g 33 mmol) in 1,2-dichloroethane (40 mL) was added dropwise to the cold resulting mixture. During the slow addition (over 2 h), the reaction temperature was kept below 5 °C. The reaction mixture was then stirred at 10 °C for 30 min and then poured into cold H_2O (1000 mL). The layers were then separated, and the aqueous layer was extracted twice 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, containing a mixture of the ethyl ester **8b** (the more polar component) with the ethyl ester **9b** (the less polar component), was purified by chromatography on silica gel (eluent: diethyl ether/pentane 1/9).

Wolff–Kishner Reduction. The ethyl ester **8b** (2.9 g, 8.1 mmol) was then directly mixed with hydrazine monohydrate (0.83 g, 16.6 mmol) and KOH (1.8 g, 32 mmol) in triethylene glycol (20 mL). The reaction was heated to 210 °C for 4 h. The excess of hydrazine and water was then distilled off for 2 h under normal pressure. After cooling to 25 °C, H_2O (40 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 resulting residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate 6/4) giving pure **2b** as a white solid (2.2 g, 20.4%, over two steps): mp 57 °C; NMR ($CDCl_3$) δ 7.36–7.09 (m, 5 H), 6.67 (br s, 1 H), 6.59 (br s, 1 H), 3.16–2.87 (m, 4 H), 2.53 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.87–1.19 (m, 8 H); IR (KBr, cm^{-1}) 1709; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S.

The same procedure, but starting from **9b** (4.3 g, 12 mmol), hydrazine monohydrate (2.2 mL, 45.3 mmol), and KOH (3.4 g, 60.6 mmol) in triethylene glycol (60 mL), and after purification by chromatography on silica gel (eluent: dichloromethane/methanol 9/1), gave pure **4b** as a colorless oil (2.6 g, 24.5%, over two steps): NMR ($CDCl_3$) δ 7.46–7.12 (m, 5 H), 7.06 (d, J = 5 Hz, 1 H), 6.80 (d, J = 5 Hz, 1 H), 3.17–2.85 (m, 4 H), 2.44 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.76–1.18 (m, 8 H); IR (film, cm^{-1}) 1708; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S.

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

7-[2-(3-Phenylpropyl)-3-thienyl]hexanoic Acid (4a) was prepared from ethyl 7-(3-thienyl)heptanoate[14] and 3-phenylpropionyl chloride (24.4%, over two steps): mp 34 °C; NMR ($CDCl_3$) δ 7.35–7.12 (m, 5 H), 7.02 (d, J = 5 Hz, 1 H), 6.80 (d, J = 5 Hz, 1 H), 2.82–2.60 (m, 4 H), 2.475 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.975 (qui, J = 7.5 Hz, 2 H), 1.75–1.20 (m, 8 H); IR (KBr, cm^{-1}) 1708; MS m/z 330 (M^+). Anal. ($C_{20}H_{26}O_2S$) C, H, O, S.

7-[5-[3-(4-Chlorophenyl)propyl]-3-thienyl]hexanoic acid (2d) and 7-[2-[3-(4-chlorophenyl)propyl]-3-thienyl]hexanoic acid (4d) were prepared from ethyl 7-(3-thienyl)heptanoate[17] and 3-(4-chlorophenyl)propionyl chloride **2d** (17.6%, over two steps): mp 54 °C; NMR ($CDCl_3$) δ 7.225 (d, J = 8.75 Hz, 2 H), 7.09 (d, J = 8.75 Hz, 2 H), 6.675 (br s, 1 H), 6.59 (br s, 1 H), 2.78 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.96 (qui, J = 7.5 Hz, 2 H), 1.76–1.49 (m, 4 H), 1.46–1.24 (m, 4 H); IR (KBr, cm^{-1}) 1696; MS m/z 364 (M^+). Anal. ($C_{20}H_{25}ClO_2S$) C, H, Cl, O, S. **4d**: (31.2%, over two steps); mp 37 °C; NMR ($CDCl_3$) δ 7.175 (br d, J = 7.5 Hz, 2 H), 7.075 (br d, J = 7.5 Hz, 2 H), 6.94 (d, J = 5 Hz, 1 H), 6.725 (d, J = 5 Hz, 1 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.26 (t, J = 7.5 Hz, 2 H), 1.825 (qui, J = 7.5 Hz, 2 H), 1.65–1.12 (m, 8 H); IR (KBr, cm^{-1}) 1708; MS m/z 364 (M^+). Anal. ($C_{20}H_{25}ClO_2S$) C, H, Cl, O, S.

7-[5-[3-(4-Methoxyphenyl)propyl]-3-thienyl]hexanoic acid (2e), 7-[5-[3-(4-hydroxyphenyl)propyl]-3-thienyl]hexanoic acid (2f), and 7-[2-[3-(4-methoxyphenyl)propyl]-3-thienyl]-hexanoic acid (4e) were prepared from ethyl 7-(3-thienyl)heptanoate[17] and 3-(4-methoxyphenyl)propionyl chloride **2e** (1.2%, over two steps): mp 52 °C; NMR ($CDCl_3$) δ 7.09 (d, J = 8.75 Hz, 2 H), 6.82 (d, J = 8.75 Hz, 2 H), 6.675 (br s, 1 H), 6.59 (br s, 1 H), 3.79 (s, 3 H), 2.79 (t, J = 7.5 Hz, 2 H), 2.625 (t, J = 7.5 Hz, 2 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.96 (qui, J = 7.5 Hz, 2 H), 1.75–1.49 (m, 4 H), 1.46–1.24 (m, 4 H); IR (KBr cm^{-1}) 1703; MS m/s 360 (M^+). Anal. ($C_{21}H_{28}O_3S$) C, H, O, S. **2f**: (12%, over two steps); mp 73 °C; NMR ($CDCl_3$) δ 7.03 (br d, J = 8.75 Hz, 2 H), 6.74 (br d, J = 8.75 Hz, 2 H), 6.66 (br s, 1 H), 6.59 (br s, 1 H), 2.775 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.54 (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), 1.76–1.49 (m, 4 H), 1.45–1.22 (m, 4 H); IR (KBr, cm^{-1}) 1699, 1516; MS m/z 346 (M^+). Anal. ($C_{20}H_{26}O_3S$) C, H, O, S. **4e**: (14.5%, over two steps); mp 38 °C; NMR ($CDCl_3$) δ 7.40 (d, J = 8.75 Hz, 2 H), 7.05 (d, J = 5 Hz, 1 H), 6.85 (d, J = 8.75 Hz, 2 H), 6.825 (d, J = 5 Hz, 1 H), 3.81 (s, 3 H), 2.75 (t, J = 7.5 Hz, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.475 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.925 (qui, J = 7.5 Hz, 2 H),

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1.75–1.25 (m, 8 H); IR (KBr, cm^{-1}) 1707; MS m/z 360 (M^+). Anal. ($C_{21}H_{28}O_3S$) H, O, S; C: calcd 69.96, found 70.6.

Route B: 7-[5-Methyl-2-(3-phenylpropyl)-3-thienyl]heptanoic Acid (4c). Tin(IV) chloride (20.6 g, 79 mmol) was added dropwise to a cold mixture of 5-methyl-2-(3-phenylpropyl)-thiophene (**10b**) (14.3 g, 66.2 mmol) (prepared by the route A but starting from 2-methylthiophene and 3-phenylpropionyl chloride, $bp_{0.04mmHg}$ = 102–105 °C (54% over two steps)), ethyl 6-(chloroformyl)hexanoate[18] (13.6 g, 66 mmol), and 1,2-dichloroethane (100 mL). During the addition (over 1 h), the reaction temperature was kept below 10 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then poured into cold H_2O (300 mL). The layers were then separated, and the aqueous layer was extracted twice with CH_2Cl_2. 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 chromatographed on a silica gel column (eluent: dichloromethane) to yield the corresponding ethyl ester **12c** as a pale yellow oil (4.7 g, 18%). The title compound was directly obtained from **12c** by using the Wolff–Kischner procedure described above in the route A, as a pale yellow oil (2.6 g, 63%); NMR ($CDCl_3$) δ 7.35–7.11 (m, 5 H), 6.44 (s, 1 H), 2.675 (t, J = 7.5 Hz, 4 H), 2.47–2.27 (m, 4 H), 2.39 (br s, 3 H), 1.92 (qui, J = 7.5 Hz, 2 H), 1.72–1.22 (m, 8 H); IR (film, cm^{-1}) 1708; MS m/z 344 (M^+). Anal. ($C_{21}H_{28}O_2S$) C, H, O, S.

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

2-Methyl-7-[5-methyl-2-(3-phenylpropyl)-3-thienyl]heptanoic acid (4h) was prepared from **10b** and ethyl 6-(chloroformyl)-2-methylhexanoate[19] (8.7%, over two steps): oil; NMR ($CDCl_3$) δ 7.34–6.99 (m, 5 H), 6.38 (br s, 1 H), 2.75–2.50 (m, 4 H), 2.47–2.22 (m, 3 H), 2.31 (br s, 3 H), 1.80 (qui, J = 7.5 Hz, 2 H), 1.67–1.10 (m, 8 H), 1.09 (d, J = 6.25 Hz, 3 H); IR (film, cm^{-1}) 1705; MS m/z 358 (M^+). Anal. ($C_{22}H_{30}O_2S$) C, H, O, S.

2,2-Dimethyl-7-[5-phenyl-2-(3-phenylpropyl)-3-thienyl]heptanoic acid (4i) was prepared from **10a** (prepared by the route A but starting from 2-phenylthiophene[20] and 3-phenylpropionyl chloride (42% over two steps)) and ethyl 6-(chloroformyl)-2,2-dimethylhexanoate **11c** (21.4%, over two steps): mp 58–59 °C; NMR ($CDCl_3$) δ 7.55 (d, J = 6.25 Hz, 2 H), 7.42–7.14 (m, 8 H), 7.04 (s, 1 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.72 (t, J = 7.5 Hz, 2 H), 2.45 (t, J = 7.5 Hz, 2 H), 1.99 (qui, J = 7.5 Hz, 2 H), 1.66–1.44 (m, 4 H), 1.39–1.19 (m, 4 H), 1.19 (br s, 6 H); IR (KBr, cm^{-1}) 1700; MS m/z 434 (M^+). Anal. ($C_{28}H_{34}O_2S$) H, O, S; C: calcd 77.38, found 76.7.

Route C: Ethyl 7-(2-Bromo-3-thienyl)heptanoate (13). A suspension of *N*-bromosuccinimide (6.3 g, 35.6 mmol) in an ethyl acetate/chloroform 1/1 mixture (25 mL) was added in one portion to a solution of ethyl 7-(3-thienyl)heptanoate[17] (8.1 g, 33.7 mmol) in an ethyl acetate/chloroform 1/1 mixture (40 mL). The resulting white suspension was stirred for 2 min. H_2O (40 mL) was added and the layers were separated. The organic layer was washed with a saturated $NaHCO_3$ solution and with H_2O, dried over Na_2SO_4, and then evaporated to yield **13** as a pale yellow oil (10 g, 92.8%): NMR ($CDCl_3$) δ 7.20 (d, J = 5 Hz, 1 H), 6.80 (d, J = 5 Hz, 1 H), 4.14 (q, J = 7.5 Hz, 2 H), 2.575 (t, J = 7.5 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 1.86–1.23 (m, 8 H), 1.26 (t, J = 7.5 Hz, 3 H); MS m/z 273 (M – OEt^+), 275 (M + 2 – OEt^+).

Ethyl 7-[2-bromo-5-(3-phenylpropionyl)-3-thienyl]heptanoate (14a) was prepared by using the Friedel–Crafts procedure described in the route B, but starting from **13** (19.2 g, 60 mmol), 3-phenylpropionyl chloride (12.2 g, 66.8 mmol), and tin(IV) chloride (27.7 g, 106 mmol). After purification by flash chromatography on silica gel (eluent: hexane/ethyl acetate 95/5), **14a** was obtained as a pale yellow oil (16.6 g, 61%): NMR ($CDCl_3$) δ 7.42–7.14 (m, 6 H), 4.12 (q, J = 7.5 Hz, 2 H), 3.24–2.97 (m, 4 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.29 (t, J = 7.5 Hz, 2 H), 1.84–1.17 (m, 8 H), 1.25 (t, J = 7.5 Hz, 3 H); MS m/z 450 (M^+), 452 (M + 2)$^+$.

By the same procedure, but starting from benzoyl chloride, **ethyl 7-(2-bromo-5-benzoyl-3-thienyl)heptanoate (14b)** was obtained as a pale yellow oil (41%): MS m/z 422 (M^+), 424 (M+2)$^+$.

Ethyl 7-[5-(3-Phenylpropionyl)-3-thienyl]heptanoate (8a). Zinc powder (24.3 g, 372 mmol) was added portionwise to a mixture of **14a** (30.2 g, 67 mmol) and acetic acid (9.1 mL) in H_2O (28 mL). The reaction mixture was stirred at room temperature for 24 h. Diethyl ether (450 mL) was then added, and the resulting mixture was stirred for 1 h. After filtration, the organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel (eluent: hexane/acetone 10/5), yielding **8a** as a pale yellow oil (10.3 g, 50%); MS m/z 358 (M^+). By the same procedure, but starting from **14b**, **ethyl 7-(5-benzoyl-3-thienyl)heptanoate (8c)** was obtained as a pale yellow oil (66%), MS m/z 330 (M^+).

7-[5-(3-Phenylpropyl)-3-thienyl]heptanoic acid (2a) was prepared by using the Wolff–Kishner procedure described in the route A, but starting from **8a** (10.3 g, 27.7 mmol), hydrazine monohydrate (2.9 g, 58 mmol), and KOH (1.8 g, 110 mmol) in triethylene glycol (70 mL), yielding pure **2a** as a pale yellow oil (8.4 g, 92%): NMR ($CDCl_3$) δ 7.42–7.11 (m, 5 H), 6.70 (br s, 1 H), 6.63 (br s, 1 H), 2.81 (t, J = 7.5 Hz, 2 H), 2.69 (t, J = 7.5 Hz, 2 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 2.00 (qui, J = 7.5 Hz, 2 H), 1.78–1.48 (m, 4 H), 1.47–1.20 (m, 4 H); IR (film, cm^{-1}) 1708; MS m/z 330 (M^+). Anal. ($C_{20}H_{26}O_2S$) C, H, O, S.

By the same procedure, but starting from **8c**, **7-(5-benzyl-3-thienyl)heptanoic acid (2c)** was obtained as a white solid (43%): mp 63–64 °C; NMR ($CDCl_3$) δ 7.42–7.13 (m, 5 H), 6.725 (br s, 1 H), 6.625 (br s, 1 H), 4.1 (s, 2 H), 2.525 (t, J = 7.5 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.75–1.47 (m, 4 H), 1.45–1.22 (m, 4 H); IR (KBr, cm^{-1}) 1700; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S.

General Procedures for the Preparation of Compounds 3 and 5. Route D: 5-[4-(3-Phenylpropyl)-2-thienyl]pentanoic Acid (3d) and 5-[3-(3-Phenylpropyl)-2-thienyl]pentanoic Acid (5d). Friedel–Crafts Acylation. By using the Friedel–Crafts procedure described in the route B, but starting from 3-(3-phenylpropyl)thiophene (**15a**) (prepared by the Wolff–Kishner reduction of 1-phenyl-3-(3-thienyl)-1-propanone,[21] $bp_{0.01mmHg}$ = 80–85 °C (76%)) and methyl 4-(chloroformyl)butanoate, the methyl ester **16d** (the more polar component) and the methyl ester **17d** (the less polar component) were isolated.

Wolff–Kishner Reduction. By using the Wolff–Kishner procedure described in the route A, the methyl ester **16d** was directly converted to **3d**, obtained as a pale yellow oil (20%, over two steps): NMR ($CDCl_3$) δ 7.31–7.09 (m, 5 H), 6.67 (br s, 1 H), 6.60 (br s, 1 H), 2.79 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.575 (t, J = 7.5 Hz, 2 H), 2.375 (t, J = 7.5 Hz, 2 H), 1.93 (qui, J = 7.5 Hz, 2 H), 1.76–1.57 (m, 4 H); IR (film, cm^{-1}) 1708; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S.

The same procedure, but starting from **17d** gave pure **5d** as a yellow oil (28.3%, over two steps): NMR ($CDCl_3$) δ 7.31–7.07 (m, 5 H), 7.00 (d, J = 5 Hz, 1 H), 6.79 (d, J = 5 Hz, 1 H), 2.76 (m, 6 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.89 (qui, J = 7.5 Hz, 2 H), 1.76–1.52 (m, 4 H); IR (film, cm^{-1}) 1707; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S.

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

7-[4-(3-Phenylpropyl)-2-thienyl]heptanoic acid (3a) and 7-[3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5a) were prepared from **15a** and ethyl 6-(chloroformyl)hexanoate.[18] **3a** (10.4%, over two steps): NMR ($CDCl_3$) δ 7.34–7.12 (m,, 5 H), 6.69 (br, s, 1 H), 6.61 (br s, 1 H), 2.75 (t, J = 7.5 Hz, 2 H), 2.65 (t, J

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= 7.5 Hz, 2 H), 2.59 (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), 1.75–1.52 (m, 4 H), 1.47–1.25 (m, 4 H); IR (film, cm^{-1}) 1708; MS m/z 330 (M^+). Anal. ($C_{20}H_{26}O_2S$) C, H, O, S. **5a** (27%, over two steps): NMR ($CDCl_3$) δ 7.34–7.09 (m, 5 H), 7.025 (d, J = 5 Hz, 1 H), 6.81 (d, J = 5 Hz, 1 H), 2.72–2.47 (m, 4 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.89 (qui, J = 7.5 Hz, 2 H), 1.77–1.15 (m, 10 H); IR (film, cm^{-1}) 1707.5; MS m/z 330 (M^+). Anal. ($C_{20}H_{26}O_2S$) C, O, S; H: calcd 7.93, found 7.4.

7-(4-Benzyl-2-thienyl)heptanoic acid (3b) and 7-(3-benzyl-2-thienyl)heptanoic acid (5b) were prepared from 3-benzylthiophene (**15b**)[22] and ethyl 6-(chloroformyl)hexanoate.[18] **3b** (33.8%, over two steps): mp 39 °C; NMR ($CDCl_3$) δ 7.36–7.11 (m, 5 H), 6.66 (br s, 1 H), 6.56 (br s, 1 H), 3.89 (s, 2 H), 2.725 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.45–1.22 (m, 4 H); IR (KBr, cm^{-1}) 1708; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S. **5b** (40%, over two steps): mp 65 °C; NMR ($CDCl_3$) δ 7.32–7.06 (m, 5 H), 7.02 (d, J = 5 Hz, 1 H), 6.725 (d, J = 5 Hz, 1 H), 3.89 (s, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 4 H), 1.45–1.22 (m, 4 H); IR (KBr, cm^{-1}) 1705; MS m/z 302 (M^+). Anal. ($C_{18}H_{22}O_2S$) C, H, O, S.

7-[4-(5-Phenylpentyl)-2-thienyl]heptanoic acid (3c) and 7-[3-(5-phenylpentyl)-2-thienyl]heptanoic acid (5c) were prepared from 3-(5-phenylpentyl)thiophene **15c** and ethyl 6-(chloroformyl)hexanoate.[18] **3c** (21.4%, over two steps): NMR ($CDCl_3$) δ 7.31–7.09 (m, 5 H), 6.66 (br s, 1 H), 6.58 (br s, 1 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.53 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.75–1.25 (m, 14 H); IR (film, cm^{-1}) 1708; MS m/z 358 (M^+). Anal. ($C_{22}H_{30}O_2S$) C, H, O, S. **5c** (28.7%, over two steps): NMR ($CDCl_3$) δ 7.30–7.10 (m, 5 H), 6.99 (d, J = 5 Hz, 1 H), 6.77 (d, J = 5 Hz, 1 H), 2.70 (t, J = 7.5 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 2.49 (t, J = 7.5 Hz, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.75–1.50 (m, 8 H), 1.45–1.24 (m, 6 H); IR (film, cm^{-1}) 1708; MS m/z 358 (M^+). Anal. ($C_{22}H_{30}O_2S$) C, H, O, S.

6-[4-(3-Phenylpropyl)-2-thienyl]hexanoic acid (3e) and 6-[3-(3-phenylpropyl)-2-thienyl]hexanoic acid (5e) were prepared from **15a** and methyl 5-(chloroformyl)pentanoate.[23] **3e** (12.1%, over two steps): NMR ($CDCl_3$) δ 7.34–7.07 (m, 5 H), 6.675 (br s, 1 H), 6.59 (br s, 1 H), 2.78 (t, J = 7.5 Hz, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.59 (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), 1.78–1.56 (m, 4 H), 1.49–1.31 (m, 2 H); IR (film, cm^{-1}) 1708; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S. **5e** (11.2%, over two steps): NMR ($CDCl_3$) δ 7.31–7.10 (m, 5 H), 7.01 (d, J = 5 Hz, 1 H), 6.80 (d, J = 5 Hz, 1 H), 2.68 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.89 (qui, J = 7.5 Hz, 2 H), 1.75–1.51 (m, 4 H), 1.47–1.29 (m, 2 H); IR (film, cm^{-1}) 1708; MS m/z 316 (M^+). Anal. ($C_{19}H_{24}O_2S$) C, H, O, S.

7-(4-Phenyl-2-thienyl)heptanoic acid (3f) was prepared from 3-phenylthiophene **15d**[20] and ethyl 6-(chloroformyl)hexanoate[18] (23.1%, over two steps): mp 98 °C; NMR ($CDCl_3$) δ 7.56–7.43 (m, 2 H), 7.37–7.14 (m, 4 H), 7.03 (br s, 1 H), 2.77 (t, J = 7.5 Hz, 2 H), 2.28 (t, J = 7.5 Hz, 2 H), 1.74–1.50 (m, 4 H), 1.44–1.21 (m, 4 H); IR (film, cm^{-1}) 1697; MS m/z 288 (M^+). Anal. ($C_{17}H_{20}O_2S$) H, O; C: calcd 70.80, found 70.0.

7-[5-Methyl-3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5f) was prepared from 2-methyl-4-(3-phenylpropyl)thiophene **15e** and ethyl 6-(chloroformyl)hexanoate[18] (45.4%, over two steps): NMR ($CDCl_3$) δ 7.35–7.10 (m, 5 H), 6.47 (br s, 1 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.46 (t, J = 7.5 Hz, 2 H), 2.39 (s, 3 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.86 (qui, J = 7.5 Hz, 2 H), 1.74–1.46 (m, 4 H), 1.45–1.25 (m, 4 H); IR (film, cm^{-1}) 1708; MS m/z 344 (M^+). Anal. ($C_{21}H_{28}O_2S$) H, O, S, C: calcd 73.21, found 73.9.

2-Methyl-7-[5-methyl-3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5m) was prepared from **15e** and ethyl 2-methyl-6-(chloroformyl)hexanoate[19] (39.3%, over two steps): NMR ($CDCl_3$) δ 7.36–7.12 (m, 5 H), 6.46 (br s, 1 H), 2.71–2.34 (m, 7 H), 2.40 (s, 3 H), 1.86 (qui, J = 7.5 Hz, 2 H), 1.76–1.24 (m, 8 H), 1.175 (d, J = 7.5 Hz, 3 H); IR (film, cm^{-1}) 1705; MS m/z 358 (M^+). Anal. ($C_{22}H_{30}O_2S$) C, H, O, S.

2,2-Dimethyl-7-[5-methyl-3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5n) was prepared from **15e** and methyl 2,2-dimethyl-6-(chloroformyl)hexanoate **11c** (40.1%, over two steps): NMR ($CDCl_3$) δ 7.26–7.00 (m, 5 H), 6.375 (br s, 1 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.51 (t, J = 7.5 Hz, 2 H), 2.375 (t, J = 7.5 Hz, 2 H), 2.29 (s, 3 H), 1.74 (qui, J = 7.5 Hz, 2 H), 1.59–1.05 (m, 8 H), 1.1 (br s, 6 H); IR (film, cm^{-1}) 1698.5; MS m/z 372 (M^+). Anal. ($C_{23}H_{32}O_2S$) C, H, O, S.

Route E: 5-[3-(3-Phenylpropyl)-2-thienyl]-1-pentanol (18). To a suspension of lithium aluminum hydride (0.42 g, 11 mmol) in diethyl ether (10 mL) was added dropwise (over 30 min) **5d** (4 g, 13.1 mmol), dissolved in diethyl ether (13 mL). The reaction mixture was stirred at room temperature for 2 h. After cooling to 10 °C, H_2O (2.2 mL) were carefully added. After filtration, the layers were separated and the aqueous layer was extracted twice diethyl ether. The combined organic extracts were dried over Na_2SO_4 and evaporated to yield **18** as a yellow oil (2.9 g, 76%).

1-Bromo-5-[3-(3-phenylpropyl)-2-thienyl]pentane (19). 1,1′-Carbonyldiimidazole (5.8 g, 35.7 mmol) was added in one portion to a solution of **18** (10.3 g, 35.7 mmol) in acetonitrile (50 mL). Allyl bromide (21.6 g, 178.5 mmol) was then added dropwise over 30 min. The reaction mixture was heated at reflux for 2 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 by H_2O. After drying over Na_2SO_4, the organic layer was filtered and evaporated. After purification by chromatography on silica gel (eluent: dichloromethane), **19** was obtained as a yellow oil (11.2 g, 89%).

2,2-Dimethyl-7-[3-(3-phenylpropyl)-2-thienyl]heptanoic Acid (5k). To a solution of LDA in THF (prepared from n-BuLi (14.2 mL, 1.60 M in hexane), diisopropylamine (2.3 g, 22.7 mmol), and 10 mL THF) at 0 °C were added dropwise isobutyric acid (0.91 g, 10.3 mmol) and HMPA (1.9 g, 10.6 mmol). The reaction mixture was then heated to 50 °C for 2 h. After cooling to 0 °C, **19** (4 g, 11.4 mmol) 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 on silica gel (eluent: diethyl ether/hexane 1/1), yielding pure **5k** as a pale yellow oil (1.1 g, 30%): NMR ($CDCl_3$) δ 7.37–7.15 (m, 5 H), 7.06 (d, J = 5 Hz, 1 H), 6.86 (d, J = 5 Hz, 1 H), 2.76–2.49 (m, 6 H), 1.90 (qui, J = 7.5 Hz, 2 H), 1.71–1.19 (m, 8 H), 1.19 (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.

2-Methyl-7-[3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5l) was prepared by the same procedure but starting from **19** and propionic acid, yielding pure **5l** as a pale yellow oil (30%): NMR ($CDCl_3$) δ 7.40–7.17 (m, 5 H), 7.07 (d, J = 5 Hz, 1 H), 6.89 (d, J = 5 Hz, 1 H), 2.75–2.39 (m, 7 H), 1.90 (qui, J = 7.5 Hz, 2 H), 1.79–1.25 (m, 8 H), 1.18 (d, J = 8.75 Hz, 3 H); IR (film, cm^{-1}) 1705; MS m/z 344 (M^+). Anal. ($C_{21}H_{28}O_2S$), C, H, O, S.

Route F: 7-[5-Phenyl-3-(3-phenylpropyl)-2-thienyl]heptanoic Acid (5g). Friedel–Crafts Acylation. By using the Friedel–Crafts procedure described in the route A, but starting from **20a**[11] and 3-phenylporpionyl chloride, the ethyl ester **21a** was obtained as a yellow oil (56%).

Wolff–Kishner Reduction. By using the Wolff–Kishner procedure described in the route A, the ethyl ester **21a** was directly converted to **5g**, obtained as a pale yellow oil (29%, over two steps): NMR ($CDCl_3$) δ 7.55 (br d, J = 7.5 Hz, 2 H), 7.45–7.10 (m, 8 H), 7.04 (s, 1 H), 2.69 (t, J = 7.5 Hz, 4 H), 2.56 (t, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.93 (qui, J = 7.5 Hz, 2 H), 1.77–1.52 (m, 4 H), 1.50–1.22 (m, 4 H); IR (film, cm^{-1}) 1707; MS m/z 406 (M^+). Anal. ($C_{26}H_{30}O_2S$) C, H, O, S.

2,2-Dimethyl-7-[5-phenyl-3-(3-phenylpropyl)-2-thienyl]heptanoic acid (5o) was prepared by the same procedure but starting from **20b**[11], yielding pure **5o** as a pale yellow solid (28.6% over two steps): mp 54 °C; NMR ($CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 2 H), 7.42–7.09 (m, 8 H), 7.025 (s, 1 H), 2.67 (t, J = 7.5 Hz, 4 H),

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2.54 (t, J = 7.5 Hz, 2 H), 1.925 (qui, J = 7.5 Hz, 2 H), 1.80–1.09 (m, 8 H), 1.19 (br s, 6 H); IR (film, cm^{-1}) 1697; MS m/z 434 (M^+). Anal. ($C_{28}H_{34}O_2S$) C, H, O, S.

7-[2-(3-Phenylpropionyl)-3-thienyl]heptanoic Acid (4f). The ester **9a** (19 g, 51 mmol) (see preparation of **4a** by the route A) was dissolved in ethanol (400 mL), and NaOH (6.2 g, 155 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 pure **4f** as a white solid (16.3 g, 93%): mp 61–62 °C; NMR ($CDCl_3$) δ 7.39 (d, J = 5 Hz, 1 H), 7.35–7.14 (m, 5 H), 6.98 (d, J = 5 Hz, 1 H), 3.25–2.92 (m, 6 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.74–1.50 (m, 4 H), 1.48–1.25 (m, 4 H); IR (KBr, cm^{-1}) 1711, 1697, 1665; MS m/z 344 (M^+). Anal. ($C_{20}H_{24}O_3S$) C, H, O, S.

7-[5-Methyl-2-(3-phenylpropyl)-3-thienyl]-7-oxoheptanoic acid (4g) was prepared by the same procedure but starting from **12c** (see preparation of **4c** by the route B), yielding pure **4g** as a white solid (95%): mp 72 °C; NMR ($CDCl_3$) δ 7.34–7.11 (m, 5 H), 6.99 (br s, 1 H), 3.16 (t, J = 7.5 Hz, 2 H), 2.78 (t, J = 7.5 Hz, 2 H), 2.72 (t, J = 7.5 Hz, 2 H), 2.43 (s, 3 H), 2.39 (t, J = 7.5 Hz, 2 H), 1.99 (qui, J = 7.5 Hz, 2 H), 1.80–1.59 (m, 4 H), 1.49–1.30 (m, 2 H); IR (KBr, cm^{-1}) 1710, 1666; MS m/z 358 (M^+). Anal. ($C_{21}H_{26}O_3S$) C, H, O, S.

7-[3-(3-Phenylpropyl)-2-thienyl]-7-oxoheptanoic acid (5i) was prepared by the same procedure but starting from **17a** (see preparation of **5a** by the route D), yielding pure **5i** as a white solid (89%): mp 56 °C; NMR ($CDCl_3$) δ 7.43 (d, J = 5 Hz, 1 H), 7.37–7.15 (m, 5 H), 7.025 (d, J = 5 Hz, 1 H), 3.075 (t, J = 7.5 Hz, 2 H), 2.86 (t, J = 7.5 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.10–1.85 (m, 2 H), 1.84–1.60 (m, 4 H), 1.52–1.32 (m, 2 H); IR (KBr, cm^{-1}) 1697.5, 1651; MS m/z 344 (M^+). Anal. ($C_{20}H_{24}O_3S$) C, H, O, S.

6-[[5-Methyl-3-(3-phenylpropyl)-2-thienyl]thio]hexanoic Acid (5h). To a cooled solution (0 °C) of **15e** (3 g, 13.9 mmol) in dry diethyl ether (50 mL) was added dropwise n-BuLi (10 mL, 1.60 M in hexane). After stirring for 15 min, sulfur (0.51 g, 15.9 mmol) was added portionwise at 0 °C. The mixture was allowed to warm to 25 °C and stirred for 30 min. The mixture was cooled to 0 °C, and ethyl 6-bromohexanoate (3.8 g, 17 mmol) was then added dropwise. The reaction mixture was then allowed to warm to 25 °C and stirred for 16 h. The mixture was poured into cold H_2O, the layers were separated, and the aqueous layer was extracted twice with diethyl ether. The combined extracts were washed with H_2O, dried over Na_2SO_4, and evaporated, giving an oily residue. The ethyl ester **22** was isolated by chromatography on a silica gel column (eluent: diethyl ether/pentane 2/8). **22** (2.2 g, 5.6 mmol) was directly saponified by using the hydrolysis procedure described for compound **4f**, yielding pure **5h** as a pale yellow oil (1.4 g, 28% over two steps): NMR ($CDCl_3$) δ 7.35–7.01 (m, 5 H), 6.53 (s, 1 H), 2.72–2.49 (m, 6 H), 2.34 (s, 3 H), 2.27 (t, J = 7.5 Hz, 2 H), 1.89–1.67 (m, 2 H), 1.64–1.24 (m, 6 H); IR (KBr, cm^{-1}) 1707.5; MS m/z 362 (M^+). Anal. ($C_{20}H_{26}O_2S_2$) H, S, C: calcd 66.26, found 67.0.

7-Hydroxy-7-[3-(3-phenylpropyl)-2-thienyl]heptanoic Acid (5j). Sodium borohydride (0.55 g, 14.5 mmol) in H_2O (1.5 mL) was added to a solution of **5i** (2.5 g, 6.9 mmol) in NaOH (20 mL, 1 N). The reaction mixture was then stirred for 16 h at room temperature. Cold H_2O (100 mL) was added. The aqueous layer was acidified to pH = 5 with HCl (1 N) and extracted three times with diethyl ether. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, and evaporated to give pure **5j** as a white solid (2.43 g, 96%): mp 94–95 °C; NMR ($CDCl_3$) δ 7.36–7.12 (m, 6 H), 6.84 (d, J = 5 Hz, 1 H), 4.89 (t, J = 6.25 Hz, 1 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.625 (t, J = 7.5 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 2.02–1.20 (m, 10 H); IR (KBr, cm^{-1}) 1708; MS m/z 346 (M^+). Anal. ($C_{20}H_{26}O_3S$) C, H, S.

Methyl 6-(Chloroformyl)-2,2-dimethylhexanoate (11c). Methyl 6-bromo-2,2-dimethylhexanoate[24] (25.4 g, 107 mmol) was added dropwise at 80 °C to a solution of NaCN (6.5 g, 133 mmol) in DMSO. The reaction mixture was allowed to cool to room temperature, and H_2O (1.2 L) was added. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated, giving crude methyl 6-cyano-2,2-dimethylhexanoate as a yellow oil (18.6 g, 92%).

A solution of the crude nitrile (22.4 g, 122 mmol) in methanol (500 mL), maintained at −10 °C, was saturated with HCl. After 5 h at −10 °C, the reaction mixture was allowed to warm to 20 °C and was stirred for 16 h. The solvent was then removed, and the residue was taken up in H_2O (300 mL). The aqueous layer was then extracted three times with CH_2Cl_2. The combined organic extracts were washed with water, aqueous $NaHCO_3$ (saturated) and water, dried over Na_2SO_4, and evaporated to give the corresponding diester as a yellow oil (22 g, 83%).

A mixture of the crude diester (22 g, 102 mmol) and KOH (5.5 g, 98 mmol) in ethanol (200 mL) was stirred for 32 h at room temperature. The solvent was then removed, and the residue was taken up in H_2O (400 mL). The aqueous layer was extracted twice with diethyl ether and acidified to pH = 1 with 1 N HCl. The acidic aqueous layer was then extracted three times with diethyl ether. The combined organic extracts were then dried over $MgSO_4$ and evaporated. The oily residue was purified by distillation to give 6-methoxycarbonyl-5,5-hexanoic acid as a pale yellow oil (15.7 g, 76%): $bp_{0.04mmHg}$ = 92 °C. A mixture of the acid (15.7 g, 78 mmol) prepared above and $SOCl_2$ (13.9 g, 117 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 16 h. After concentration to dryness, the oily residue was purified by distillation to give **11c** as pale yellow oil (13 g, 76%): $bp_{0.04mmHg}$ = 58 °C.

5-Phenyl-1-(3-thienyl)-1-pentanol (24a). To a cooled (0 °C) solution of (4-phenylbutyl)magnesium bromide (prepared from 1-bromo-4-phenylbutane (147 g, 690 mmol) and magnesium (16.7 g, 690 mmol) in dried THF (750 mL)) was added 3-thiophenecarboxaldehyde (61.8 g, 550 mmol) in THF (300 mL). The reaction mixture was allowed to warm to room temperature and was then heated at reflux for 1 h. After cooling to 0 °C, NH_4Cl (aqueous, saturated) was added. The aqueous layer was then acidified to pH = 1 with 2 N HCl. The layers were then separated and the aqueous one extracted twice with diethyl ether. The combined organic extracts were washed with $NaHCO_3$ (aqueous, 5% w/w) and brine, dried over Na_2SO_4, and evaporated. After purification by chromatography on silica gel (eluent: dichloromethane), **24a** was obtained as a yellow oil (113.7 g, 84%), MS m/z 246 (M^+).

4-Phenylbutyl 3-Thienyl Ketone (25a). To a mixture of pyridinium chlorochromate (51.7 g, 240 mmol) and NaOAc (5.17 g, 63 mmol) in CH_2Cl_2 (400 mL) was added dropwise **24a** (59 g, 240 mmol) in CH_2Cl_2 (200 mL) over 15 min. The inner temperature rose to 40 °C. The reaction mixture was allowed to cool to room temperature and was stirred for 1 h. The black resulting mixture was filtered through a short silica gel column. After washing with CH_2Cl_2, the organic phase was evaporated, yielding **25a** as a yellow oil (55 g, 94%) and used without further purification in the next step, MS m/z 244 (M^+).

3-(5-Phenylpentyl)thiophene (15c) was prepared by Wolff–Kishner reduction of **25a**, using the procedure described in the route A but starting from **25a** (160 g, 660 mmol), hydrazine monohydrate (124 g, 1.98 mol), KOH (147 g, 2.62 mol), and triethylene glycol (800 mL). **15c** was isolated by distillation as a pale yellow oil (114 g, 75.5%): $bp_{0.04mmHg}$ = 118 °C; NMR ($CDCl_3$) δ 7.35–7.10 (m, 6 H), 6.94–6.82 (m, 2 H), 2.69–2.50 (m, 4 H), 1.79–1.55 (m, 4 H), 1.46–1.27 (m, 2 H); MS m/z 230 (M^+).

5-Methyl-3-(3-phenylpropyl)thiophene (15e) was prepared by the same three-step procedure as described for compound **15c**, but starting from 5-methyl-3-thiophenecarboxaldehyde and 1-bromo-2-phenylethane to give **15e** as a pale yellow oil (55.3% over three steps): $bp_{0.02mmHg}$ = 95 °C; NMR ($CDCl_3$) δ 7.36–7.14 (m, 5 H), 6.675 (br s, 1 H), 6.61 (br s, 1 H), 2.72–2.50 (m, 4 H), 2.45 (s, 3 H), 1.93 (qui, J = 7.5 Hz, 2 H); MS m/z 216 (M^+).

Biological Methods. LTA_4 Hydrolase Inhibition Assay. The porcine leukocyte homogenates, prepared as previously described[5], 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

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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 minutes and terminated by the addition of 0.2 vol of 1% formic acid. The mixture was then extracted with 2 vol of chloroform/methanol 1:1 (w/w) and then with 0.8 vol 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 a HPLC-Monitor (LB 505, Berthold, Wilbad, Germany). 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.

LTB_4 Receptor Binding Assay. Tritiated LTB_4 preparations with a specific activity of 150–220 Ci/mmol and a radiochemical purity of ≥95% were obtained from Amersham. Nonradioactive LTB_4 was purchased from Sigma. All other chemicals were commercial reagent-grade materials. Female Hartley guinea pigs (weight = 250 g) were decapitated and spleens were removed, washed, and placed in a cold Tris-buffered (50 mmol/L, pH = 7) solution. The pooled tissue was minced and homogenized by Polytron. The crude membrane preparation was isolated by differential centrifugation according to the method previously described by J. B. Cheng et al.[25] The effectiveness of compounds to inhibit binding of [^{3}H]LTB_4 was measured by using an adaptation of the radioligand-binding assay developed by J. B. Cheng et al.[25] Binding studies were performed in a cold Tris-buffered (50 mmol/L, pH = 7) solution containing the membrane preparation (final concentration: 0.25 mg protein/mL), 1 nmol/L [^{3}H]LTB_4, 1 mg/mL ovalbumin, and 0.1 mmol/L PMSF with a competitor. The mixture was then incubated at 4 °C for 1 h. After incubation, cold Tris-buffered (50 mmol/L, pH = 7) solution was added and the sample was immediately filtered through Whatman GF/B glass fiber filter to separate free and bound [^{3}H]LTB_4. The filter was then washed with the cold Tris-buffered solution and dried, and the radioactivity bound to the membranes was measured by liquid scintillation spectrometry. Nonspecific binding was determined by measuring the amount of the label bound when cells and [^{3}]LTB_4 were incubated with a 1000-fold excess of unlabeled LTB_4. Appropriate corrections for nonspecific binding were made when analyzing the data. The LTB_4 binding activity was calculated from the percent inhibition of specific [^{3}H]LTB_4 binding at various concentrations. IC_{50} values were derived by graphical analysis. Each value is the mean of three replicates. The inhibitory activity of most compounds was evaluated on only one preparation. However an estimate of the precision of the measurements can be obtained from the inhibition observed with compounds **5k** and **5l**. At 10^{-6} M, the mean percent inhibition and standard error for compound **5k** were 89.0 and 2.3, respectively, and for compound **5l**, 85.0 and 5.3, respectively. At 10^{-7} M, the corresponding values were for compound **5k**, 50.2 and 8.4, respectively, and for compound **5l**, 37.2 and 12.3, respectively. At 3×10^{-7} M the corresponding values were for compound **5k**, 38.2 and 8.9, respectively, and for compound **5l**, 17.8 and 7.9, respectively.

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Registry No. 1, 142260-04-6; **2a**, 142422-48-8; **2b**, 142422-49-9; **2c**, 142422-50-2; **2d**, 142422-51-3; **2e**, 142422-52-4; **2f**, 142422-53-5; **3a**, 142422-54-6; **3b**, 142422-55-7; **3c**, 142422-56-8; **3d**, 142422-57-9; **3e**, 142422-58-0; **3f**, 142422-59-1; **4a**, 142422-60-4; **4b**, 142422-61-5; **4c**, 142422-62-6; **4d**, 142422-63-7; **4e**, 142422-64-8; **4f**, 142422-65-9; **4g**, 142422-66-0; **4h**, 142422-67-1; **4i**, 142422-68-2; **5a**, 142422-69-3; **5b**, 142422-70-6; **5c**, 142422-71-7; **5d**, 142422-72-8; **5e**, 142422-73-9; **5f**, 142422-74-0; **5g**, 142422-75-1; **5h**, 142422-76-2; **5i**, 142422-77-3; **5j**, 142422-78-4; **5k**, 142422-79-5; **5l**, 142422-80-8; **5m**, 142422-81-9; **5n**, 142422-82-0; **5o**, 142422-83-1; **6**, 142422-84-2; **7** (n = 2, Ar = Ph), 103-80-0; **7** (n = 3, Ar = Ph), 645-45-4; **7** (n = 3, Ar = C_6H_4-p-Cl), 52085-96-8; **7** (n = 3, Ar = C_6H_4-p-OMe), 15893-42-2; **8a**, 142422-85-3; **8b**, 142422-86-4; **8c**, 142422-87-5; **9b**, 142422-88-6; **10a**, 142422-89-7; **10b**, 142422-90-0; **11c**, 142422-91-1; **11** (R = Et, R_1 = R_2 = H), 14794-32-2; **11** (R = Et, R_1 = Me, R_2 = H), 142422-92-2; **12c**, 142422-93-3; **13**, 142422-94-4; **14a**, 142422-95-5; **14b**, 142422-96-6; **15a**, 120245-35-4; **15b**, 27921-48-8; **15c**, 142422-97-7; **15d**, 2404-87-7; **15e**, 142422-98-8; **16d**, 142422-99-9; **17a**, 142423-00-5; **17d**, 142423-01-6; **18**, 142423-02-7; **19**, 142423-03-8; **20a**, 142423-04-9; **20b**, 142423-05-0; **21a**, 142423-06-1; **22**, 142423-07-2; **23a**, 498-62-4; **23b**, 29421-72-5; **24a**, 142423-08-3; **25a**, 142423-09-4; 2-methylthiophene, 554-14-3; 1-phenyl-3-(3-thienyl)-1-propanone, 71778-01-3; methyl 4-(chloroformyl)butanoate, 1501-26-4; 1-bromo-4-phenylbutane, 13633-25-5; 2-phenylthiophene, 825-55-8; methyl 6-cyano-2,2-dimethylhexanoate, 142423-10-7; methyl 6-(methoxycarbonyl)-2,2-dimethylhexanoate, 142423-11-8; 6-(methoxycarbonyl)-6,6-dimethylhexanoic acid, 142423-12-9; methyl 6-bromo-2,2-dimethylhexanoate, 92518-61-1.

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