ω-[(4-Phenyl-2-quinolyl)oxy]alkanoic Acid Derivatives: A New Family of Potent LTB_4 Antagonists

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A series of ω-[(4-phenyl-2-quinolyl)oxy]alkanoic acid derivatives was prepared which inhibited the binding of the leukotriene B_4 to its receptors on guinea pig spleen membranes and on human polymorphonuclear leukocytes. A structure–activity relationship was investigated. The length of the carboxylic acid side chain was important for potent binding activity. The replacement of the oxygen atom at the beginning of the chain with other polar or nonpolar linking groups led to considerable loss of potency, indicating that the oxygen linking atom might be involved in the receptor recognition. α-Substitution on the carboxylic acid side chain led to substantially more potent compounds. Substitution on the phenyl ring and on the quinoline ring was also evaluated.

Leukotriene B_4, 5(*S*),12(*R*)-dihydroxy-6,14-*cis*,8,10-*trans*-eicosatetraenoic acid (LTB_4), is a product of arachidonic acid metabolism by the 5-lipoxygenase pathway. LTB_4 is released from neutrophils, monocytes, mast cells, and alveolar macrophages in response to a wide variety of stimuli. Among all its biological activities, the most significant are certainly the activation of various neutrophil functions. It stimulates aggregation[1] and degranulation[2] of human neutrophils, induces chemotaxis of leukocytes[3] and is a promoter of superoxide generation.[4] Moreover, inhalation of an LTB_4 aerosol provokes an important neutrophil and eosinophil infiltration into the trachea and bronchial airways of guinea pigs[5] and neutrophil accumulation into the bronchial lavage fluids collected from dogs.[6] Many of these cellular functions, stimulated by LTB_4, are involved in the inflammation process. Therefore, LTB_4 has been proposed as an important mediator of inflammation. In man, LTB_4 has been detected in rheumatoid synovial[7] and gouty arthritic[8] fluids, in inflammatory gastrointestinal mucosa,[9] and in psoriatic skin.[10]

Neutrophils possess specific membrane-bound receptors for LTB_4 which mediate most of the cellular responses to LTB_4.[2,11] Therefore specific LTB_4-receptor antagonists could find applications in the treatment of certain inflammatory conditions such as psoriasis and ulcerative colitis or any disease where LTB_4 plays the role of a pathological mediator.

Some research groups have already reported synthetic LTB_4-receptor antagonists (see Figure 1). Structurally, these compounds fall into three principal categories: leukotriene analogs, based on the natural product, such as SM-9064[12] or U-75302,[13] hydroxyacetophenone derivatives, related to the prototype LTD_4 antagonist FPL55712, such as LY255283[14a,b] or SC-41930,[15] and dicarboxylic acids

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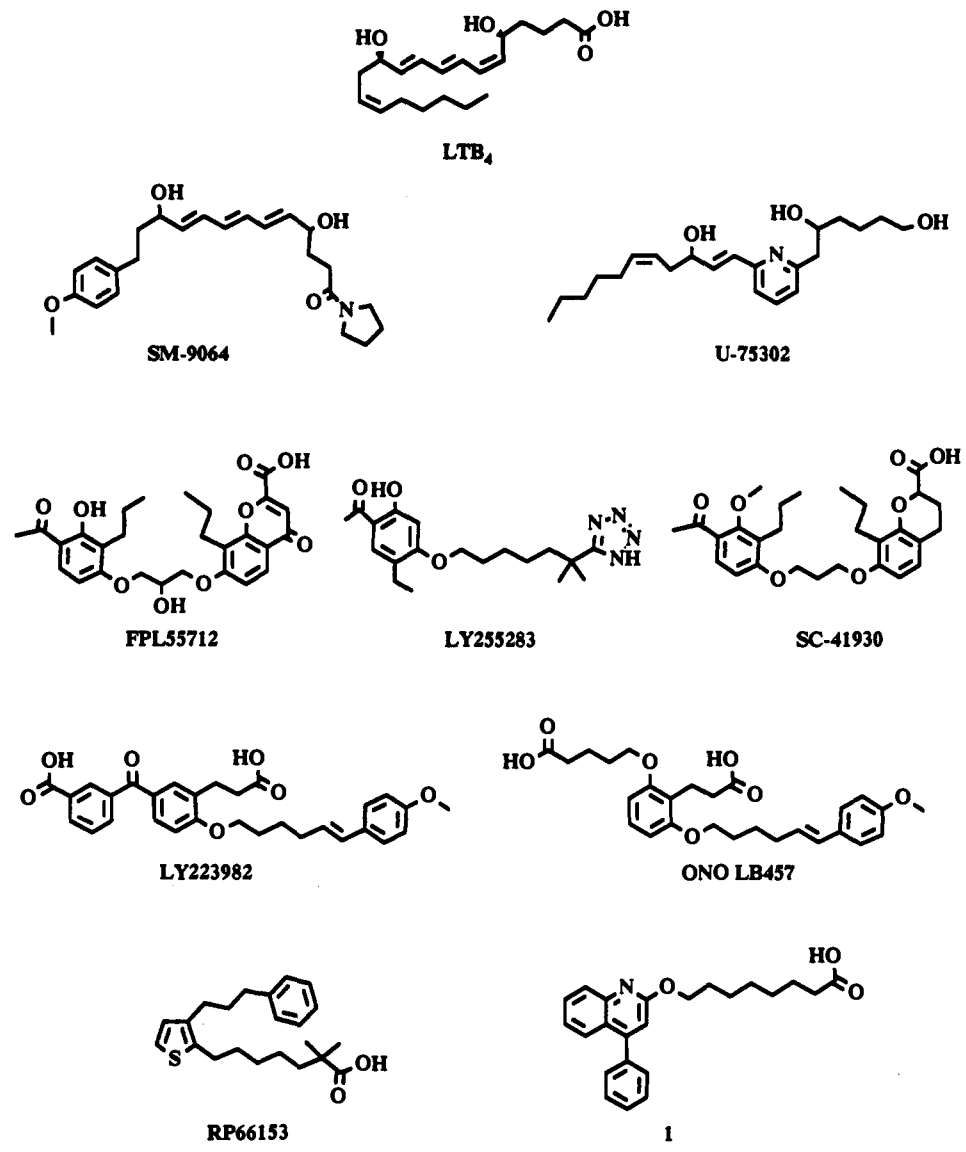

Figure 1.

such as LY223982[14c-e] and ONO LB457.[16] All these antagonists of leukotrienes are based on the stabilization of fatty acids by aromatic or heteroaromatic rings and are somewhat related to each other. For example, it is worth noting that the simple migration of the alkyl residue on the phenyl ring[14a] or the simple methylation of the hydroxyl group[15] in the hydroxyacetophenone part of the LTD_4 antagonist FPL55712 allows the design of specific LTB_4-receptor antagonists. In our ω-[(ω-arylalkyl)thienyl]-alkanoic acid series, we have similarly described the design of specific LTB_4-receptor antagonists, for example RP66153 (see Figure 1), from specific LTA_4 hydrolase inhibitors by changing the relative orientation of the two side chains on the central thiophene ring.[17]

We subsequently focused our efforts to find other potent LTB_4 antagonists containing other heteroaromatic rings and especially a N-heteroaromatic nucleus. A preliminary substructure research in our structural database, based on these structural requirements, led to the discovery of the 8-[(4-phenyl-2-quinolyl)oxy]octanoic acid (1, see Figure 1) which displays a promising LTB_4-receptor binding activity on the guinea pig spleen membrane with an IC_{50} of 2 μM. We report herein the syntheses and the structure–activity relationships for some ω-[(4-phenyl-2-quinolyl)oxy]alkanoic acid derivatives, structurally related to 1. An accompanying paper discusses the replacement of the (4-phenyl-2-quinolyl)oxy moiety by a (4,6-diphenyl-2-pyridyl)oxy group.[18]

Chemistry

The ω-[(4-phenyl-2-quinolyl)oxy]alkanoic acid derivatives, shown in Tables I and II, were prepared by the synthetic route A (Scheme I). The 4-phenyl-2-quinolinone derivative 2 was alkylated by an excess of ω-bromoalkanoate 3 to afford the O-alkylation product 4. Silver carbonate in toluene was used as base to give only O-alkylation, avoiding N-alkylation.[19] The ester 4, which was often contaminated with some amount of the starting

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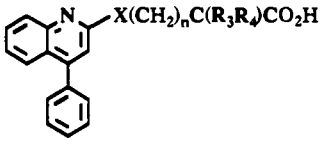
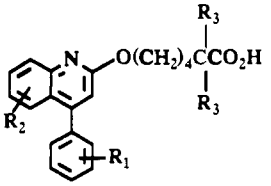
Table I. Influence of the Carboxylic Acid Side Chain on the LTB_4-Receptor Binding Activity



compd	X	n	R_3	R_4	mp, °C	formula	anal.[a]	route[b]	IC_{50},[c] nM
1	O	6	H	H	68	$C_{23}H_{25}NO_3$		A	2000
5a	O	5	H	H	62–65	$C_{22}H_{23}NO_3$	C,H,N,O	A	1800
5b	O	4	H	H	80–81	$C_{21}H_{21}NO_3$	C,H,N,O	A	700
5c	O	3	H	H	113–115	$C_{20}H_{19}NO_3$	C,H,N,O	A	(0)[d]
5d	O	4	Me	Me	118–120	$C_{23}H_{25}NO_3$	C,H,N,O	A	183
5e	O	4	H	Me	81	$C_{22}H_{23}NO_3$	H,N,O,C[e]	A	550
14	S	4	Me	Me	95–96	$C_{23}H_{25}NO_2S$	C,H,N,O,S	C	(33)[d]
15	NH	4	Me	Me	176–177	$C_{23}H_{26}N_2O_2$	C,H,N,O	C	(0)[d]
18	CH=CH	3	H	H	152–154	$C_{22}H_{21}NO_2$	C,H,N,O	D	(27)[d]
19	CH_2	4	H	H	137–139	$C_{22}H_{23}NO_2$	C,H,N,O	D	(34)[d]

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [d] Percentage of [^{3}H]LTB_4 binding inhibition at 10 μM. [e] C: calcd, 75.62; found, 74.6.

Table II. Variation of the LTB_4-Receptor Binding Activity with Aromatic Substitutions



compd	R_1	R_2	R_3	mp, °C	formula	anal.[a]	route[b]	IC_{50},[c] nM
5f	4-CF_3	H	Me	128–129	$C_{24}H_{24}F_3NO_3$	C,H,F,N	A	300
5g	4-Cl	H	H	75–77	$C_{21}H_{20}ClNO_3$	H,Cl,O,C[d]	A	30
5h	4-Cl	H	Me	110–111	$C_{23}H_{24}ClNO_3$	C,H,Cl,N,O	A	15
5i	4-OMe	H	Me	108–109	$C_{24}H_{27}NO_4$	H,N,O,C[e]	A	10
5j	4-Me	H	Me	93–94	$C_{24}H_{27}NO_3$	H,N,C[f]	A	30
5k	4-NO_2	H	Me	85–92	$C_{23}H_{24}N_2O_5$	C,H,N,O	A	150
5l	4-NH_2	H	Me	150–151	$C_{23}H_{26}N_2O_3$	C,H,N,O	*g*	40
5m	4-NHCOMe	H	Me	166–167	$C_{25}H_{28}N_2O_4$	C,H,N,O	*h*	(23)[i]
5n	3-OMe	H	Me	oil	$C_{24}H_{27}NO_4$	C,H,N,O	A	300
5o	3-Cl	H	Me	115	$C_{23}H_{24}ClNO_3$	C,H,Cl,N,O	A	1100
5p	2-OMe	H	Me	152	$C_{24}H_{27}NO_4$	C,H,N,O	A	(36)[i]
5q	2-F	H	Me	91	$C_{23}H_{24}FNO_3$	C,H,F,N	A	800
5r	H	3-Me	Me	148–149	$C_{24}H_{27}NO_3$	C,H,N,O	A	8000
5s	H	6-Cl	Me	141	$C_{23}H_{24}ClNO_3$	C,H,Cl,N,O	A	2500
5t	H	7-Cl	Me	102	$C_{23}H_{24}ClNO_4$	C,H,Cl,N,O	A	2000
LY223982								2

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [d] C: calcd, 68.20; found, 67.7. [e] C: calcd, 73.26; found, 71.7. [f] C: calcd, 76.36; found, 75.0. [g] Prepared by reduction of the nitro analog, see Experimental Section. [h] Prepared by acylation of **5l**, see Experimental Section. [i] Percentage of [^{3}H]LTB_4 binding inhibition at 10 μM.

bromide **3**, was directly saponified to the desired acid **5** (route A, Scheme I). In the case of some hindered carboxylic acids (R_3 and $R_4 \neq$ H), more drastic conditions were required and this step was performed by reacting **4** with lithium iodide in collidine.[20] The tetrazole-containing derivatives **8** were prepared from the corresponding nitrile **7** with sodium azide in DMF, in the presence of ammonium chloride[21] (route B, Scheme I). The nitrile **7** was prepared as described before for the ester **4**, but starting from the corresponding 6-bromohexanenitrile **6**.

Compounds **14** and **15**, with a sulfur or a nitrogen atom at the beginning of the carboxylic acid side chain, were prepared by nucleophilic substitutions on the 2-chloro-4-phenylquinoline (**9**, route C, Scheme II). Reaction of **9** with the thiol ester **10**, in the presence of sodium hydride, afforded the sulfur analog **12**, which was saponified with KOH in ethanol to yield the desired acid **14** (39%, over the two steps). Reaction of **9** with the amino ester **11**, at 100 °C, without solvent, gave rise to the amino analog **13**, giving the attempted acid **15** after saponification (7%, over the two steps).

The carbon analogs **18** and **19** were prepared from the 4-phenyl-2-quinolinecarboxaldehyde (**16**), by using the Wittig olefination reaction (route D, Scheme II). The ylide derived from (5-carboxypentyl)triphenylphosphonium iodide (**17**), prepared in toluene by reaction with potassium *tert*-butylate, was reacted with **16** to give the attempted *E* isomer **18**[22] (25%). The saturated derivative **19** was prepared by the catalytic hydrogenation of **18**, using Pd on carbon as catalyst (47%).

The synthesis of compounds not available through the

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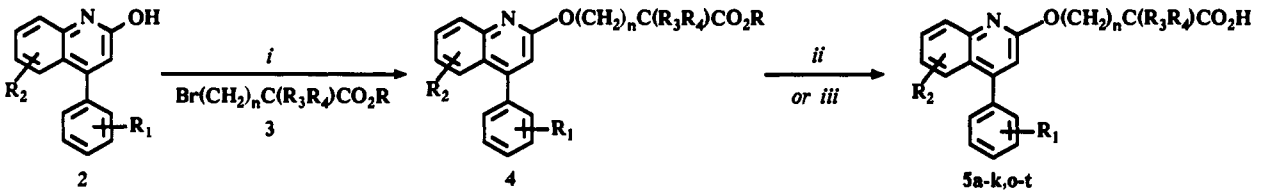
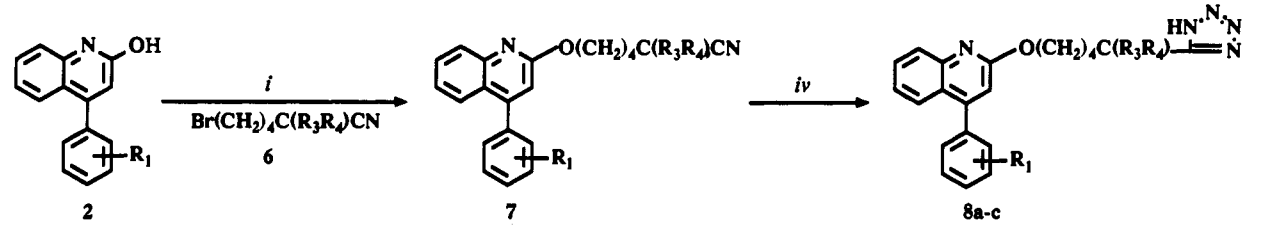
Scheme I[a]

Route A:



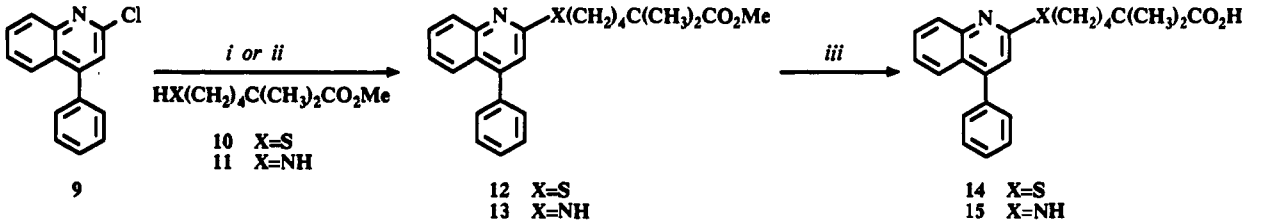
Route B:



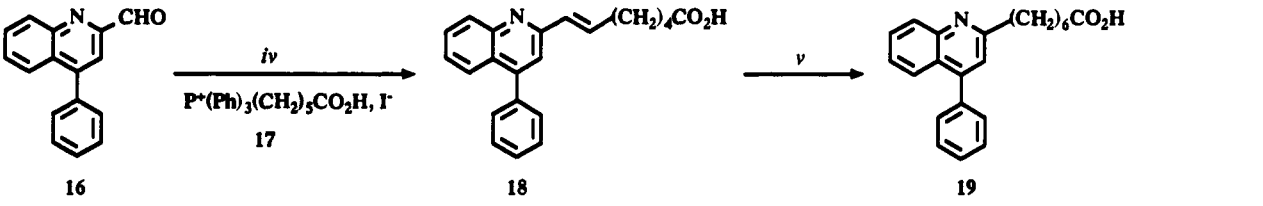
[a] (i) Ag_2CO_3, PhMe, reflux; (ii) NaOH or KOH, EtOH, reflux; (iii) LiI, 2,4,6-collidine, reflux; (iv) NaN_3, NH_4Cl, 120 °C, DMF.

Scheme II[a]

Route C:



Route D:



[a] (i) NaH, DMF, 60 °C; (ii) neat, 100 °C; (iii) KOH, EtOH, reflux; (iv) *t*-BuOK, PhMe, room temperature; (v) H_2, Pd/C, THF.

general methods, along with commercially unavailable materials, are described in the Experimental Section.

Biological Investigations

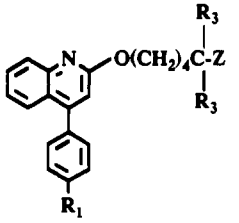
For the LTB_4-receptor binding assays, the activity of a compound was determined by measuring the percent inhibition of specific binding of [^{3}H]LTB_4 in the presence of the tested compound. The guinea pig spleen membranes were incubated with 1 nM [^{3}H]LTB_4 for 1 h at 4 °C. The human PMNs were incubated with 0.5 nM [^{3}H]LTB_4 for 15 min at 0 °C (see Experimental Section).

Results and Discussion

All of the compounds (Tables I–III) were assayed for their ability to selectively inhibit the binding of [^{3}H]LTB_4 to receptors on guinea pig spleen membranes. Some of the best compounds were also evaluated in a LTB_4-receptor binding assay on human polymorphonuclear leukocytes (PMNs).

The LTB_4-receptor binding activity was greatly affected by the carboxylic acid side-chain length (Table I). Optimal activity was observed with the hexanoic acid analog **5b**, corresponding to a 6-membered link between the central aromatic ring and the carboxylic acid function. This result is in accordance with the structure–activity relationship observed in the ω-[(ω-arylalkyl)thienyl]alkanoic acid series.[17] This optimal length from the carboxylic acid to the planar quinoline ring is similar to the length from the C1 to the triene moiety of LTB_4. A shorter chain gave rise to a fully inactive compound (**5c**, Table I), with longer chains leading to substantially less potent analogs (**1** and **5a**, Table I). α-Substitution on the carboxylic acid side chain had a marked positive effect on the LTB_4-receptor binding activity, as previously observed in the ω-[(ω-arylalkyl)thienyl]alkanoic acid series.[17] The α,α-dimethyl derivative **5d** was found around 5-fold more potent than its linear counterpart **5b** (Table I). However, the α-monomethyl analog **5e** was found only slightly more potent than **5b**.

Table III. Variation of the LTB_4-Receptor Binding Activity with the Terminal Functionality



compd	Z	R_1	R_3	mp, °C	formula	anal.[a]	route[b]	IC_{50},[c] nM
8a		H	Me	170–172	$C_{23}H_{25}N_5O$	C,H,N,O	B	400
8b		H	H	134	$C_{21}H_{21}N_5O$	C,H,N,O	B	500
8c		Cl	Me	165–167	$C_{23}H_{24}ClN_5O$	C,H,Cl,N,O	B	30
20		H	H	52–54	$C_{25}H_{28}N_2O_2$	C,H,N,O	*d*	(12)[e]
21	CH_2OH	H	H	46–48	$C_{21}H_{23}NO_2$	C,H,N,O	*f*	(14)[e]

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [d] Prepared from **5b**, see Experimental Section. [e] Percentage of [^{3}H]LTB_4 binding inhibition at 10 μM. [f] Prepared from **4b**, see Experimental Section.

The nature of the atom linking the carboxylic acid side chain and the quinoline ring profoundly affected the observed binding activity. The carbon, sulfur, and nitrogen derivatives were found at least 50-fold less potent than their oxygen counterparts (**14**, **15**, **18**, and **19**, Table I). The important difference between the oxygen derivative **5d** and its sulfur analog **14** (Table I) could indicate a strong electrostatic interaction of this part of the molecule (imino ether moiety) with the LTB_4 receptors.

Substitutions have been studied on the phenyl and on the quinoline rings (Table II). Substitutions on the phenyl ring were critical for an optimal binding activity. Para substituents, such as the chlorine atom or the methoxyl group, greatly enhanced the LTB_4-receptor binding activity of **5d**. The corresponding analogs **5h** and **5i** were found, respectively, 12- and 18-fold more potent than their unsubstituted counterpart (Table II). This dramatic effect was likewise observed in the case of the linear *p*-chloro analog **5g**. This compound was found more than 20-fold more potent than the unsubstituted linear analog **5b** (Table II). Para substitution by a methyl group or by a more hydrophilic and electron-donating group, such as NH_2, also led to potent LTB_4-receptor binding activities (**5n–p**, Table II). On the other hand, para substitution by electron-withdrawing groups, such as NO_2 or CF_3, gave rise to as potent or slightly less active analogs (**5f** and **5k**, Table II). Moreover, N-acylation of the amino-substituted analog **5l** led to substantially less active compound (**5m**, Table II). Optimal binding activity was obtained by substitution in the para position of the phenyl ring. Meta and ortho substituents on the phenyl ring gave rise to substantially less potent compounds (**5n–p**, Table II). Even the 2-fluoro analog **5q** displayed a 5-fold less potent activity than **5d** for the LTB_4-receptors (Table II). All these results seem to indicate bulk intolerance in these parts of the molecule.

The very low activity of compound **5r**, with a methyl substituent in the 3-position of the quinoline ring, also indicated a strong steric hindrance in this region. Substitution in other positions of the quinoline ring equally led to compounds of dramatically reduced activity (**5s**,t, Table II).

Table IV. LTB_4-Receptor Binding Activity on Human PMNs

compd	IC_{50}, nM[a]
5d	4000
5g	150
5i	140
5j	100
5l	250
8c	50
LY223982	3.5

[a] Inhibition of [^{3}H]LTB_4 binding on human PMNs.

Replacement of the terminal carboxylic acid function has been studied. Derivatives in which the acidic function was replaced with weakly or nonacidic groups displayed very low LTB_4-receptor binding activity (**20** and **21**, Table III). However, replacement of the carboxylic acid group by the isosteric tetrazole ring led to analogs as potent as the corresponding carboxylic acid derivatives (**8a–c**, Table III).

As previously observed for the acid derivatives, the addition of a *p*-chloro substituent to the phenyl ring in the tetrazole derivative greatly increased the LTB_4-receptor binding activity (**8c**, Table III). On the other hand, in the tetrazole series, the α,α-dimethyl derivative **8a** was comparable in activity to the linear tetrazole analog **8b** (Table III).

Some of the best compounds were assayed for their ability to inhibit the binding of [^{3}H]LTB_4 to receptors on human PMNs (Table IV). The same important structure–activity relationships were observed in human PMNs binding assay. The positive effect of chloro (**5g**), methoxyl (**5i**), methyl (**5j**), and amino (**5l**) para substituents was also clearly observed on human PMNs LTB_4 receptors. Among the compounds tested, the tetrazole analog **8c** has displayed the best binding activity with K_i equal to 22 nM (Table IV). Further biochemical studies, for example the inhibition of LTB_4-induced elastase release in human

PMNs, indicated that some of the best compounds in this series, for example **5h**, **5i**, and **8c**, were potent and specific LTB_4-receptor antagonists (data not shown).

In conclusion, the ω-[(4-aryl-2-quinolyl)oxy]alkanoic acid series represents a class of potent and selective LTB_4 antagonists. The SAR studies have demonstrated the positive influence of the α-substitution on the optimal hexanoic acid side chain to display potent LTB_4-receptor binding activity. Para substitution on the phenyl ring was also important for optimal binding activity on guinea pig spleen membranes and on human PMN LTB_4 receptors. These antagonists may serve as useful agents in elucidating the pathophysiological role of LTB_4 in human diseases.

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. 7-[(4-Phenyl-2-quinolyl)oxy]heptanoic Acid (5a). A suspension obtained by mixing 4-phenyl-2-quinolinone[23] (3 g, 13.6 mmol), ethyl 7-bromoheptanoate (4.8 g, 20.4 mmol), and silver carbonate (1.9 g, 6.7 mmol) in toluene (100 mL) and protected from the light was refluxed for 48 hours. The reaction mixture was allowed to cool to room temperature and was then filtered. The filtrate was evaporated. The resulting residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 95/5) to give the ethyl ester of the title compound **4a**, used without further purification in the next hydrolysis step. To a solution of **4a** (2.1 g, 5.6 mmol) in ethanol (50 mL) was added NaOH pellets (0.35 g, 8.4 mmol). The reaction mixture was refluxed for 2 h and then concentrated to dryness under reduced pressure. The resulting residue was dissolved in H_2O. The pH of the aqueous phase was adjusted to about 5 by addition of HCl (2 N). The aqueous layer was then extracted three times with CH_2Cl_2. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated. The solid residue was purified by recrystallization from a hexane/ethyl acetate mixture (10/1) to give pure **5a** as a white solid (1.7 g, 35.8% over two steps): mp 62–65 °C; NMR ($CDCl_3$) δ 7.89 (d, J = 8.75 Hz, 1 H), 7.75 (d, J = 8.75 Hz, 1 H), 7.61 (br t, J = 8.75 Hz, 1 H), 7.48 (br s, 5 H), 7.30 (br t, J = 8.75 Hz, 1 H), 6.85 (s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 2.375 (t, J = 7.5 Hz, 2 H), 1.95–1.35 (m, 8 H); IR (KBr, cm^{-1}) 1709; MS m/z 349 (M^+). Anal. ($C_{22}H_{23}NO_3$) C, H, N, O.

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

8-[(4-Phenyl-2-quinolyl)oxy]octanoic acid (1) was prepared from 4-phenyl-2-quinolinone[23] and ethyl 8-bromooctanoate (56% over two steps): mp 68 °C; NMR ($CDCl_3$) δ 7.85 (d, J = 8.75 Hz, 1 H), 7.69 (d, J = 8.75 Hz, 1 H), 7.62 (br t, J = 8.75 Hz, 1 H), 7.56–7.40 (m, 5 H), 7.32 (br t, J = 8.75 Hz, 1 H), 6.81 (s, 1 H), 4.45 (t, J = 6.25 Hz, 2 H), 2.17 (t, J = 7.5 Hz, 2 H), 1.83 (qui, J = 7.5 Hz, 2 H), 1.72–1.29 (m, 8 H); IR (KBr, cm^{-1}) 1708; MS m/z 363 (M^+).

6-[(4-Phenyl-2-quinolyl)oxy]hexanoic acid (5b) was prepared from 4-phenyl-2-quinolinone[23] and ethyl 6-bromohexanoate (67% over two steps): mp 80–81 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.77 (d, J = 8.75 Hz, 1 H), 7.62 (br t, J = 8.75 Hz, 1 H), 7.50 (br s, 5 H), 7.32 (br t, J = 8.75 Hz, 1 H), 6.86 (s, 1 H), 4.525 (t, J = 6.25 Hz, 2 H), 2.425 (t, J = 7.5 Hz, 2 H), 1.97–1.49 (m, 6 H); IR (KBr, cm^{-1}) 1704; MS m/z 335 (M^+). Anal. ($C_{21}H_{21}NO_3$) C, H, N, O.

5-[(4-Phenyl-2-quinolyl)oxy]pentanoic acid (5c) was prepared from 4-phenyl-2-quinolinone[23] and ethyl 5-bromopentanoate (34.2% over two steps): mp 113–5 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.77 (d, J = 8.75 Hz, 1 H), 7.64 (br t, J = 8.75 Hz, 1 H), 7.51 (br s, 5 H), 7.33 (br t, J = 8.75 Hz, 1 H), 6.875 (s, 1 H), 4.54 (t, J = 6.25 Hz, 2 H), 2.49 (t, J = 7.5 Hz, 2 H), 2.00–1.75 (m, 4 H); IR (KBr, cm^{-1}) 1708, 1610; MS m/z 321 (M^+). Anal. ($C_{20}H_{19}NO_3$) C, H, N, O.

2,2-Dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (5d) was prepared from 4-phenyl-2-quinolinone[23] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (15% over two steps): mp 118–20 °C; NMR ($CDCl_3$) δ 7.92 (d, J = 8.75 Hz, 1 H), 7.77 (d, J = 8.75 Hz, 1 H), 7.62 (br t, J = 8.75 Hz, 1 H), 7.50 (br s, 5 H), 7.33 (br t, J = 8.75 Hz, 1 H), 6.88 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 1.94–1.39 (m, 6 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1694; MS m/z 363 (M^+). Anal. ($C_{23}H_{25}NO_3$) C, H, N, O.

2-Methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (5e) was prepared from 4-phenyl-2-quinolinone[23] and methyl 6-bromo-2-methylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (17% over two steps): mp 81 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.77 (d, J = 8.75 Hz, 1 H), 7.64 (br t, J = 8.75 Hz, 1 H), 7.26 (br s, 5 H), 7.31 (br t, J = 8.75 Hz, 1 H), 6.86 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 2.62–2.40 (m, 1 H), 1.99–1.45 (m, 6 H), 1.22 (d, J = 6.25 Hz, 3 H); IR (KBr, cm^{-1}) 1721; MS m/z 349 (M^+). Anal. ($C_{22}H_{23}NO_3$): H, N, O; C: calcd, 75.62; found, 74.6.

6-[[4-(4-Chlorophenyl)-2-quinolyl]oxy]hexanoic acid (5g) was prepared from 4-(4-chlorophenyl)-2-quinolinone[25] and ethyl 6-bromohexanoate, using KOH (in place of NaOH) for the hydrolysis step (6% over two steps): mp 75–77 °C; NMR ($CDCl_3$) δ 7.92 (d, J = 8.75 Hz, 1 H), 7.72 (d, J = 8.75 Hz, 1 H), 7.66 (br t, J = 8.75 Hz, 1 H), 7.58–7.29 (m, 5 H), 6.84 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.97–1.50 (m, 6 H); IR (KBr, cm^{-1}) 16970, 1605; MS m/z 369 (M^+). Anal. ($C_{21}H_{20}ClNO_3$) H, Cl, N, O; C: calcd, 68.20; found, 67.7.

6-[[4-(4-Chlorophenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5h) was prepared from 4-(4-chlorophenyl)-2-quinolinone[25] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (40% over two steps): mp 110–111 °C; NMR ($CDCl_3$) δ 7.92 (d, J = 8.75 Hz, 1 H), 7.77–7.25 (m, 7 H), 6.82 (s, 1 H), 4.51 (t, J = 6.25 Hz, 2 H), 1.84 (qui, J = 7.5 Hz, 2 H), 1.75–1.39 (m, 4 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1700, 1611; MS m/z 397 (M^+). Anal. ($C_{23}H_{24}ClNO_3$) C, H, Cl, N, O.

6-[[4-(4-Methoxyphenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5i) was prepared from 4-(4-methoxyphenyl)-2-quinolinone[25] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (19% over two steps): mp 108–109 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.83 (d, J = 8.75 Hz, 1 H), 7.63 (br t, J = 8.75 Hz, 1 H), 7.46 (d, J = 8.75 Hz, 2 H), 7.33 (br t, J = 8.75 Hz, 1 H), 7.06 (d, J = 8.75 Hz, 2 H), 6.85 (s, 1 H), 4.51 (t, J = 6.25 Hz, 2 H), 3.90 (s, 3 H), 1.92–1.40 (m, 6 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1711, 1605; MS m/z 393 (M^+). Anal. ($C_{24}H_{27}NO_4$) H, N, O; C: calcd, 73.26; found, 71.7.

6-[[4-(4-Tolyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5j) was prepared from 4-(4-tolyl)-2-quinolinone[25] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (53% over two steps): mp 93–94 °C; NMR

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($CDCl_3$) δ 7.89 (d, J = 8.75 Hz, 1 H), 7.79 (d, J = 8.75 Hz, 1 H), 7.61 (br t, J = 8.75 Hz, 1 H), 7.45–7.23 (m, 5 H), 6.86 (s, 1 H), 4.51 (t, J = 6.25 Hz, 2 H), 2.46 (s, 3 H), 1.86 (qui, J = 7.5 Hz, 2 H), 1.74–1.39 (m, 4 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1712; MS m/z 377 (M^+). Anal. ($C_{24}H_{27}NO_3$) H, N; C: calcd, 73.36; found, 75.0.

6-[[4-(3-Methoxyphenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5n) was prepared from 4-(3-methoxyphenyl)-2-quinolinone[26] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (27% over two steps): oil; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.81 (d, J = 8.75 Hz, 1 H), 7.64 (br t, J = 8.75 Hz, 1 H), 7.49–7.25 (m, 2 H), 7.12–6.99 (m, 3 H), 6.86 (s, 1 H), 4.51 (t, J = 6.25 Hz, 2 H), 3.86 (s, 3 H), 1.85 (qui, J = 7.5 Hz, 2 H), 1.74–1.40 (m, 4 H), 1.22 (br s, 6 H); IR (film, cm^{-1}) 1699, 1598; MS m/z 393 (M^+). Anal. ($C_{24}H_{27}NO_4$) C, H, N, O.

6-[[4-(3-Chlorophenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5o) was prepared from 4-(3-chlorophenyl)-2-quinolinone, obtained following the method described by A. L. Searles and D. Ressler[27] from (3-chlorobenzoyl)acetanilide[28] (86%, mp = 233 °C), and methyl 6-bromo-2,2-dimethylhexanoate[24] (21% over two steps): mp 115 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.75–7.54 (m, 2 H), 7.52–7.25 (m, 5 H), 6.86 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 1.94–1.37 (m, 6 H), 1.21 (br s, 6 H); IR (KBr, cm^{-1}) 1696; MS m/z 397 (M^+). Anal. ($C_{23}H_{24}ClNO_3$) C, H, Cl, N, O.

6-[[4-(2-Methoxyphenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5p) was prepared from 4-(2-methoxyphenyl)-2-quinolinone, obtained by cyclization of (2-methoxybenzoyl)-acetanilide[29] with PPA (56%, mp = 241 °C), and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (61% over two steps): mp 152 °C; NMR ($CDCl_3$) δ 7.89 (d, J = 8.75 Hz, 1 H), 7.58 (br t, J = 8.75 Hz, 1 H), 7.51–7.38 (m, 2 H), 7.34–7.19 (m, 2 H), 7.14–6.99 (m, 2 H), 6.84 (s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 3.71 (s, 3 H), 1.84 (qui, J = 7.5 Hz, 2 H), 1.74–1.41 (m, 4 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1711, 1614; MS m/z 393 (M^+). Anal. ($C_{24}H_{27}NO_4$): C, H, N, O.

6-[[4-(2-Fluorophenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5q) was prepared from 4-(2-fluorophenyl)-2-quinolinone, obtained following the method described by A. L. Searles and D. Ressler[27] from (2-fluorobenzoyl)acetanilide[29] (38%, mp = 258 °C), and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (18% over two steps): mp 91 °C; NMR ($CDCl_3$) δ 7.80 (d, J = 8.75 Hz, 1 H), 7.72–7.16 (m, 7 H), 6.90 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 1.96–1.39 (m, 6 H), 1.23 (br s, 6 H); IR (KBr, cm^{-1}) 1697; MS m/z 381 (M^+). Anal. ($C_{23}H_{24}FNO_3$) C, H, F, N.

6-[[3-Methyl-4-phenyl-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5r) was prepared from 3-methyl-4-phenyl-2-quinolinone[27] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (63% over two steps): mp 148–149 °C; NMR ($CDCl_3$) δ 7.87 (d, J = 8.75 Hz, 1 H), 7.65–7.41 (m, 4 H), 7.34–7.17 (m, 4 H), 4.54 (t, J = 6.25 Hz, 2 H), 2.09 (s, 3 H), 1.87 (qui, J = 7.5 Hz, 2 H), 1.74–1.45 (m, 4 H), 1.21 (br s, 6 H); IR (KBr, cm^{-1}) 1697; MS m/z 377 (M^+). Anal. ($C_{24}H_{27}NO_3$) C, H, N, O.

6-[[6-Chloro-4-phenyl-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5s) was prepared from 6-chloro-4-phenyl-2-quinolinone[30] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (14% over two steps): mp 141 °C; NMR ($CDCl_3$) δ 7.83 (d, J = 8.75 Hz, 1 H), 7.73 (br s, 1 H), 7.64–7.39 (m, 6 H), 6.87 (s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 1.84 (qui, J = 7.5 Hz, 2 H), 1.72–1.37 (m, 4 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1700, 1611; MS m/z 397 (M^+). Anal. ($C_{23}H_{24}ClNO_3$) C, H, Cl, N, O.

6-[[7-Chloro-4-phenyl-2-quinolyl]oxy]-2,2-dimethylhexanoic acid (5t) was prepared from 7-chloro-4-phenyl-2-quinolinone[31] and methyl 6-bromo-2,2-dimethylhexanoate,[24] using KOH (in place of NaOH) for the hydrolysis step (2% over two steps): mp 102 °C; NMR ($CDCl_3$) δ 7.92 (br s, 1 H), 7.69 (d, J = 8.75 Hz, 1 H), 7.59–7.38 (m, 5 H), 7.27 (br d, J = 8.75 Hz, 1 H), 6.84 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 1.92–1.39 (m, 6 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1697, 1597; MS m/z 397 (M^+). Anal. ($C_{23}H_{24}ClNO_3$) C, H, Cl, N, O.

2,2-Dimethyl-6-[[4-(4-nitrophenyl)-2-quinolyl]oxy]hexanoic Acid (5k). A mixture of the methyl ester **4k** of the title compound (2.95 g, 7 mmol), prepared from 4-(4-nitrophenyl)-2-quinolinone[27] and methyl 6-bromo-2,2-dimethylhexanoate[24] as described in the above general procedure (46%, mp = 111–112 °C), and LiI (6.1 g, 45.6 mmol) in 2,4,6-collidine (115 mL) was refluxed, under inert atmosphere, for 1.5 h. The reaction mixture was allowed to cool to room temperature and was then poured into 2 N HCl (150 mL) at 0 °C. The aqueous phase was then extracted three times with diethyl ether. The combined organic extracts were then washed with H_2O until neutral, dried over Na_2SO_4, and evaporated. After purification of the residue by chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1), pure **5k** was obtained as a white solid (1.3 g, 46%): mp 85–92 °C; NMR ($CDCl_3$) δ 8.42 (d, J = 8.75 Hz, 2 H), 7.97 (d, J = 8.75 Hz, 1 H), 7.80 (m, 4 H), 7.37 (br t, J = 8.75 Hz, 1 H), 6.90 (s, 1 H), 4.54 (t, J = 6.25 Hz, 2 H), 1.86 (qui, J = 7.5 Hz, 2 H), 1.75–1.41 (m, 4 H), 1.24 (br s, 6 H); IR (KBr, cm^{-1}) 1697, 1593; MS m/z 408 (M^+). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N, O.

2,2-Dimethyl-6-[[4-[4-(trifluoromethyl)phenyl]-2-quinolyl]oxy]hexanoic acid (5f) was prepared as described above for **5h** but starting from 4-[4-(trifluoromethyl)phenyl]-2-quinolinone[25] and methyl 6-bromo-2,2-dimethylhexanoate[24] (15% over two steps): mp 128–129 °C; NMR ($CDCl_3$) δ 7.94 (d, J = 8.75 Hz, 1 H), 7.80 (d, J = 8.75 Hz, 2 H), 7.73 (m, 4 H), 7.35 (br t, J = 8.75 Hz, 1 H), 6.86 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 1.85 (qui, J = 7.5 Hz, 2 H), 1.74–1.40 (m, 4 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1698, 1604; MS m/z 431 (M^+). Anal. ($C_{24}H_{24}F_3NO_3$) C, H, F, N.

Route B. General Procedure. 5-[1,1-Dimethyl-5-[(4-phenyl-2-quinolyl)oxy]pentyl]-1*H*-tetrazole (8a). To a solution of 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanenitrile (8.2 g, 23.8 mmol), prepared by using the O-alkylation procedure described in the route A but starting from 4-phenyl-2-quinolinone[23] and 6-bromo-2,2-dimethylhexanenitrile[31] (83%, mp = 35 °C), in DMF (20 mL) was added sodium azide (4.64 g, 71.4 mmol) and ammonium chloride (3.82 g, 71.4 mmol). The reaction mixture was heated for 96 h to 120 °C. The reaction mixture was taken up in H_2O and extracted twice with ethyl acetate. The combined organic extracts was washed with H_2O, dried over Na_2SO_4, and evaporated. After purification of the resulting residue by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) and recrystallization from toluene, pure **8a** was obtained as a white solid (1.13 g, 12%): mp 170–172 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.79 (d, J = 8.75 Hz, 1 H), 7.65 (br t, J = 8.75 Hz, 1 H), 7.52 (br s, 5 H), 7.34 (br t, J = 8.75 Hz, 1 H), 6.85 (s, 1 H), 4.475 (t, J = 6.25 Hz, 2 H), 1.95–1.65 (m, 4 H), 1.55–1.20 (m, 2 H), 1.47 (br s, 6 H); MS m/z 387 (M^+). Anal. ($C_{23}H_{25}N_5O$) C, H, N, O.

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

5-[5-[(4-Phenyl-2-quinolyl)oxy]pentyl]-1*H*-tetrazole (8b) was prepared from 4-phenyl-2-quinolinone[23] and 6-bromohexanenitrile[31] (4% over two steps): mp 134 °C; NMR ($CDCl_3$) δ 8.04 (d, J = 8.75 Hz, 1 H), 7.81 (d, J = 8.75 Hz, 1 H), 7.67 (br t, J = 8.75 Hz, 1 H), 7.51 (br s, 5 H), 7.36 (br t, J = 8.75 Hz, 1 H), 6.90 (s, 1 H), 4.46 (t, J = 6.25 Hz, 2 H), 3.15 (t, J = 7.5 Hz, 2 H), 2.12–1.81 (m, 4 H), 1.75–1.50 (m, 2 H); MS m/z 359 (M^+). Anal. ($C_{21}H_{21}N_5O$) C, H, N, O.

5-[1,1-Dimethyl-5-[[4-(4-chlorophenyl)-2-quinolyl]oxy]pentyl]-1*H*-tetrazole (8c) was prepared from 4-(4-chloro-

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phenyl)-2-quinolinone[25] and 6-bromo-2,2-dimethylhexanenitrile[31] (4% over two steps): mp 165–167 °C; NMR ($CDCl_3$) δ 7.89 (d, J = 8.75 Hz, 1 H), 7.75–7.55 (m, 2 H), 7.53–7.21 (m, 5 H), 6.775 (s, 1 H), 4.425 (t, J = 6.25 Hz, 2 H), 2.04–1.67 (m, 4 H), 1.59–1.22 (m, 2 H), 1.50 (br s, 6 H); MS m/z 421 (M^+). Anal. ($C_{23}H_{24}ClN_5O$) C, H, Cl, N, O.

Route C. 2,2-Dimethyl-6-[(4-phenyl-2-quinolyl)thio]hexanoic Acid (14). To a solution of methyl 2,2-dimethyl-6-mercaptohexanoate[24] (4 g, 21 mmol) in DMF (100 mL) was added NaH (50% w/w dispersion in mineral oil) (1.1 g, 22.9 mmol). The mixture was stirred for 2 h until effervescence had stopped. A solution of 2-chloro-4-phenylquinoline[23] (9; 5 g, 20.8 mmol) in 50 mL of DMF was then added. The resulting mixture was heated to 60 °C for 8 h. After cooling, 10 mL of methanol was added and the mixture evaporated. The resultant residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 8/2) to give the methyl ester 12 of the title compound as an yellow oil, used without further purification in the next step. The title compound was directly obtained from 12 (4.3 g, 10.9 mmol) by using the saponification conditions described in the route A (KOH, 1.2 g, 21.4 mmol), yielding, after purification by crystallization from a mixture hexane/diethyl ether (9/1) and recrystallization from hexane, pure 14 as a white solid (1.6 g, 20% over two steps): mp 95–96 °C; NMR ($CDCl_3$) δ 8.01 (d, J = 8.75 Hz, 1 H), 7.79 (d, J = 8.75 Hz, 1 H), 7.66 (br t, J = 8.75 Hz, 1 H), 7.50 (br s, 5 H), 7.37 (br t, J = 8.75 Hz, 1 H), 7.15 (s, 1 H), 3.39 (t, J = 7.5 Hz, 2 H), 1.82 (qui, J = 7.5 Hz, 2 H), 1.74–1.42 (m, 4 H), 1.24 (br s, 6 H); IR (KBr, cm^{-1}) 1697; MS m/z 379 (M^+). Anal. ($C_{23}H_{25}NO_2S$) C, H, N, O, S.

2,2-Dimethyl-6-[(4-phenyl-2-quinolyl)amino]hexanoic Acid (15). A mixture of 9 (3.2 g, 13.4 mmol) and methyl 6-amino-2,2-dimethylhexanoate[32] (5.9 g, 34.1 mmol) was heated to 100 °C for 8 h. After cooling, the residue was purified by chromatography on silica gel (eluent: dichloromethane/methanol, 98/2). The methyl ester 13 of the title compound was then obtained as an oil, used without further purification in the next step. The title compound was directly obtained from 13 (1.4 g, 3.7 mmol) by using the saponification conditions described in the route A (KOH; 1 g, 17.8 mmol), yielding, after purification by chromatography on silica gel (eluent: dichloromethane/methanol, 98/2), pure 15 as a yellowish solid (0.35 g, 7% over two steps): mp 176–177 °C; NMR ($CDCl_3$) δ 7.67 (d, J = 8.75 Hz, 1 H), 7.59–7.35 (m, 7 H), 7.03 (br t, J = 8.75 Hz, 1 H), 6.62 (s, 1 H), 6.54 (br s, 1 H), 3.39 (m, 2 H), 1.80–1.41 (m, 6 H), 1.25 (br s, 6 H); IR (KBr, cm^{-1}) 1677, 1616; MS m/z 362 (M^+). Anal. ($C_{23}H_{26}N_2O_2$) C, H, N, O.

Route D. 7-(4-Phenyl-2-quinolyl)-6-heptenoic Acid (18). To a suspension of (5-carboxypentyl)triphenylphosphonium iodide (47.6 g, 94.4 mmol) in toluene (600 mL) was added potassium *tert*-butoxide (21.2 g, 189 mmol). The mixture was heated to 90 °C for 2 h under a nitrogen atmosphere. After cooling to room temperature, a solution of 4-phenyl-2-quinolinecarboxaldehyde[33] (10 g, 42.9 mmol) in toluene (150 mL) was added dropwise to the resulting orange suspension. The mixture was then poured into H_2O (800 mL), and the organic layer was discarded. The aqueous layer was acidified to pH 5 with 1 N HCl 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 flash chromatographed on silica gel (eluent: hexane/ethyl acetate, 92/8) and recrystallized from acetone to give pure 18 as a whitish solid (3.5 g, 25%): mp 152–154 °C; NMR ($CDCl_3$) δ 8.14 (d, J = 8.75 Hz, 1 H), 7.84 (d, J = 8.75 Hz, 1 H), 7.70 (br t, J = 8.75 Hz, 1 H), 7.51 (br s, 5 H), 7.49 (s, 1 H), 7.19 (br t, J = 8.75 Hz, 1 H), 6.96–6.71 (m, 2 H), 2.46–2.26 (m, 4 H), 1.84–1.51 (m, 4 H); IR (KBr, cm^{-1}) 1708, 1651, 1605; MS m/z 331 (M^+). Anal. ($C_{22}H_{21}NO_2$) C, H, N, O.

7-(4-Phenyl-2-quinolyl)heptanoic Acid (19). A mixture of 18 (1.75 g, 5.3 mmol) and palladium on activated carbon (10% w/w) (0.18 g) in THF (100 mL) was hydrogenated under normal pressure for 1 h at room temperature. After filtration and concentration in vacuo, the solid residue was stirred in diethyl ether (100 mL) and then recrystallized from acetone to give pure 19 as a whitish solid (0.8 g, 47%): mp 137–139 °C; NMR ($CDCl_3$) δ 8.13 (d, J = 8.75 Hz, 1 H), 7.89 (d, J = 8.75 Hz, 1 H), 7.71 (br t, J = 8.75 Hz, 1 H), 7.62–7.39 (m, 6 H), 7.26 (s, 1 H), 3.01 (t, J = 7.5 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 1.97–1.30 (m, 8 H); IR (KBr, cm^{-1}) 1714; MS m/z 333 (M^+). Anal. ($C_{22}H_{23}NO_2$) C, H, N, O.

6-[[4-(4-Aminophenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic Acid (5l). A mixture of 4k (7 g, 16.6 mmol) (see the preparation of 5k) and tin(II) chloride (16 g, 84.4 mmol) in methanol (250 mL) was heated for 2 h at reflux. The solvent was then evaporated and the oily residue was taken up in H_2O. The pH was set to 11 with 6 N NaOH, and the resulting aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated, giving, after chromatography on silica gel (eluent: hexane/ethyl acetate, 5/3), the methyl ester of the title compound as a solid residue (2.87 g), which was directly saponified by the procedure described in the route A (KOH, 1.23 g, 21.9 mmol). After purification by chromatography on silica gel (eluent: dichloromethane/methanol, 98/2) and recrystallization from a mixture diethyl ether/pentane, pure 5l was obtained as a pale yellow solid (1.5 g, 24% over two steps): mp 150–151 °C; NMR ($CDCl_3$) δ 7.92 (d, J = 8.75 Hz, 1 H), 7.86 (d, J = 8.75 Hz, 1 H), 7.60 (br t, J = 8.75 Hz, 1 H), 7.37 (m, 3 H), 6.81 (s, 1 H), 6.79 (d, J = 7.5 Hz, 2 H), 5.71 (br s, 3 H), 4.49 (t, J = 6.25 Hz, 2 H), 1.92–1.39 (m, 6 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1696, 1634, 1607; MS m/z 378 (M^+). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N, O.

6-[[4-(4-Acetamidophenyl)-2-quinolyl]oxy]-2,2-dimethylhexanoic Acid (5m). Acetyl chloride (0.1 g, 1.4 mmol) dissolved in chloroform (10 mL) was added to a mixture of 5l (0.5 g, 1.3 mmol) and triethylamine (0.13 g, 1.3 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at room temperature overnight. The solvent was then evaporated and the residue taken up in 2 N NaOH. The aqueous layer was then washed twice with diethyl ether and acidified with acetic acid (aqueous, 2 N). After extraction with diethyl ether, the combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The solid residue was recrystallized from a mixture acetone/pentane, giving pure 5m as a white solid (0.3 g, 55%): mp 166–167 °C; NMR ($CDCl_3$) δ 7.87 (d, J = 8.75 Hz, 1 H), 7.75 (d, J = 8.75 Hz, 1 H), 7.69–7.54 (m, 3 H), 7.50 (m, 4 H), 6.81 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 2.24 (s, 3 H), 1.91–1.375 (m, 6 H), 1.22 (br s, 6 H); IR (KBr, cm^{-1}) 1700, 1662, 1604; MS m/z 420 (M^+). Anal. ($C_{25}H_{23}N_2O_4$) C, H, N, O.

1-[6-[(4-Phenyl-2-quinolyl)oxy]hexanoyl]pyrrolidine (20). To a solution of 5b (5 g, 14.9 mmol) in THF (120 mL) was added 1,1'-carbonyldiimidazole (2.9 g, 17.9 mmol). The mixture was heated for 2 h to 50 °C. After cooling, pyrrolidine (1.3 g, 18.3 mmol) was added and the mixture was stirred at room temperature overnight. THF was removed in vacuo, and the residue was partitioned between ethyl acetate and H_2O. The ethyl acetate solution was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was then purified by flash chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 3/7) to give pure 20 (2.3 g, 40%) as a white solid: mp 52–54 °C; NMR ($CDCl_3$) δ 7.91 (d, J = 8.75 Hz, 1 H), 7.77 (d, J = 8.75 Hz, 1 H), 7.63 (br t, J = 8.75 Hz, 1 H), 7.51 (br s, 5 H), 7.32 (br t, J = 8.75 Hz, 1 H), 6.87 (s, 1 H), 4.525 (t, J = 6.25 Hz, 2 H), 3.56–3.32 (m, 4 H), 2.31 (t, J = 7.5 Hz, 2 H), 2.02–1.46 (m, 10 H); IR (KBr, cm^{-1}) 1650; MS m/z 388 (M^+). Anal. ($C_{25}H_{23}N_2O_2$) C, H, N, O.

6-[(4-Phenyl-2-quinolyl)oxy]hexanol (21). To a suspension of lithium aluminum hydride (0.7 g, 17.2 mmol) in THF (100 mL) was added dropwise a solution of 4b (5 g, 13.8 mmol) (see preparation of 5b by the route A) in THF (40 mL). The reaction mixture was stirred at room temperature for 1 h. H_2O and sulfuric acid were then carefully added. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with H_2O until neutral, dried over Na_2SO_4, and evaporated. The solid residue was then recrystallized from a hexane/ethyl acetate mixture, yielding pure 21 as a white solid: mp 46–48 °C; NMR ($CDCl_3$) δ 7.94 (d, J = 8.75 Hz, 1 H), 7.79 (d, J = 8.75 Hz, 1 H), 7.66 (br

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t, J = 8.75 Hz, 1 H), 7.51 (br s, 5 H), 7.32 (br t, J = 8.75 Hz, 1 H), 6.87 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 3.76–3.61 (m, 2 H), 1.875 (qui, J = 7.5 Hz, 2 H), 1.73–1.32 (m, 7 H); MS m/z 321 (M^+). Anal. ($C_{21}H_{23}NO_2$) C, H, N, O.

Biological Methods. Binding Assay Studies. 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.

Binding on Guinea Pig Spleen Membranes. Female Hartley guinea pigs (weight = 250 g) were decapitated, and the 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 Cheng et al.[34] 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 Cheng et al.[34] Binding studies were performed in a cold Tris-buffered (50 mmol/L, pH = 7) solution containing the membrane preparation (final concentration: 0.25 mg of a protein/mL), 1 nmol/L [^{3}H]LTB_4, 1 mg/mL of ovalbumin, and 0.1 mmol/L of 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}H]LTB_4 were incubated with a 100-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 compound **5d**. At 10^{-6} M, the mean percent inhibition and standard error for compound **5d** were 81.3 and 3.8, respectively. At 10^{-7} M, the corresponding values were 47.7 and 11.6, respectively. In a few cases where compounds were tested on more than one membrane preparation, an estimate of the precision can be obtained by the mean IC_{50} and standard error obtained for compound **5d** (n = 3, 183.3 and 57.7, respectively).

Binding on Human PMNs. Peripherical blood PMN from normal subjects were prepared by standard techniques of dextran T500 sedimentation followed Ficoll-Hypaque gradient centrifugation and hypotonic lysis. 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 A. H. Lin et al.[35] LTB_4 binding studies were performed in propylene tubes containing 0.5 nmol/L of [^{3}H]LTB_4, competitive compound, and cells suspended in Hank's balanced salt solution containing HEPES buffer (5 mmol/L) and ovalbumin (1 g/L) (final volume: 1 mL). The tubes were then incubated on ice for 15 min. The binding reaction was terminated by filtration through Whatman GF/C glass fiber filter to separate free and bound [^{3}H]LTB_4. The filter were than washed three times with 5 mL of cold Hank's balanced salt solution and placed into scintillation vials. The radioactivity was measured by liquid scintillation spectrometry. Nonspecific binding was determined by measuring the amount of the label bound when cells and [^{3}H]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 concentration. 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 compound **5d**. At 10^{-5} M, the mean percent inhibition and standard error for compound **5d** were 72.5 and 0.7, respectively. At 10^{-6} M, the corresponding values were 39.3 and 3.8, respectively.

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