ω-[(4,6-Diphenyl-2-pyridyl)oxy]alkanoic Acid Derivatives: A New Family of Potent and Orally Active LTB_4 Antagonists

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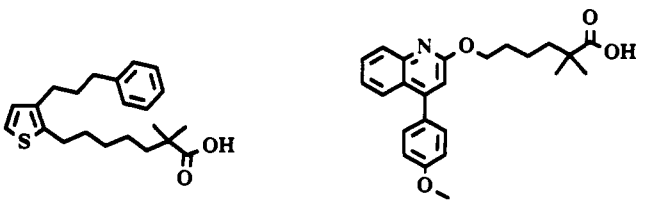
A series of ω-[(4,6-diphenyl-2-pyridyl)oxy]alkanoic acid derivatives was prepared which inhibited the binding of leukotriene B_4 to its receptors on guinea pig spleen membranes and on human polymorphonuclear leukocytes (PMNs) and selectively antagonized the LTB_4-induced elastase release in human PMNs. On the basis of these three screens, a structure–activity relationship was investigated. α-Substitution on the carboxylic acid side chain led to only small changes in the binding affinities but greatly enhanced the LTB_4 antagonist activity. Substitution on the phenyl rings was also evaluated. The terminal carboxylic acid function can be replaced by a tetrazole ring without loss in activity. The best in vitro LTB_4 antagonists of this series were investigated in vivo in the inhibition of LTB_4-induced leukopenia in rabbits. Compound **9b** (RP69698) displayed potent LTB_4 antagonist activity, after oral administration, with an ED_{50} value of 6.7 mg/kg.

We have previously described the design of specific LTB_4-receptor antagonists, analogs of RP66153 (see Figure 1), by structural variation in a series of specific LTA_4 hydrolase inhibitors.[1] We subsequently focused our efforts to find more potent LTB_4 antagonists containing other heteroaromatic rings, and especially a N-heteroaromatic nucleus. A first series of ω-[(4-phenyl-2-quinolyl)oxy]-alkanoic acid derivatives was developed, leading to RP69061 (see Figure 1), having potent binding affinities for human PMN and guinea pig spleen LTB_4-receptors[2] (IC_{50} = 140 and 10 nM, respectively). We report herein the syntheses and the structure–activity relationships for some alkanoic acid derivatives, structurally related to RP69061, in which a 4,6-diphenyl-2-pyridyl moiety replaces the 4-phenyl-2-quinoline ring.



RP66153 RP69061

Figure 1.

Chemistry

The ω-[(4,6-diphenyl-2-pyridyl)oxy]alkanoic acid derivatives **6**, shown in Tables I and II, were prepared by the synthetic route A (Scheme I). The 4,6-diphenyl-2-pyridine analog **3** was alkylated by an excess of ω-bromoalkanoate **4** to afford the O-alkylation product **5**. Silver carbonate in toluene at reflux or in DMF at 100 °C was used as base to give only O-alkylation, avoiding N-alkylation.[3] The ester **5**, which was often isolated with some amount of the starting bromide **4**, was directly saponified to the desired acid **6** (route A, Scheme I). The starting pyridines **3** were prepared from the corresponding chalcones **1** by reaction with the pyridinium salt **2** in an addition–cylization process, according to the method described by J. Thesing and A. Müller[4,5] (Table I).

The tetrazole-containing derivatives **9** were prepared from the corresponding nitrile **8** with sodium azide in DMF, in the presence of ammonium chloride[6] (route B, Scheme I). The nitrile **8** was prepared as described before for the ester **5**, but starting from the corresponding 6-bromohexanonitrile **7**.

Amino-substituted compounds **6n–p** were synthesized in two steps from the corresponding nitro analogs **5m** and **10a,b**, prepared from **3f** by the route A (Scheme II). Reduction of the nitro group by $SnCl_2$ in methanol or ethanol[7] gave the corresponding amino esters (**5n** and **11a–b**), which were saponified to the desired acids (**6n–p**) with KOH in ethanol.

N-Alkylamino-substituted compounds (**6q,r**) were synthesized from **5n** as shown in Scheme III. Reaction of **5n** with ethyl orthoformate, in the presence of catalytic amount of trifluoroacetic acid afforded the corresponding

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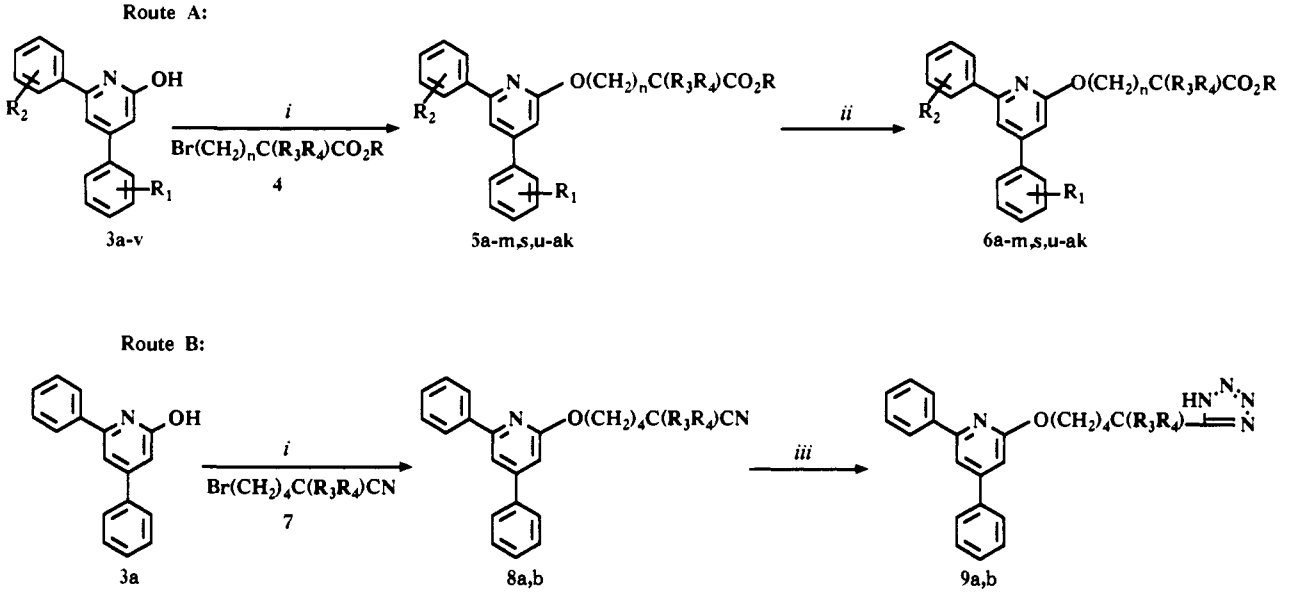
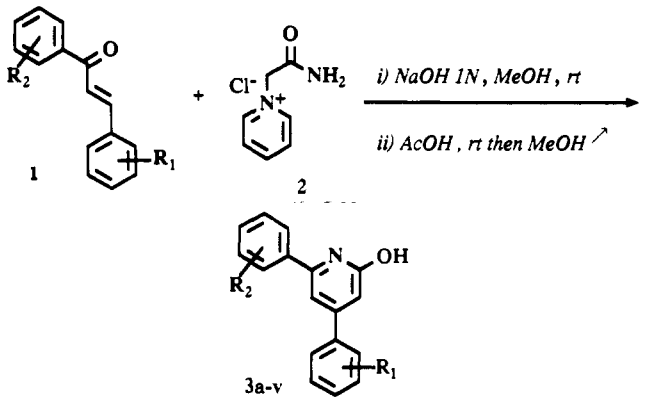
Scheme I [a]



[a] (i) Ag_2CO_3, DMF 110 °C or PhMe reflux; (ii) KOH, EtOH reflux; (iii) NaN_3, NH_4Cl, DMF, 120 °C.

Table I. Preparation of the 4,6-Diphenyl-2-pyridone Derivatives 3a-v



no.	R_1	R_2	% yield	mp, °C	starting material[a]
3a	H	H	71	209–212	1a
3b	4-OMe	H	69	227–229	1b
3c	4-Cl	H	77.5	241–243	1c
3d	4-Me	H	80	248	1d
3e	4-CF_3	H	76	228–229	1e[b]
3f	4-NO_2	H	72	284–285	1f
3g	4-NMe_2	H	68	254–256	1g[c]
3h	3-OMe	H	69.5	187–188	1h[c]
3i	3,4-$(OMe)_2$	H	46	233	1i
3j	3,5-$(OMe)_2$	H	50	256	1j[d]
3k	3,4-OCH_2O	H	86	254–255	1k
3l	3-Cl	H	88.5	209–210	1l
3m	2-Cl	H	41.5	238	1m
3n	2-F	H	79	211–213	1n[c]
3o	H	4-F	52	220	1o
3p	H	4-Me	73	260–261	1p
3q	H	4-CF_3	30	266	1q[e]
3r	H	4-OMe	38	243–245	1r
3s	H	3-OMe	73	202–203	1s[c]
3t	H	2-F	63	224–225	1t[f]
3u	H	2-Cl	75	213	1u[g]
3v	3,4-OCH_2O	2-Cl	24	250–251	1v[h]

[a] Commercially available, unless otherwise indicated. [b] For preparation see ref 5a. [c] For preparation see ref 5b. [d] For preparation see ref 5c. [e] For preparation see ref 5d. [f] For preparation see ref 5e. [g] For preparation see ref 5f. [h] For preparation see ref 5g.

imino acetal which was directly reduced in ethanol by $NaBH_4$[8] to yield the methyl amino analog **12a**. The corresponding *N*-isopropylamino-substituted compound **12b** was prepared by reductive alkylation of **5n** with acetone and $NaBH_4$ in acetic acid.[9] Saponification of the esters **12a,b** afforded the desired acids **6q,r**.

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

Pharmacology

For the 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 the Experimental Section).

In vitro, the antagonist activity of a compound was determined by measuring the inhibition of the LTB_4-induced (3 nM LTB_4) elastase release in human PMNs. Elastase release was measured as change in relative fluorescence of the reaction mixture over time, fluorescence being due to 7-amino-4-methylcoumarin liberated by elastase cleavage of a specific substrate (N-(methoxysuccinyl)-Ala-Ala-Pro-Val-7-amino-4-methylcoumarin) (see the Experimental Section).

In vivo, the antagonist activity of a compound was evaluated by measuring the inhibition of the LTB_4-induced (1 μg/kg LTB_4) leukopenia in rabbit. The tested compound was given either intravenously immediately after LTB_4 iv administration or orally 1 h before LTB_4 injection. White cells were counted at 30 s, 1, 2, 3, and 10 min after LTB_4 injection. The inhibition was calculated based upon AUC relative to the control values (see Experimental Section).

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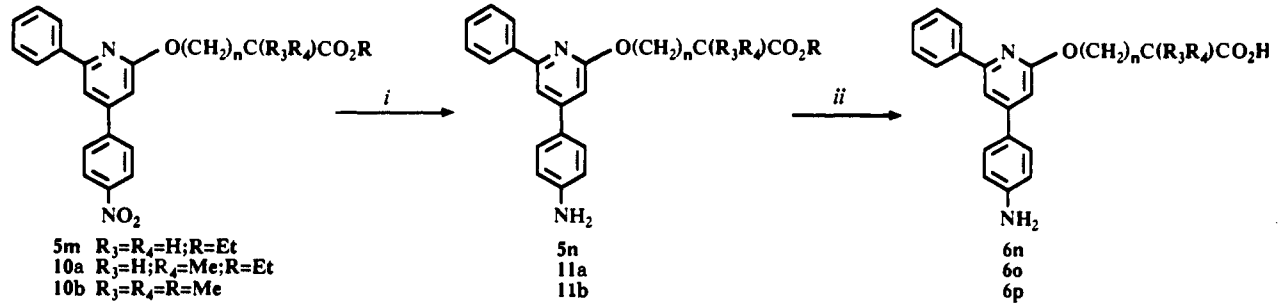
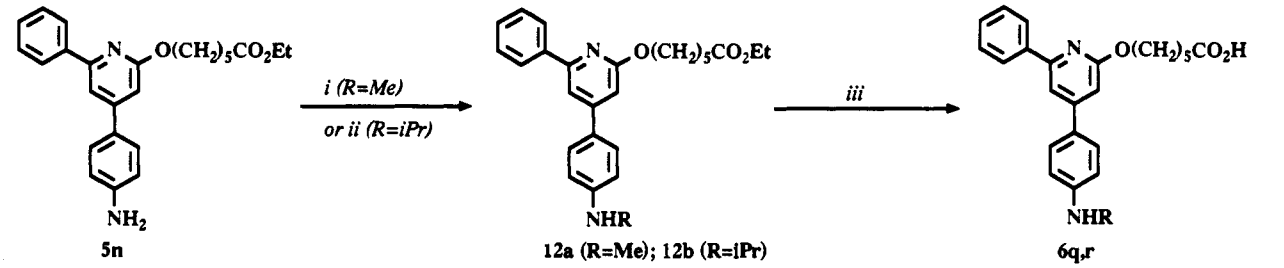
Scheme II [a]



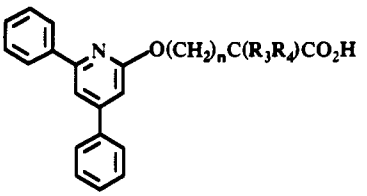
i) $SnCl_2$, ROH, reflux; ii) KOH, EtOH, reflux

Scheme III [a]



[a] (i) 1-HC(OEt)$_3$, ϵ-TFA-2-$NaBH_4$, EtOH; (ii) MeCOMe, $NaBH_4$, AcOH; (iii) KOH, EtOH, reflux.

Table II. Influence of the Carboxylic Acid Side Chain on the LTB_4 Antagonist Activity



				IC$_{50}$, nM		
				[^{3}H]LTB_4 binding		inhib of
no.	n	R_3	R_4	guinea pig spleen[a]	human PMNs[b]	LTB_4-induced elastase release[c]
6a	2	H	H	300		
6b	3	H	H	50	300	20000
6c	4	H	H	3	30	2000
6d	4	H	Me	4	30	22
6e	4	Me	Me	5	30	160
6f	5	H	H	25	15	2500
6g	5	Me	Me	15	50	100
6h	6	Me	Me	22	60	100
LY223982				2	3.5	1000

[a] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [b] [^{3}H]LTB_4-receptor binding on human PMNs. [c] Inhibition of LTB_4-induced (vs 3 nM LTB_4) elastase secretion in human PMNs.

Results and Discussion

The structure–activity relationships for this series of ω-[(4,6-diphenyl-2-pyridyl)oxy]alkanoic acid derivatives were investigated by evaluating the ability of the compounds to inhibit the binding of [^{3}H]LTB_4 to receptors on guinea pig spleen membranes and on human PMNs and to antagonize the LTB_4-induced elastase release in human PMNs. Some of the best compounds were also evaluated for their capacity to inhibit LTB_4-induced leukopenia in rabbit, after intravenous or oral administration. The results in Tables II–IV reflect the rather good correlation between the binding activities on both receptors.

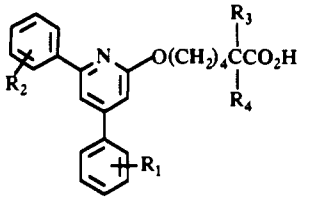
Optimal activity in the three screens was obtained with the hexanoic acid derivatives (Table II), consistent with the results previously obtained in our ω-[(ω-arylalkyl)-thienyl]alkanoic acid[1] and ω-[(4-phenyl-2-quinolyl)oxy]-alkanoic acid[2] series. Shorter side chains gave compounds with significantly lower affinity for LTB_4 receptors (**6a,b**). Longer side chains gave compounds with slightly less potent affinity for LTB_4 receptors (**6f–h**, Table II).

Previous results in our ω-[(ω-arylalkyl)thienyl]alkanoic acid[1] and ω-[(4-phenyl-2-quinolyl)oxy]alkanoic acid[2] series demonstrated the great importance of α-substitution on the acid side chain for an optimal binding activity. In this new seriers of ω-[(4,6-diphenyl-2-pyridyl)oxy]alkanoic acid derivatives, α-substitution led to only small changes in binding affinity for both receptors (**6d,e,g**, Table II). On the other hand, a dramatic effect was observed in the inhibition of the LTB_4-induced elastase release in human PMNs. α-Substitution on the carboxylic acid side chain greatly enhanced the antagonist activity, the α-methyl and the α,α-dimethyl analogs of **6c** being 100- and 10-fold more potent, respectively (**6d** and **6e**, Table II). This dramatic effect was observed for most of the compounds in this series, not only in the LTB_4-induced elastase release assay but also in other functional tests, such as LTB_4-induced human PMN chemotaxis or LTB_4-induced guinea pig lung parenchyma strip contractions (data not shown). These results demonstrated the pertinence of using such functional test, following binding assays, to design and select potent LTB_4 antagonists. Furthermore, the compounds of this series are specific antagonist of LTB_4, as they did not inhibit PAF- or fMLP-induced elastase release in human PMNs (i.e. compound **9b** displayed 99%, 9%, and 0% inhibition in the LTB_4-, PAF-, and FMLP-induced elastase release respectively).

Substitutions on the two phenyl rings were extensively investigated. The comparison of the structure–activity relationships observed on the two phenyl rings, in the 4-position (**6i–ac**, Table III) and in the 6-position (**6ad–aj**, Table III) on the pyridine ring, clearly demonstrated the asymmetry of the ω-[(4,6-diphenyl-2-pyridyl)oxy]-alkanoic acid derivatives towards LTB_4 binding sites.

Concerning the phenyl ring in the 4-position (called 4-phenyl ring), the electronic properties of substituents

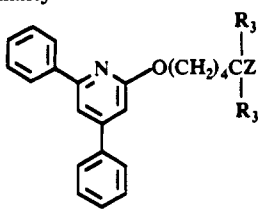
Table III. Variation of the LTB_4-Receptor Binding Activity with Aromatic Substitutions



no.	R_1	R_2	R_3	R_4	IC_{50}, nM: [^{3}H]LTB_4 binding, guinea pig spleen[a]	IC_{50}, nM: [^{3}H]LTB_4 binding, human PMNs[b]	IC_{50}, nM: inhib of LTB_4-induced elastase release[c]
6i	4-OMe	H	H	Me	4	11	3000
6j	4-Cl	H	H	Me	5	40	3000
6k	4-Me	H	H	Me	13	30	570
6l	4-CF_3	H	H	H	10	150	10000
6m	4-NO_2	H	H	H	50	600	
6n	4-NH_2	H	H	H	2	45	900
6o	4-NH_2	H	H	Me	5	30	15
6p	4-NH_2	H	Me	Me	6.6	9.5	15
6q	4-NHMe	H	H	H	5	150	>1000
6r	4-NHiPr	H	H	H	22	300	
6s	4-NMe_2	H	H	H	30	110	>10000
6t	4-$NHCOCF_3$	H	H	H	150		>10000
6u	3-OMe	H	H	Me	2	7	1300
6x	3,4-OCH_2O	H	H	H	1	6	2000
6y	3,4-OCH_2O	H	H	Me	4.2	6.6	120
6z	3,4-OCH_2O	H	Me	Me	7	20	120
6aa	3-Cl	H	H	Me	5	40	1000
6ab	2-Cl	H	H	H	200		>10000
6ac	2-F	H	H	H	10	30	10000
6ad	H	4-F	H	H	30	30	>10000
6ae	H	4-Me	H	H	300		
6af	H	4-CF_3	H	H	1200		>10000
6ag	H	4-OMe	H	H	1000		
6ah	H	3-OMe	H	H	500		
6ai	H	2-F	H	Me	4	18	70
6aj	H	2-Cl	H	Me		6	40
6ak	3,4-OCH_2O	2-Cl	H	Me	2	12	12
LY223982					2	3.5	1000

[a] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [b] [^{3}H]LTB_4-receptor binding on human PMNs. [c] Inhibition of LTB_4-induced (vs 3 nM LTB_4) elastase secretion in human PMNs.

Table IV. Variation of the LTB_4 Antagonist Activity with the Terminal Functionality



no.	Z	R_3	IC_{50}, nM: [^{3}H]LTB_4 binding, guinea pig spleen[a]	IC_{50}, nM: [^{3}H]LTB_4 binding, human PMNs[b]	IC_{50}, nM: inhib of LTB_4-induced elastase release[c]
5c	CO_2Me	H	40	100	1000
8a	CN	H	700		
9a	Tet[d]	H	10	50	200
9b	Tet[d]	Me	7	20	8
10	$CONH_2$	H	160	150	
LY223982			2	3.5	1000

[a] [^{3}H]LTB_4-receptor binding on guinea pig spleen membranes. [b] [^{3}H]LTB_4-receptor binding on human PMNs. [c] Inhibition of LTB_4-induced (vs 3 nM LTB_4) elastase secretion in human PMNs. [d] Tet = 5-tetrazolyl.

in the para position greatly influenced the binding affinity (Table III). Compounds with electron-withdrawing groups, such as trifluoromethyl (**6l**) and nitro (**6m**), displayed substantially lower affinity on both receptors. On the other hand, methyl (**6k**), halogen (**6j**), methoxy (**6i**), and amino (**6n–p**) substituents gave compounds with binding activities comparable to the corresponding unsubstituted analogs. Nevertheless, only the amino substituent, having strong electron-donating and hydrophilic properties, gave compounds (**6n–p**) with activities in the LTB_4-induced elastase release assay comparable to the corresponding unsubstituted analogs (**6c–e**, Table II). All the other substituents so far examined gave compounds with lower antagonist activities. More particularly, chloro- (**6j**), methoxy- (**6i**), and methyl-substituted (**6k**) compounds were found considerably less potent than **6d** and **6o** in the elastase release assay, in spite of similar binding activities for human PMN receptors. N-Alkylated and N-acylated derivatives of **6n** displayed lower affinities for LTB_4 receptors (**6q–t**, Table III).

The effect of the position of the substituents on the 4-phenyl ring was probed with the methoxy- and chloro-substituted derivatives (**6i,u,j,aa,ab**, Table III). There was not much difference in the activity between the meta (**6u,aa**) and para isomers (**6i,j**). On the other hand, the ortho-substituted chloro derivative **6ab** displayed a substantially less potent affinity for LTB_4 receptors. Moreover the ortho-substituted fluoro analog **6ac**, almost equally active for inhibition of [^{3}H]LTB_4 binding, was found 5-fold less potent than the unsubstituted derivative **6c** in the LTB_4-induced elastase release assay. These results seem to indicate the necessity to maintain qua-

siplanar the two π-systems, the pyridine and the 4-phenyl rings, for an optimal antagonist activity.

Some surprising results were obtained with disubstituted 4-phenyl rings (Table III). Compounds having methoxy groups in both meta and para positions (**6v**) or in both meta positions (**6w**) showed low binding activity for LTB_4 receptors (21% and 50% inhibition at 10 μM, respectively), whereas the corresponding meta (**6u**) and para monosubstituted (**6i**) derivatives displayed high affinities. On the other hand, compounds having a 3,4-methylenedioxy substituent on the 4-phenyl ring displayed high affinities for LTB_4 receptors and potent antagonism (**6x–z**, Table III), comparable to the activities displayed by the corresponding unsubstituted analogs (**6c–e**, Table II). Some strong steric intolerance around the 4-phenyl ring could explain, in part, these results.

Concerning the phenyl ring in the 6-position on the central pyridine ring (called 6-phenyl ring), para and meta substitution gave considerably less active compounds than the unsubstituted analog **6c**, whatever the electronic properties of the substituent (**6ae–ah**, Table III), indicating bulk intolerance in this region of the molecule. The para-substituted fluoro derivative **6ad** was found slightly less potent in both binding assays but substantially less active in the functional test. On the other hand, ortho-substituted fluoro (**6ai**) and chloro (**6aj**) compounds displayed high LTB_4 antagonist activities, being among the most potent antagonist in this series. In fact, there seems to be no strict requirement for a quasi planar relation between the central pyridine ring and the 6-phenyl ring. Compound **6ak**, substituted on both phenyl rings with some of the best substituents, displayed high LTB_4-receptor antagonist activities, among the most potent in this series.

Replacement of the terminal carboxylic acid function was investigated (Table IV). Derivatives in which the carboxylic acidic function was replaced with weakly or nonacidic groups displayed lower LTB_4-receptor binding activities than the parent compounds, the ester analog **5c** being more potent than the corresponding amide and nitrile **10** and **8a**, respectively. However, replacement of the carboxylic acid group by the isosteric tetrazole ring led to analogs as potent as the corresponding acid derivatives (**9a,b**, Table IV). As previously observed for the acid derivatives, the α,α-dimethyl tetrazole derivative **9b** was found 25-fold more potent than the linear analog **9a** in the inhibition of LTB_4-induced elastase release. The tetrazole derivative **9b** displayed the best antagonist activity in this series (IC_{50} = 8 nM).

Almost all the molecules which were found active in the in vitro receptor test displayed oral activity in the Writhing test (data not shown). The most potent in vitro antagonists in this series were assayed in vivo for their ability to inhibit LTB_4-induced leukopenia in rabbit (Table V). All these compounds inhibited LTB_4-induced leukopenia after iv administration with ED_{50} inferior to 10 mg/kg. The observed activities were consistent with the observed in vitro structure–activity relationships. The lowest potency was displayed by the linear analog **6c**, which was found, in our hand, equipotent to the Lilly compound LY223982. α-Substitution greatly enhanced the antagonist activity (**6d,e**, Table V). The substituted compounds also displayed high antagonist potencies in vivo, again confirming their potent in vitro activities (**6p**, **6y**, **6aj**, and **6ak**). The best activities were obtained for the acid derivatives **6d**, **6p**, **6y**, and **6aj** and for the tetrazole analog **9b** with ED_{50} values ranging from 0.1 to 0.3 mg/kg iv (Table V). Furthermore, some of these compounds were also found highly active after oral administration, with ED_{50} values ranging from 3.3 to 13 mg/kg po. (**6y**, **9b**, and **6p**, Table V).

In conclusion, the ω-[(4,6-diphenyl-2-pyridyl)oxy]alkanoic acid series represents a new class of potent, selective and orally active LTB_4 antagonists. α-Substitution on

Table V. Inhibition of LTB_4-Induced Leukopenia in Rabbit

	inhibition of LTB_4-induced leukopenia[a]	
no.	ED_{50}, mg/kg iv	ED_{50}, mg/kg po
6c	3–10	ND[b]
6d	0.2	>10
6e	1.5	>10
6p	0.1	3.3
6y	0.3	13
6aj	0.2	ND[b]
6ak	1.3	ND[b]
9b	0.3	6.7
LY223982	3–10[c]	ND[b]

[a] Inhibition of LTB_4-induced (vs 10^{-6} g/kg LTB_4 iv) leukopenia in rabbit. [b] Not determined. [c] In-house results.

Table VI. Preparation and Physical Data for **5c**, **6a–ak**, **8a**, **9a,b**, and **10**

no.	mp, °C	formula	anal.[a]	route[b]
5c	57–58	$C_{24}H_{25}NO_3$	C,H,N,O	A
6a	125–128	$C_{21}H_{19}NO_3$	C,H,N,O	A
6b	160–163	$C_{22}H_{21}NO_3$	C,H,N,O	A
6c	87–88	$C_{23}H_{23}NO_3$	C,H,N,O	A
6d	50–52	$C_{24}H_{25}NO_3$	C,H,N,O	A
6e	109–111	$C_{25}H_{27}NO_3$	C,H,N,O	A
6f	104–106	$C_{24}H_{25}NO_3$	C,H,N,O	A
6g	98–99	$C_{26}H_{29}NO_3$	C,H,N,O	A
6h	84	$C_{27}H_{31}NO_3$	C,H,N,O	A
6i	86	$C_{25}H_{27}NO_4$	C,H,N,O	A
6j	97–98	$C_{24}H_{24}ClNO_3$	C,H,Cl,N,O	A
6k	83–85	$C_{25}H_{27}NO_3$	C,H,N,O	A
6l	90–91	$C_{24}H_{22}F_3NO_3$	C,H,F,N	A
6m	118–119	$C_{23}H_{22}N_2O_5$	C,H,N,O	A
6n	131–133	$C_{23}H_{24}N_2O_3$	C,H,N,O	c
6o	134–136	$C_{24}H_{28}N_2O_3$	C,H,N,O	c
6p	123–125	$C_{25}H_{28}N_2O_3$	C,H,N,O	c
6q	115–117	$C_{24}H_{28}N_2O_3$	C,H,N,O	d
6r	100–102	$C_{26}H_{30}N_2O_3$	C,H,N,O	d
6s	159	$C_{25}H_{28}N_2O_3$	H,N,O,C[e]	A
6t	178–180	$C_{25}H_{28}F_3N_2O_4$	C,H,F,N	f
6u	103	$C_{25}H_{27}NO_4$	C,H,N,O	A
6v	103	$C_{25}H_{27}NO_5$	C,H,N,O	A
6w	99	$C_{25}H_{27}NO_5$	C,H,N,O	A
6x	124–126	$C_{24}H_{23}NO_5$	H,N,O,C[g]	A
6y	123–125	$C_{25}H_{25}NO_5$	C,H,N,O	A
6z	166–167	$C_{26}H_{27}NO_5$	C,H,N,O	A
6aa	55–57	$C_{24}H_{24}ClNO_3$	C,H,N,O	A
6ab	73	$C_{23}H_{22}ClNO_3$	C,H,Cl,N,O	A
6ac	100–101	$C_{23}H_{22}FNO_3$	C,H,F,N	A
6ad	94–95	$C_{23}H_{22}FNO_3$	C,H,F,N	A
6ae	76–78	$C_{24}H_{25}NO_3$	H,N,O,C[h]	A
6af	113–114	$C_{24}H_{22}F_3NO_3$	C,H,F,N	A
6ag	88–90	$C_{24}H_{25}NO_4$	C,H,N,O	A
6ah	91	$C_{24}H_{25}NO_4$	C,H,N,O	A
6ai	87	$C_{24}H_{24}FNO_3$	C,H,F,N	A
6aj	89	$C_{24}H_{24}ClNO_3$	H,N,O,C[i]	A
6ak	109	$C_{25}H_{24}ClNO_5$	C,H,Cl,N	A
8a	65	$C_{23}H_{22}N_2O$	C,H,N,O	B
9a	144–145	$C_{23}H_{23}N_5O$	C,H,N,O	B
9b	160–162	$C_{25}H_{27}N_5O$	C,H,N,O	B
10	118–120	$C_{23}H_{24}N_2O_2$	H,N,O,C[j]	f

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation. [c] See Scheme II. [d] See Scheme III. [e] C: calcd, 74.23; found, 73.7. [f] See Experimental Section. [g] C: calcd, 71.10; found, 71.6. [h] C: calcd, 76.77; found, 76.1. [i] C: calcd, 70.32; found, 69.5. [j] C: calcd, 76.64; found, 76.0.

the carboxylic acid side chain greatly enhanced the antagonist activity, although no significant effect was observed on the binding potency. The SAR studies of the two phenyl rings have demonstrated the asymmetry of the molecules. These results could indicate a favorable orientation of these compounds toward the LTB_4 receptors due to the nitrogen and/or imino ether moiety, confirming the importance of the imio ether moiety for binding activity observed in the ω-[(4,6-diphenyl-2-quinolyl)oxy]alkanoic acid series.[2] The best substituents for optimal binding and antagonist activities were the *p*-amino and the 3,4-methylenedioxy groups on the 4-phenyl ring and the *o*-fluoro and *o*-chloro groups on the 6-phenyl ring. Furthermore the terminal tetrazole analogs were found at least equipotent to the carboxylic acid derivatives. Among the best in vitro antagonists, some compounds have displayed potent inhibitory activities in the LTB_4-induced leukopenia in rabbits, after oral administration. For example, compounds **6p** (RP69618), **6y** (RP69699), and **9b** (RP-69698) are potent orally active LTB_4 antagonists with ED_{50} values of 3.3, 13, and 6.7 mg/kg po, respectively. RP69698 (**9b**) has been chosen for clinical trials.

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Brucker W 200 SY spectrometer and proton chemical shift 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, sext = sextuplet, 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. LY223982 was prepared according to the method described by D. M. Gapinski et al.[10]

Preparation of the 4,6-Diphenyl-2-pyridone Derivatives 3. General Procedure. 4,6-Diphenyl-2-pyridone (3a). To a solution of *N*-carbamoylmethylpyridinium chloride[11] (34.4 g, 200 mmol) and benzylideneacetophenone (41.6 g, 200 mmol) in methanol (600 mL) was added, at room temperature, 1 N NaOH (200 mL). The initial yellow solution turned orange and a yellow solid precipitated. The reaction mixture was stirred at room temperature for 15 min and acetic acid (400 mL) was then added. The resulting green solution was stirred at room temperature for 1 h. The solvent was then distilled over 4 h under normal pressure. The reuslting solid residue was taken up in H_2O (500 mL). After stirring the suspension for 1 h at room temperature, the solid was separated by filtration, washed three times with H_2O and dried under reduced pressure at 60 °C to give **3a** as a whitish solid (42.5 g, 71.1%), mp 209–212 °C.

Compounds **3b–v** were prepared as above.

Route A. General Procedure. 4-[(4,6-Diphenyl-2-pyridyl)oxy]butanoic Acid (6a). A suspension obtained by mixing **3a** (4 g, 16.2 mmol), ethyl 4-bromobutanoate (4.7 g, 24.3 mmol), and silver carbonate (2.2 g, 8.1 mmol) in toluene (160 mL) and protected from the light was refluxed for 34 h. 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 **5a** of the title compound, used without further purification in the next hydrolysis step. To a solution of **5a** (4.5 g, 12.5 mmol) in ethanol (130 mL) was added KOH pellets (1.1 g, 18.7 mmol). The reaction mixture was refluxed for 4 hours and then concentrated to dryness under reduced pressure. The resulting residue was dissolved in water. 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 an hexane/ethyl acetate mixture 10/1 to give pure **6a** as a white solid (3 g, 55.4% over two steps): mp 125–128 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.67 (br d, J = 7.5 Hz, 2 H), 7.57 (br s, 1 H), 7.61–7.32 (m, 6 H), 6.87 (br s, 1 H), 4.55 (t, J = 6.25 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.19 (qui, J = 7.5 Hz, 2 H); IR (KBr, cm^{-1}) 1712; MS m/z 333 (M^+). Anal. ($C_{21}H_{19}NO_3$) C, H, N, O.

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

5-[(4,6-Diphenyl-2-pyridyl)oxy]pentanoic acid (6b) was prepared from ethyl 5-bromopentanoate and **3a** (53.5%, over two steps): mp 160–163 °C; NMR ($CDCl_3$) δ 8.11 (br d, J = 8.75 Hz, 2 H), 7.71 (br d, J = 8.75 Hz, 2 H), 7.59 (br s, 1 H), 7.64–7.37 (m, 6 H), 6.90 (br s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 2.50 (t, J = 7.5 Hz, 2 H), 2.04–1.79, (m, 4 H); IR (KBr, cm^{-1}) 1706; MS m/z 347 (M^+). Anal. ($C_{22}H_{21}NO_3$) C, H, N, O.

6-[(4,6-Diphenyl-2-pyridyl)oxy]hexanoic acid (6c) was prepared from ethyl 6-bromohexanoate and **3a** (65.8%, over two steps): mp 87–88 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 8.75 Hz, 2 H), 7.66 (br d, J = 8.75 Hz, 2 H), 7.54 (br s, 1 H), 7.56–7.30 (m, 6 H), 6.87 (br s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 2.40 (t, J = 7.5 Hz, 2 H), 1.95–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1717; MS m/z 361 (M^+). Anal. ($C_{23}H_{23}NO_3$) C, H, N, O.

2-Methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (6d) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3a**, using DMF (110 °C) in the first step in place of toluene (49.6%, over two steps): mp 50–52 °C; NMR ($CDCl_3$) δ 8.14 (br d, J = 7.5 Hz, 2 H), 7.70 (br d, J = 8.75 Hz, 2 H), 7.54 (s, 1 H), 7.60–7.36 (m, 6 H), 6.89 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 2.53 (sext, J = 6.25 Hz, 1 H), 1.97–1.46 (m, 6 H), 1.22 (d, J = 6.25 Hz, 3 H); IR (KBr, cm^{-1}) 1704; MS m/z 375 (M^+). Anal. ($C_{24}H_{25}NO_3$) C, H, N, O.

2,2-Dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (6e) was prepared from methyl 6-bromo-2,2-dimethylhexanoate[12] and **3a** (44.7%, over two steps): mp 109–111 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 8.75 Hz, 2 H), 7.82–7.30 (m, 9 H), 6.88 (br s, 1 H), 4.47 (t, J = 6.25 Hz, 2 H), 2.05–1.40 (m, 6 H), 1.22 (s, 6 H); IR (KBr, cm^{-1}) 1699; MS m/z 389 (M^+). Anal. ($C_{25}H_{27}NO_3$) C, H, N, O.

7-[(4,6-Diphenyl-2-pyridyl)oxy]heptanoic acid (6f) was prepared from ethyl 7-bromo-heptanoate and **3a** (58.4%, over two steps): mp 104–106 °C; NMR ($CDCl_3$) δ 8.11 (br d, J = 8.75 Hz, 2 H), 7.70 (br d, J = 8.75 Hz, 2 H), 7.57 (br s, 1 H), 7.62–7.37 (m, 6 H), 6.90 (br s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 2.40 (t, J = 7.5 Hz, 2 H), 1.95–1.35 (m, 6 H); IR (KBr, cm^{-1}) 1712; MS m/z 375 (M^+). Anal. ($C_{24}H_{25}NO_3$) C, H, N, O.

2,2-Dimethyl-7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoic acid (6g) was prepared from methyl 7-bromo-2,2-dimethylheptanoate[13] and **3a**, using DMF (110 °C) in the first step in place of toluene (41.5%, over two steps): mp 98–99 °C; NMR ($CDCl_3$) δ 8.12 (br d, J = 8.75 Hz, 2 H), 7.71 (br d, J = 7.5 Hz, 2 H), 7.59 (br s, 1 H), 7.60–7.36 (m, 6 H), 6.91 (br s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 1.86 (qui, J = 7.5 Hz, 2 H), 1.66–1.24 (m, 6 H), 1.21 (s, 6 H); IR (KBr, cm^{-1}) 1696; MS m/z 403 (M^+). Anal. ($C_{26}H_{29}NO_3$) C, H, N, O.

2,2-Dimethyl-8-[(4,6-diphenyl-2-pyridyl)oxy]octanoic acid (6h) was prepared from methyl 8-bromo-2,2-dimethyloctanoate[13] and **3a**, using DMF (110 °C) in the first step in place of toluene

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(16%, over two steps): mp 84 °C; NMR ($CDCl_3$) δ 8.06 (br d, J = 8.75 Hz, 2 H), 7.67 (br d, J = 8.75 Hz, 2 H), 7.67 (br d, J = 8.75 Hz, 2 H), 7.54 (br s, 1 H), 7.56–7.32 (m, 6 H), 6.87 (br s, 1 H), 4.46 (t, J = 6.25 Hz, 2 H), 1.84 (qui, J = 7.5 Hz, 2 H), 1.65–1.20 (m, 8 H), 1.19 (s, 6 H); IR (KBr, cm^{-1}) 1712; MS m/z 417 (M^+). Anal. ($C_{27}H_{31}NO_3$) C, H, N, O.

2-Methyl-6-[[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6i) was prepared from ethyl 6-bromo-2-metylhexanoate[12] and **3b**, using DMF (110 °C) in the first step in place of toluene (51.1%, over two steps): mp 86 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.63 (d, J = 8.75 Hz, 2 H), 7.55–7.35 (m, 4 H), 7.00 (d, J = 8.75 Hz, 2 H), 6.87 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 3.88 (s, 3 H), 2.53 (sext, J = 7.5 Hz, 1 H), 1.98–1.48 (m, 6 H), 1.22 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1705; MS m/z 405 (M^+). Anal. ($C_{25}H_{27}NO_4$) C, H, N, O.

6-[[4-(4-Chlorophenyl)-6-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6j) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3c**, using DMF (110 °C) in the first step in place of toluene (28.4%, over two steps): mp 97–98 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.59 (d, J = 8.75 Hz, 2 H), 7.53–7.35 (m, 6 H), 6.83 (br s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 2.52 (sext, J = 6.25 Hz, 1 H), 1.95–1.45 (m, 6 H), 1.23 (d, J = 6.25 Hz, 3 H); IR (KBr, cm^{-1}) 1700.5; MS m/z 409 (M^+). Anal. ($C_{24}H_{24}ClNO_3$) C, H, N, Cl, O.

2-Methyl-6-[[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6k) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3d**, using DMF (110 °C) in the first step in place of toluene (33.6%, over two steps): mp 83–85 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.62–7.26 (m, 8 H), 6.87 (s, 1 H), 4.47 (t, J = 6.25 Hz, 2 H), 2.52 (q, J = 7.5 Hz, 1 H), 2.42 (s, 3 H), 2.00–1.40 (m, 6 H), 1.22 (d, J = 6.5 Hz, 3 H); IR (KBr, cm^{-1}) 1702; MS m/z 389 (M^+). Anal. ($C_{25}H_{27}NO_3$) C, H, N, O.

6-[[4-[4-(Trifluoromethyl)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic acid (6l) was prepared from ethyl 6-bromohexanoate and **3e**, using DMF (110 °C) in the first step in place of toluene (49.6%, over two steps): mp 90–91 °C; NMR ($CDCl_3$) δ 8.08 (br d, J = 8.75 Hz, 2 H), 7.88–7.70 (m, 4 H), 7.60–7.37 (m, 4 H), 6.86 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.99–1.48 (m, 6 H); IR (KBr, cm^{-1}) 1715; MS m/z 429 (M^+). Anal. ($C_{24}H_{22}F_3NO_3$) C, H, F, N.

6-[[4-(4-Nitrophenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6m) was prepared from ethyl 6-bromohexanoate and **3f**, using DMF (110 °C) in the first step in place of toluene (26.8%, over two steps): mp 118–119 °C; NMR ($CDCl_3$) δ 8.375 (d, J = 8.75 Hz, 2 H), 8.12 (br d, J = 8.75 Hz, 2 H), 7.93 (d, J = 8.75 Hz, 2 H), 7.64 (br s, 1 H), 7.56–7.37 (m, 3 H), 6.96 (br s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 2.37 (t, J = 7.5 Hz, 2 H), 1.97–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1708; MS m/z 406 (M^+). Anal. ($C_{23}H_{22}N_2O_5$) C, H, N, O.

6-[[4-[4-(Dimethylamino)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic acid (6s) was prepared from ethyl 6-bromohexanoate and **3g**, using DMF (110 °C) in the first step in place of toluene (40%, over two steps): mp 159 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.70–7.30 (m, 6 H), 6.92–6.77 (m, 3 H), 4.48 (t, J = 6.25 Hz, 2 H), 3.03 (s, 6 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.00–1.48 (m, 6 H); IR (KBr, cm^{-1}) 1705; MS m/z 404 (M^+). Anal. ($C_{25}H_{28}N_2O_3$) H, N, O; C: calcd, 74.23; found, 73.7.

6-[[4-(3-Methoxyphenyl)-6-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6u) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3h**, using DMF (110 °C) in the first step in place of toluene (45.6%, over two steps): mp 103 °C; NMR ($CDCl_3$) δ 8.08 (br d, J = 7.5 Hz, 2 H), 7.55–7.30 (m, 5 H), 7.27–7.12 (m, 2 H), 6.96 (br d, J = 8.75 Hz, 1 H), 6.87 (s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 3.85 (s, 3 H), 2.50 (q, J = 7.5 Hz, 1 H), 1.95–1.42 (m, 6 H), 1.18 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1698; MS m/z 405 (M^+). Anal. ($C_{25}H_{27}NO_4$) C, H, N, O.

6-[[4-(3,4-Dimethoxyphenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6v) was prepared from ethyl 6-bromohexanoate and **3i** using DMF (110 °C) in the first step in place of toluene (48.4%, over two steps): mp 103 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.55–7.37 (m, 4 H), 7.25 (br d, J = 7.5 Hz, 1 H), 7.17 (br s, 1 H), 6.95 (d, J = 8.75 Hz, 1 H), 6.83 (br s, 1 H), 4.47 (t, J = 6.25 Hz, 2 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.97–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1717; MS m/z 421 (M^+). Anal. ($C_{25}H_{27}NO_5$) C, H, N, O.

6-[[4-(3,5-Dimethoxyphenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6w) was prepared from ethyl 6-bromohexanoate and **3j**, using DMF (110 °C) in the first step in place of toluene (48.4%, over two steps): mp 99 °C; NMR ($CDCl_3$) δ 8.06 (br d, J = 7.5 Hz, 2 H), 7.57–7.32 (m, 4 H), 6.85 (br s, 1 H), 6.78 (br s, 2 H), 6.53 (t, J = 5 Hz, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 3.87 (s, 6 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.00–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1709; MS m/z 421 (M^+). Anal. ($C_{25}H_{27}NO_5$) C, H, N, O.

6-[[4-[3,4-(Methylenedioxy)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic acid (6x) was prepared from ethyl 6-bromohexanoate and **3k**, using DMF (110 °C) in the first step in place of toluene (56.1%, over two steps): mp 124–126 °C; NMR ($CDCl_3$) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.54–7.35 (m, 4 H), 7.22–7.10 (m, 2 H), 6.91 (d, J = 8.75 Hz, 1 H), 6.81 (br s, 1 H), 6.03 (s, 2 H), 4.47 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.97–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1705; MS m/z 405 (M^+). Anal. ($C_{24}H_{23}NO_5$) H, N, O; C: calcd, 71.10; found, 71.6.

6-[[4-[3,4-(Methylenedioxy)phenyl]-6-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6y) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3k**, using DMF (110 °C) in the first step in place of toluene (44.9%, over two steps): mp 123–125 °C; NMR ($CDCl_3$) δ 8.03 (br d, J = 7.5 Hz, 2 H), 7.51–7.32 (m, 4 H), 7.20–7.10 (m, 2 H), 6.90 (d, J = 7.5 Hz, 1 H), 6.78 (s, 1 H), 6.02 (s, 2 H), 4.46 (t, J = 6.25 Hz, 2 H), 2.52 (q, J = 7.5 Hz, 1 H), 1.95–1.42 (m, 6 H), 1.22 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1702; MS m/z 419 (M^+). Anal. ($C_{25}H_{25}NO_5$) C, H, N, O.

6-[[4-[3,4-(Methylenedioxy)phenyl]-6-phenyl-2-pyridyl]oxy]-2,2-dimethylhexanoic acid (6z) was prepared from methyl 6-bromo-2,2-dimethylhexanoate[12] and **3k**, using DMF (110 °C) in the first step in place of toluene (51.1%, over two steps): mp 166–167 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.55–7.38 (m, 4 H), 7.22–7.10 (m, 2 H), 6.92 (d, J = 7.5 Hz, 1 H), 6.78 (s, 1 H), 6.03 (s, 2 H), 4.45 (t, J = 6.25 Hz, 2 H), 1.95–1.40 (m, 6 H), 1.20 (s, 6 H); IR (KBr, cm^{-1}) 1709; MS m/z 433 (M^+). Anal. ($C_{26}H_{27}NO_5$) C, H, N, O.

6-[[4-(3-Chlorophenyl)-6-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6aa) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3l**, using DMF (110 °C) in the first step in place of toluene (32.6%, over two steps): mp 55–57 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.62 (br s, 1 H), 7.55–7.30 (m, 7 H), 6.83 (br s, 1 H), 4.47 (t, J = 6.25 Hz, 2 H), 2.51 (sext, J = 6.25 Hz, 1 H), 1.95–1.45 (m, 6 H), 1.20 (d, J = 6.25 Hz, 3 H); IR (KBr, cm^{-1}) 1705; MS m/z 409 (M^+). Anal. ($C_{24}H_{24}ClNO_3$) C, H, N, O.

6-[[4-(2-Chlorophenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6ab) was prepared from ethyl 6-bromohexanoate and **3m**, using DMF (110 °C) in the first step in place of toluene (44.2%, over two steps): mp 73 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.57–7.30 (m, 8 H), 6.75 (s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.00–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1716; MS m/z 395 (M^+). Anal. ($C_{23}H_{22}ClNO_3$) C, H, Cl, N, O.

6-[[4-(2-Fluorophenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6ac) was prepared from ethyl 6-bromohexanoate and **3n**, using DMF (110 °C) in the first step in place of toluene (50.9%, over two steps): mp 100–101 °C; NMR ($CDCl_3$) δ 8.09 (br d, J = 7.5 Hz, 2 H), 7.61–7.10 (m, 8 H), 6.87 (br s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.98–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1717; MS m/z 379 (M^+). Anal. ($C_{23}H_{22}FNO_3$) C, H, F, N.

6-[[6-(4-Fluorophenyl)-4-phenyl-2-pyridyl]oxy]hexanoic acid (6ad) was prepared from ethyl 6-bromohexanoate and **3o**, using DMF (110 °C) in the first step in place of toluene (56.7%, over two steps): mp 94–95 °C; NMR ($CDCl_3$) δ 8.15–7.99 (m, 2 H), 7.74–7.61 (m, 2 H), 7.59–7.37 (m, 4 H), 7.16 (t, J = 8.75 Hz, 2 H), 6.90 (s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.97–1.47 (m, 6 H). IR (KBr, cm^{-1}) 1717; MS m/z 379 (M^+). Anal. ($C_{23}H_{22}FNO_3$) C, H, F, N.

6-[[6-(4-Methylphenyl)-4-phenyl-2-pyridyl]oxy]hexanoic acid (6ae) was prepared from ethyl 6-bromohexanoate and **3p** (20.9%, over two steps): mp 76–78 °C; NMR ($CDCl_3$) δ 7.99 (d, J = 8.75 Hz, 2 H), 7.75–7.40 (m, 6 H), 7.30 (d, J = 8.75 Hz, 2 H), 6.88 (s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.42 (s, 3 H), 2.00–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1717; MS m/z 375 (M^+). Anal. ($C_{24}H_{25}NO_3$) H, N, O; C: calcd, 76.77; found, 76.1.

6-[[6-[4-(Trifluoromethyl)phenyl]-4-phenyl-2-pyridyl]oxy]hexanoic acid (6af) was prepared from ethyl 6-bromohexanoate and **3q**, using DMF (110 °C) in the first step in place of toluene (37%, over two steps): mp 113–114 °C; NMR ($CDCl_3$) δ 8.22 (d, J = 8.75 Hz, 2 H), 7.89–7.45 (m, 8 H), 6.97 (s, 1 H), 4.50 (t, J = 6.25 Hz, 2 H), 2.44 (t, J = 7.5 Hz, 2 H), 1.99–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1717; MS m/z 429 (M^+). Anal. ($C_{24}H_{22}F_3NO_3$) C, H, F, N.

6-[[6-(4-Methoxyphenyl)-4-phenyl-2-pyridyl]oxy]hexanoic acid (6ag) was prepared from ethyl 6-bromohexanoate and **3r** (50%, over two steps): mp 88–90 °C; NMR ($CDCl_3$) δ 8.07 (d, J = 8.75 Hz, 2 H), 7.70 (br d, J = 8.75 Hz, 2 H), 7.60–7.37 (m, 4 H), 7.03 (d, J = 8.75 Hz, 2 H), 6.85 (br s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 3.82 (s, 3 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.10–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1716; MS m/z 391 (M^+). Anal. ($C_{24}H_{25}NO_4$) C, H, N, O.

6-[[6-(3-Methoxyphenyl)-4-phenyl-2-pyridyl]oxy]hexanoic acid (6ah) was prepared from ethyl 6-bromohexanoate and **3s**, using DMF (110 °C) in the first step in place of toluene (59%, over two steps): mp 91 °C; NMR ($CDCl_3$) δ 7.76–7.61 (m, 4 H), 7.59–7.31 (m, 5 H), 6.96 (br d, J = 8.75 Hz, 1 H), 6.89 (br s, 1 H), 4.49 (t, J = 6.25 Hz, 2 H), 3.90 (s, 3 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.98–1.48 (m, 6 H); IR (KBr, cm^{-1}) 1732; MS m/z 391 (M^+). Anal. ($C_{24}H_{25}NO_4$) C, H, N, O.

6-[[6-(2-Fluorophenyl)-4-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6ai) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3t**, using DMF (110 °C) in the first step in place of toluene (42.8%, over two steps): mp 87 °C; NMR ($CDCl_3$) δ 8.09 (br t, J = 7.50 Hz, 1 H), 7.75–7.60 (m, 3 H), 7.52–7.10 (m, 6 H), 6.91 (s, 1 H), 4.43 (t, J = 6.25 Hz, 2 H), 2.51 (q, J = 7.5 Hz, 1 H), 1.95–1.40 (m, 6 H), 1.22 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1730; MS m/z 393 (M^+). Anal. ($C_{24}H_{24}FNO_3$) C, H, F, N.

6-[[6-(2-Chlorophenyl)-4-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6aj) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3u**, using DMF (110 °C) in the first step in place of toluene (32%, over two steps): mp 89 °C; NMR ($CDCl_3$) δ 7.74–7.63 (m, 3 H), 7.55–7.20 (m, 7 H), 6.90 (s, 1 H), 4.40 (t, J = 6.25 Hz, 2 H), 2.50 (sext, J = 7.5 Hz, 1 H), 1.98–1.42 (m, 6 H), 1.30 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1702; MS m/z 409 (M^+). Anal. ($C_{24}H_{24}ClNO_3$) H, N, O; C: calcd, 70.32; found, 69.5.

6-[[6-(2-Chlorophenyl)-4-[3,4-(methylenedioxy)phenyl]-2-pyridyl]oxy]-2-methylhexanoic acid (6ak) was prepared from ethyl 6-bromo-2-methylhexanoate[12] and **3v**, using DMF (110 °C) in the first step in place of toluene (27%, over two steps): mp 109 °C; NMR ($CDCl_3$) δ 7.72 (br d, J = 7.5 Hz, 1 H), 7.56 (br d, J = 7.5 Hz, 1 H), 7.49–7.33 (m, 3 H), 7.30–7.14 (m, 2 H), 6.98 (d, J = 7.5 Hz, 1 H), 6.94 (br s, 1 H), 6.08 (s, 2 H), 4.46 (t, J = 6.25 Hz, 2 H), 2.58 (sext, J = 7.5 Hz, 1 H), 1.97–1.75 (m, 3 H), 1.68–1.52 (m, 3 H), 1.26 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1702; MS m/z 453 (M^+). Anal. ($C_{25}H_{24}ClNO_5$) C, H, Cl, N.

Route B. General Procedure. 6-[(4,6-Diphenyl-2-pyridyl)oxy]hexanenitrile (8a) was prepared using the O-alkylation procedure described in the route A, but starting from **3a** and 6-bromohexanenitrile,[14] and isolated as a white solid (75%): mp 65 °C; NMR ($CDCl_3$) δ 8.08 (br d, J = 7.5 Hz, 2 H), 7.69 (br d, J = 7.5 Hz, 2 H), 7.57 (br s, 1 H), 7.55–7.40 (m, 6 H), 6.90 (br s, 1 H), 4.51 (t, J = 6.25 Hz, 2 H), 2.40 (t, J = 7.5 Hz, 2 H), 2.00–1.55 (m, 6 H); MS m/z 342 (M^+). Anal. ($C_{23}H_{22}N_2O$) C, H, N, O.

2,2-Dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanenitrile (8b) was prepared by the same procedure but starting from **3a** and 6-bromo-2,2-dimethylhexanenitrile[14] (71%): mp 71 °C; NMR ($CDCl_3$) δ 8.09 (br d, J = 8.75 Hz, 2 H), 7.75–7.38 (m, 9 H), 6.90 (s, 1 H), 4.52 (t, J = 6.25 Hz, 2 H), 2.00–1.50 (m, 6 H), 1.35 (s, 6 H); MS m/z 370 (M^+).

5-[5-[(4,6-Diphenyl-2-pyridyl)oxy]pentyl]-1*H*-tetrazole (9a). To a solution of **8a** (5 g, 14.6 mmol) in DMF (50 mL) was added sodium azide (3.8 g, 58.5 mmol) and ammonium chloride (3.1 g, 58 mmol). The reaction mixture was heated for 96 h to 120 °C. The reaction mixture was taken up in water and extracted twice with ethyl acetate. The combined organic extracts was washed with water, 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 **9a** was obtained as a white solid (1.84 g, 33%): mp 144–145 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 8.06 (br d, J = 8.75 Hz, 2 H), 7.65 (br d, J = 7.5 Hz, 2 H), 7.60–7.35 (m, 7 H), 6.90 (s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 2.98 (t, J = 7.5 Hz, 2 H), 2.05–1.80 (m, 4 H), 1.70–1.50 (m, 2 H); MS m/z 385 (M^+). Anal. ($C_{23}H_{23}N_5O$) C, H, N, O.

5-[1,1-Dimethyl-5-[(4,6-diphenyl-2-pyridyl)oxy]pentyl]-1*H*-tetrazole (9b) was prepared by the same procedure but starting from **8b** (18%): mp 160–162 °C; NMR ($CDCl_3$) δ 8.03 (br d, J = 7.5 Hz, 2 H), 7.67 (br d, J = 7.5 Hz, 2 H), 7.56 (s, 1 H), 7.55–7.40 (m, 6 H), 6.90 (s, 1 H), 4.42 (t, J = 6.25 Hz, 2 H), 1.95–1.70 (m, 4 H), 1.54–1.27 (m, 2 H), 1.45 (s, 6 H); MS m/z 413 (M^+). Anal. ($C_{25}H_{27}N_5O$) C, H, N, O.

Methyl 6-[(4,6-Diphenyl-2-pyridyl)oxy]hexanoate (5c). To a solution of **6c** (0.5 g, 1.4 mmol) in methanol (15 mL) was added H_2SO_4 (0.1 mL, concentrated). The reaction mixture was stirred for 1 h at room temperature. After concentration to dryness, the residue was taken up in CH_2Cl_2 (50 mL) and the organic layer was then washed with H_2O, dried over Na_2SO_4, and concentrated. The solid residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 9/1), yielding pure **5c** as a white solid (0.38 g, 73%): mp 57–58 °C; NMR ($CDCl_3$) δ 8.10 (br d, J = 7.5 Hz, 2 H), 7.70 (br d, J = 7.5 Hz, 2 H), 7.61–7.36 (m, 7 H), 6.90 (br s, 1 H), 4.48 (t, J = 6.25 Hz, 2 H), 3.675 (s, 3 H), 2.37 (t, J = 7.5 Hz, 2 H), 1.98–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1728; MS m/z 375 (M^+). Anal. ($C_{24}H_{25}NO_3$) C, H, N, O.

Ethyl 6-[[4-(4-Aminophenyl)-6-phenyl-2-pyridyl]oxy]hexanoate (5n). A mixture of ethyl 6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy]hexanoate (**5m**; 30 g, 69.1 mmol) (see preparation of **6m** by the route A (67%), mp = 75–76 °C), tin(II) chloride (66 g, 346 mmol) in ethanol (500 mL) was heated for 2 h at reflux. The solvent was then removed under vacuo. The resulting residue was taken up in H_2O (300 mL), and the pH of the aqueous phase was adjusted to 11 with 6 N NaOH. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated. The oily residue was crystallized from hexane (300 mL) giving **5n** as a pale yellow solid: mp 62–64 °C; NMR ($CDCl_3$) δ 8.06 (br d, J = 7.5 Hz, 2 H), 7.56–7.32 (m, 6 H), 6.80 (br s, 1 H), 6.78 (d, J = 7.5 Hz, 2 H), 4.44 (t, J = 6.25 Hz, 2 H), 4.12 (q, J = 7.5 Hz, 2 H), 3.64 (br s, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 1.94–1.46 (m, 6 H), 1.24 (t, J = 7.5 Hz, 3 H); MS m/z 404 (M^+).

Ethyl 6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy]-2-methylhexanoate (11a) was prepared by the same procedure but starting from **10a** (prepared by the route A, starting from **3f** and ethyl 6-bromo-2-methylhexanoate[12] (65%)) to give **11a** (100%) as a yellow oil, used without further purification in the next step.

Methyl 6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy]-2,2-dimethylhexanoate (11b) was prepared by the same procedure but starting from **10b** (prepared by the route A, starting from **3f** and methyl 6-bromo-2,2-dimethylhexanoate[12] (67%), mp = 90–91 °C) to give **11b** (100%) as a yellow oil, used without further purification in the next step.

6-[[4-(4-Aminophenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid (6n) was obtained from **5n**, by using the hydrolysis procedure described in the route A, as a pale yellow solid (66.1%): mp 131–133 °C; NMR ($CDCl_3$ + CD_3OD) δ 8.05 (br d, J = 8.75 Hz, 2 H), 7.62–7.34 (m, 6 H), 6.84 (s, 1 H), 6.82 (d, J = 7.5 Hz, 2 H), 4.44 (t, J = 6.25 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.95–1.47 (m, 6 H); IR (KBr, cm^{-1}) 1706; MS m/z 376 (M^+). Anal. ($C_{23}H_{24}N_2O_3$) C, H, N, O.

6-[[4-(4-Aminophenyl)-6-phenyl-2-pyridyl]oxy]-2-methylhexanoic acid (6o) was obtained from **11a**, by using the hydrolysis procedure described in the route A, as a pale yellow solid (17%): mp 134–136 °C; NMR (DMSO-d_6) δ 12.05 (br s, 1 H), 8.15 (br d, J = 7.5 Hz, 2 H), 7.72 (s, 1 H), 7.62 (d, J = 8.75 Hz, 2 H), 7.55–7.35 (m, 3 H), 6.90 (s, 1 H), 6.65 (d, J = 8.75 Hz, 2 H), 5.52 (br s, 2 H), 4.40 (t, J = 6.25 Hz, 2 H), 2.37 (q, J = 7.5 z, 1 H), 1.90–1.35 (m, 6 H), 1.07 (d, J = 7.5 Hz, 3 H); IR (KBr, cm^{-1}) 1703; MS m/z 390 (M^+). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N, O.

(14) Larcheveque, M.; Debal, A.; Cuvigny, Th. New Preparation of ω-Halonitriles. Application to the Synthesis of δ-1-Piperidines. *Bull. Soc. Chim. Fr.* **1974**, 7–8, 1710–1714.

6-[[4-(4-Aminophenyl)-6-phenyl-2-pyridyl]oxy]-2,2-dimethylhexanoic acid (6p) was obtained from 11b, by using the hydrolysis procedure described in the Route A, as a pale yellow solid (40.5%): mp 123–125 °C; NMR ($CDCl_3$) δ 8.03 (br d, J = 7.5 Hz, 2 H), 7.55–7.30 (m, 6 H), 6.81 (br s, 1 H), 6.74 (d, J = 8.75 Hz, 2 H), 4.45 (t, J = 6.25 Hz, 2 H), 1.95–1.40 (m, 6 H), 1.22 (s, 6 H); IR (KBr, cm^{-1}) 1699; MS m/z 404 (M^+). Anal. ($C_{25}H_{28}N_2O_3$) C, H, N, O.

6-[[4-[4-(Methylamino)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic Acid (6q). A mixture of **5n** (3 g, 7.4 mmol) and TFA (25 drops) in ethyl orthoformate (5.5 mL) was refluxed for 17 h. The reaction mixture was then concentrated to dryness. The resulting oily residue (3.5 g) was taken up in ethanol (40 mL). To the resulting suspension, cooled to 5 °C, was added portionwise sodium borohydride (1.1 g, 28.9 mmol). The reaction mixture was refluxed for 1 h and poured into cooled H_2O. The aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The oily residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 7/3), giving the ethyl ester of the title compound as a yellow oil (0.93 g, 46.5%). The hydrolysis of the ester, following the procedure described in the route A, gave pure **6q** as a pale yellow solid (0.44 g, 50.7%): mp 115–117 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.65–7.30 (m, 6 H), 6.83 (br s, 1 H), 6.72 (d, J = 8.75 Hz, 2 H), 4.48 (t, J = 6.25 Hz, 2 H), 2.90 (s, 3 H), 2.42 (t, J = 7.5 Hz, 2 H), 2.00–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1708.5; MS m/z 390 (M^+). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N, O.

6-[[4-[4-(Isopropylamino)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic Acid (6r). To a cooled (15 °C) solution of **5n** (3 g, 7.4 mmol) and acetone (0.54 mL, 7.45 mmol) in acetic acid (45 mL) was added portionwise sodium borohydride (1.14 g, 3 mmol). During the addition, the reaction temperature was kept below 22 °C. The reaction mixture was stirred at room temperature for 4 h and then dropped into H_2O. The aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The oily residue was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate, 9/1), giving the ethyl ester of the title compound as a yellow oil (2.3 g, 69.2%). The hydrolysis of the ester, following the procedure described in the route A with KOH (0.51 g, 1.8 mmol), gave pure **6r** as a pale yellow solid (0.8 g, 31%): mp 100–102 °C; NMR ($CDCl_3$) δ 8.05 (br d, J = 7.5 Hz, 2 H), 7.62–7.32 (m, 6 H), 6.81 (br s, 1 H), 6.68 (d, J = 7.5 Hz, 2 H), 4.46 (t, J = 6.25 Hz, 2 H), 3.69 (qui, J = 6.25 Hz, 1 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.97–1.47 (m, 6 H), 1.26 (d, J = 6.25 Hz, 6 H); IR (KBr, cm^{-1}) 1701; MS m/z 418 (M^+). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N, O.

6-[[4-[4-(Trifluoroacetamido)phenyl]-6-phenyl-2-pyridyl]oxy]hexanoic Acid (6t). To a cold (0 °C) solution of **6n** (1 g, 2.65 mmol) in THF (15 mL) was slowly added trifluoroacetic anhydride (0.5 mL, 3.5 mmol). The reaction mixture was stirred for 1 h at room temperature and then poured into ice. THF was then evaporated under reduced pressure, and the remaining aqueous layer was then extracted with chloroform. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The solid residue was purified by chromatography on silica gel (eluent: hexane/ethyl acetate, 4/6) and then by recrystallization from toluene, yielding **6t** as a pale yellow solid (0.42 g, 33.5%): mp 178–180 °C; NMR (CD_3OD) δ 8.07 (br d, J = 7.5 Hz, 2 H), 7.77 (s, 4 H), 7.63 (s, 1 H), 7.50–7.30 (m, 3 H), 6.90 (s, 1 H), 4.43 (t, J = 6.25 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.95–1.45 (m, 6 H); IR (KBr, cm^{-1}) 1705; MS m/z 472 (M^+). Anal. ($C_{25}H_{23}F_3N_2O_4$) C, H, F, N.

6-[(4,6-Diphenyl-2-pyridyl)oxy]hexanamide (10). Dry HCl was bubbled for 4 h in a solution of **8a** (2.5 g, 7.3 mmol) in formic acid (1.1 mL, 98–100%). The reaction mixture was then taken up in ethyl acetate (100 mL). The organic phase was washed with NaOH (1 N), dried over Na_2SO_4, and evaporated. The solid residue was purified by recrystallization from toluene, yielding **10** as a white solid (0.51 g, 20%): mp 118–120 °C; NMR ($CDCl_3$) δ 8.10 (br d, J = 7.5 Hz, 2 H), 7.70 (br d, J = 8.75 Hz, 2 H), 7.60–7.40 (m, 7 H), 6.92 (s, 1 H), 5.60 (br s, 2 H), 4.52 (t, J = 6.25 Hz, 2 H), 2.27 (t, J = 7.5 Hz, 2 H), 2.05–1.40 (m, 6 H); MS m/z 360 (M^+). Anal. ($C_{23}H_{24}N_2O_2$) H, N, O; C: calcd, 76.64; found, 76.0.

Biological Methods. Binding Assay Studies. Tritiated LTB_4 preparations with a specific activity of 173 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. The effectiveness of compounds to inhibit binding of [^{3}H]LTB_4 was measured by using an adaptation of the radioligand binding assay[2] developed by Cheng et al.[15] 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 compounds **6p** and **6y** when IC_{50} values were determined three times on the same preparation. The mean IC_{50} and standard error for compound **6p** were 5.5 and 1.15, respectively, and for compound **6y** 3.3 and 1.0, 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 **6p** and **6y** (n = 3, 6.6 ± 1.6 and 4.2 ± 1.3, respectively).

Binding on Human PMNs. Peripheral 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[2] of the radioligand binding assay developed by A. H. Lin et al.[16] 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 **6u**. At 100 nM, the mean percent inhibition and standard error for compound **6u** were 93.7 and 1.5, respectively. At 30 nM, the corresponding values were 88.0 and 1.0. At 3 nM, the corresponding values were 41.7 and 6.5. In a few cases where compounds were tested on more than one cell preparation, an estimate of the precision can be obtained by the mean IC_{50} and standard error obtained for compound **6p** and **6y** (n = 4, 9.5 ± 3.4 and n = 5, 6.6 ± 1.1, respectively).

Elastase Release Assay. Peripheral blood PMNs from normal subjects were prepared according to A. Böyum et al.[17] Elastase release was measured as change in the relative fluorescence of the reaction mixtue over time, by using an adaptation of the PAF-induced elastase release assay developed by O. Marquis et al.[18] Fluorescence resulted from 7-amino-4-methylcoumarin, liberated after the elastase cleavage of a specific substrate (*N*-methoxysuccinyl-Ala-Ala-pro-Val-7-amino-4-methylcoumarin), the intensity of which was quantified by using 370 nm as the excitatory wavelength and by monitoring the emission at 460 nm with a fluorimeter (Perkin-Elmer LS5). PMNs (0.75 mL of 2.5 × 10^5 cells/mL) and cytochalasin B (0.75 mL at 20 μg/mL) were incubated in PBS supplemented with 0.25% BSA (w/v), at 37 °C, in plastic tubes and in the presence or absence of increasing concentrations of the tested compounds. After a 5-min period, exocytosis was induced by addition of LTB_4 (3 nM). The mixture was centrifuged (2300g, 10 min) after 2 min of incubation. The supernatant was transferred into clean quartz tubes. The fluorescence measurements were immediately per-

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formed after addition of an excess of substrate (0.1 mM final concentration). The fluorescence was measured each 0.5 min during 3.5 min. The rate of the enzymatic reaction was obtained by linear regression from the six fluorescence measurements. The percentage of inhibition of elastase release was calculated from the rate of the enzymatic reaction with or without inhibitor. The IC_{50} values were calculated by linear regression analysis. Each value is the mean of at least three replicates. The inhibitory activity of most compounds was evaluated on only one cell preparation, the more potent compounds being evaluated at least on two or three different cell preparations. An estimate of the precision of the measurements can be obtained from the inhibition observed with compounds **6d**. At 100 nM, the mean percent inhibition and standard error for compound **6d** were 90.9 and 1.3, respectively. At 30 nM, the corresponding values were 55.8 and 4.2. At 10 nM, the corresponding values were 34.1 and 2.4.

LTB_4-Induced Leukopenia in the Rabbit. The antagonistic activity of compounds was studied on LTB_4-induced leukopenia in the rabbit in a model described by W. J. Sweatman et al.,[19] with slight modifications. New Zealand alkino rabbits were locally anesthetized with 0.5 mL of xylocaine. A femoral artery and an ear marginal vein were canulated with heparinized catheters. Blood sampling was taken from the femoral artery. Cell counting was carried out with a Coulter counter. After 30–60 min, the number of leukocytes reached an equilibrium and LTB_4 (1 μg/kg) was injected into the ear vein, resulting, in the absence of an antagonist, in about 50% neutropenia at 0.5 min post injection. The tested compound was administered either immediately into the ear vein or was given orally 1 h prior to LTB_4. White cells were counted at 0.5, 1, 2, 5, and 10 min after LTB_4 injection. Each animal served as its own control and inhibition was calculated based upon AUC relative to the control values. EC_{50} values were derived by graphical analysis.

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