Trisubstituted Pyridine Leukotriene B_4 Receptor Antagonists: Synthesis and Structure-Activity Relationships

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A series of trisubstituted pyridines have been prepared that exhibit *in vitro* leukotriene B_4 (LTB_4, 1) receptor antagonist activity. Previous disubstituted pyridines from these labs showed high affinity for the LTB_4 receptor but demonstrated agonist activity in functional assays (e.g., **2**, K_i = 1 nM). Compound **4**, the initial lead compound of this new series, showed only modest affinity by comparison (K_i = 282 nM); however, **4** was a receptor antagonist with no demonstrable agonist activity up to 10 μM. Subsequent modifications of the lipid tail and aryl head group region led to the discovery of aniline **50** (SB 201146). This compound, also free of agonist activity, possesses high affinity for the LTB_4 receptor (K_i = 4.7 nM).

We have designed and synthesized compounds that demonstrate high affinity for LTB_4 receptors localized on the membranes of inflammatory cells.[1] These compounds were designed on the basis of a specific conformation of LTB_4 (**1**, Figure 1) and as such exhibited many of the properties of LTB_4. The compounds had receptor affinities approaching that of the natural ligand but also demonstrated LTB_4 receptor agonist activity in the functional assay. Only one analog in the study, disubstituted pyridine **3** (Figure 1), was identified that did not exhibit a significant agonist response. This loss in agonist activity, however, was accompanied by a substantial reduction in LTB_4 receptor affinity. In this report we describe the SAR for a large group of trisubstituted pyridine analogs that both lack agonist activity and have high affinity for the LTB_4 receptor. These compounds may be useful for treating inflammatory diseases where LTB_4 is proposed to be a major proinflammatory mediator.

Chemistry

The trisubstituted pyridine analogs of this study were prepared as outlined in Schemes I-VII. Scheme I illustrates the synthesis of the lipid tail fragments. For the (substituted phenyl)octyl tails, exemplified by (*p*-methoxyphenyl)octyl, the starting material was 3-octyn-1-ol (**5**). This was rearranged to the terminal acetylene **6** via potassium aminopropylamide (KAPA)[2] and the primary alcohol protected as the *tert*-butyldiphenylsilyl ether **7**. The desired aryl group was then attached utilizing a $(Ph_3P)_2PdCl_2$ catalyzed coupling reaction to give **8**. This coupling was performed using either the aryl iodides[3] or the corresponding aryl triflates[4] derived from the appropriate phenol. Hydrogenation (5% Pd-C) of the alkyne and removal of the silyl protecting group (n-Bu_4NF) afforded alcohol **9**. Conversion of the primary alcohol to the corresponding iodide (Ph_3P, I_2, imidazole) provided **10**.[5] The preparation of the (substituted phenyl)octyl tails required for compounds **60-62** was accomplished using an analogous sequence. The (*p*-methoxyphenyl)hexyl tail was prepared in a similar fashion starting from the commercially available 5-hexyn-1-ol. The phenyloctyl bromide used in the preparation of compounds **58** and **59** was prepared according to published procedures.[6]

The synthetic route used in the preparation of compounds **4**, **20**, and **41** is outlined in Scheme II. 2,6-Lutidine-α^2,3-diol (**11**) was oxidized to the corresponding aryl aldehyde **12** using MnO_2. The phenolic hydroxyl group was alkylated with the desired lipid tail fragment and the aldehyde converted to hydrazone **13**. The oxidation-alkylation sequence may be reversed; however, increased reaction times are required. Oxidation of **13** with nickel peroxide gave triazolopyridine **14**.[7] Treatment of **14** with LDA followed by condensation with 3-iodobenzaldehyde produced alcohol **15**. Palladium-catalyzed carbonylation of the iodide ($Pd(OAc)_2$, CO, MeOH, DMSO) to the methyl benzoate **16**[8] and liberation of the aryl aldehyde provided **18** via dibromide **17**. Wittig olefination of **18** gave dimethyl ester **19**, which upon hydrolysis provided compound **4** while hydrogenation of **19** followed by hydrolysis provided compound **20**.

The ether- and thioether-containing compounds were prepared from the common intermediate **25** (Scheme III). The hydroxy aldehyde **12** was alkylated with the desired lipid tail, and the aldehyde **21** reacted with methyl (triphenylphosphoranylidene)acetate giving acrylate **22**. Conversion to the pyridine N-oxide **23** using MCPBA followed by TFAA rearrangement afforded the (hydroxymethyl)pyridine **24**.[9] Treatment of **24** with $SOCl_2$ provided the (chloromethyl)pyridine **25** as a hydrochloride salt.[10] It was necessary to prepare **25** as a salt as the free base was found to be unstable. The ether **26a** and thioether **26b** were prepared from **25** by reaction with the corresponding phenol or thiophenol (Scheme IV). Hydrolysis of the esters then provided the target compounds (e.g., **27a** and **27b**). The ether **26a** was converted to the pyridine N-oxide **29** (Scheme V) while the thioether **26b** was converted to both the sulfoxide **31** and the sulfone **33** (Scheme VI).

The aryl amino group of **34**, prepared by the method outlined in Scheme IV, was derivatized according to Scheme VII. Acylation or sulfonylation was achieved under standard conditions, giving **35**. The compound was either hydrolyzed directly to **36** or first oxidized to the sulfoxide **39**; hydrolysis provided compound **40**. The N,N-dimethylanilines were prepared by reductive alkylation

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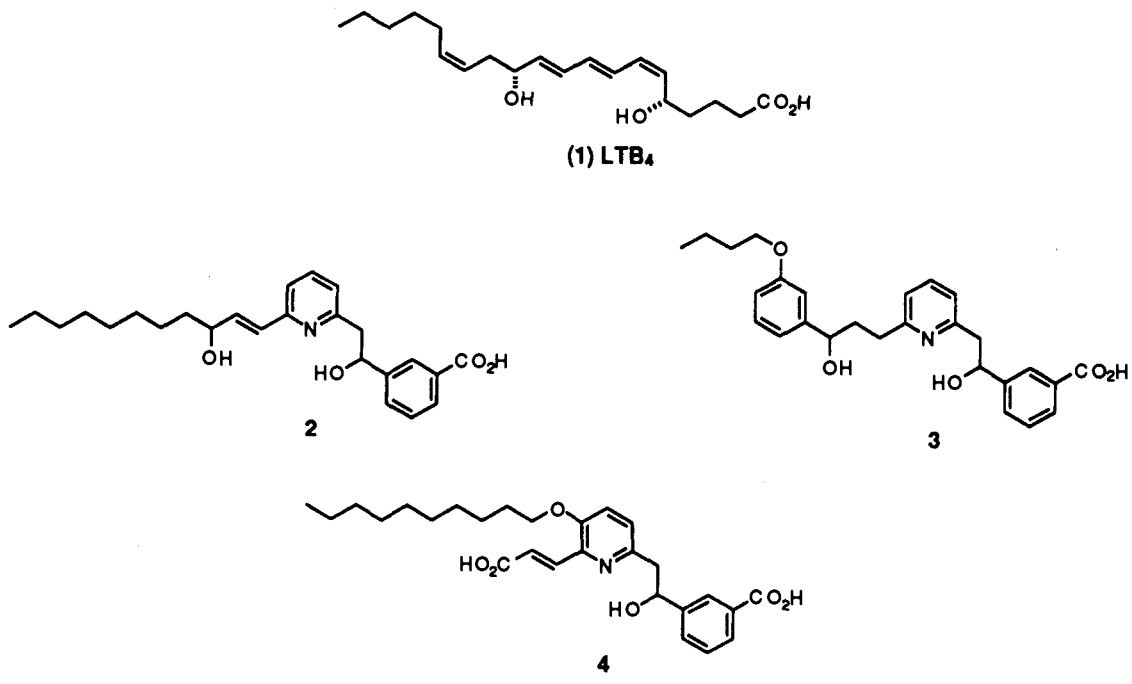
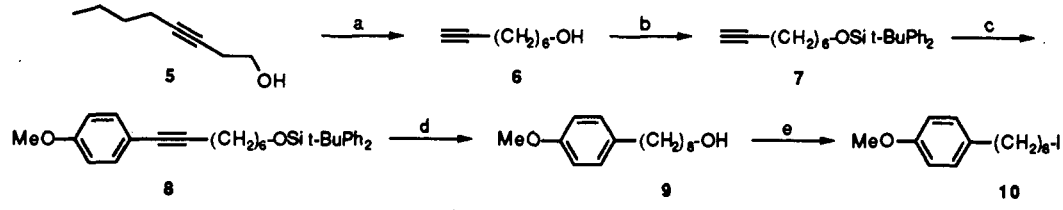


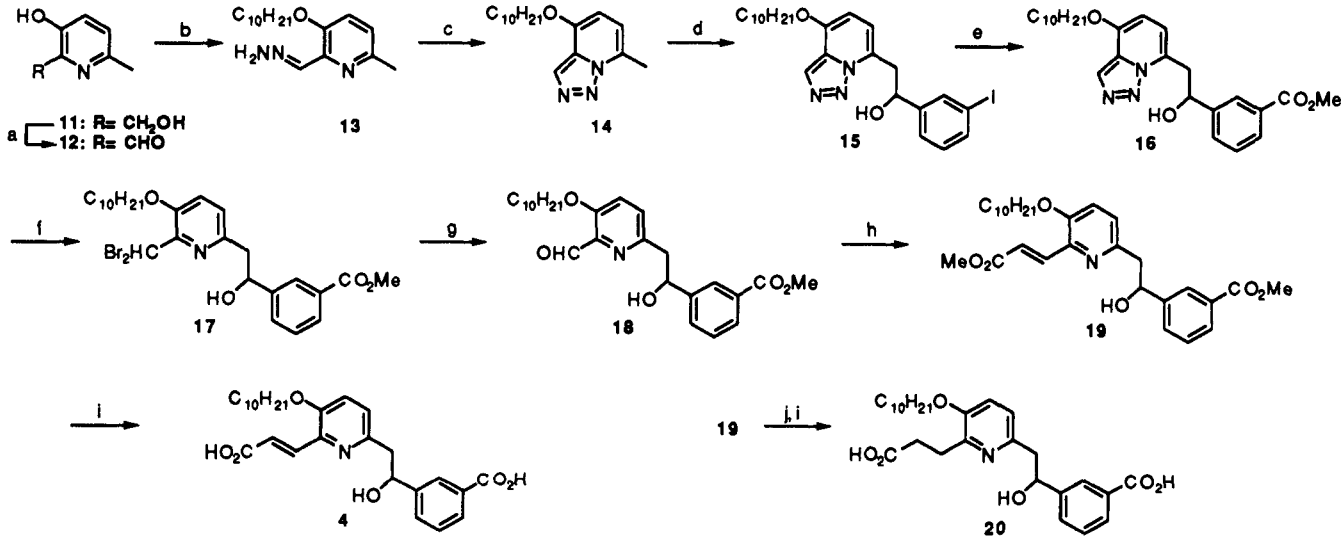
Figure 1.

Scheme I[a]



[a] (a) KAPA; (b) *tert*-$BuPh_2SiCl$, imidazole, DMF; (c) 4-iodoanisole, $(Ph_3P)_2PdCl_2$, CuI, TEA, 50 °C; (d) (1) 5% Pd–C, EtOH-EtOAc, H_2; (2) *n*-Bu_4NF, THF; (e) Ph_3P, imidazole, I_2.

Scheme II[a]



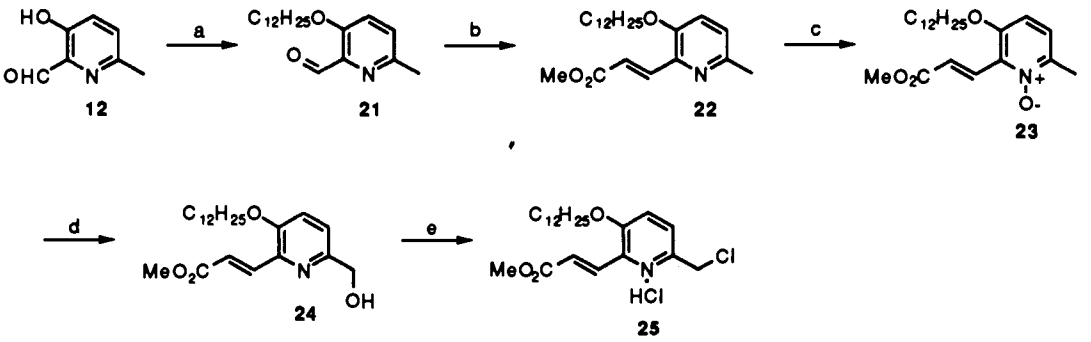
[a] (a) MnO_2, CH_2Cl_2, (b) (1) $C_{10}H_{21}I$, K_2CO_3, DMF, 90 °C, (2) H_2NNH_2, 100 °C; (c) NiO_2, benzene; (d) LDA, 3-iodobenzaldehyde, Et_2O; (e) $Pd(OAc)_2$, dppp, TEA, CO, DMSO, MeOH, 75°C; (f) Br_2, CH_2Cl_2, 0°C; (g) $AgNO_3$, EtOH, H_2O; (h) Ph_3PCHCO_2Me, toluene, 50 °C; (i) aq. LiOH, THF, MeOH; (j) H_2, 5% Pd/C, EtOH.

of **34** to give **37**.[11] Compound **37** was then converted to either sulfide **38** or sulfoxide **56**.

Results and Discussion

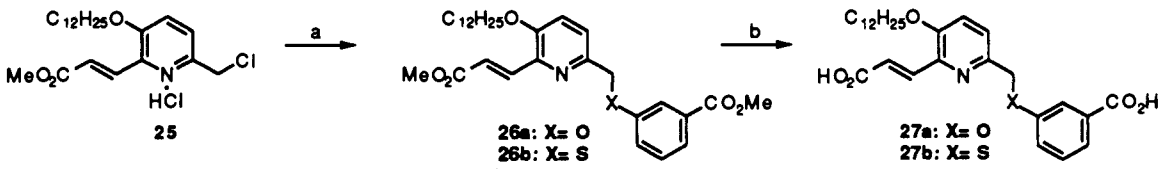
The LTB_4 receptor affinities of the test compounds were determined by evaluating the ability of the compounds to compete with the binding of [^{3}H]LTB_4 to receptors on intact human polymorphonuclear leukocytes (PMNs). Since human PMNs are the primary target inflammatory cells of interest, we used PMNs rather than U-937 cells, as in our earlier study, as the preferred cell type for testing. In addition, all compounds were evaluated further in a whole-cell LTB_4 receptor functional assay. In this case, the compounds were tested in the LTB_4-induced calcium

Scheme III[a]



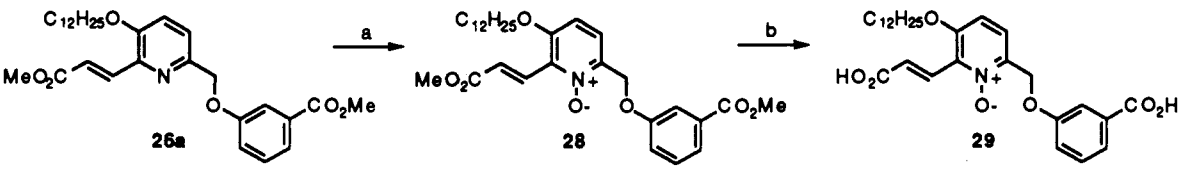
[a] (a) R-I, K_2CO_3, DMF, 90 °C; (b) Ph_3PCHCO_2Me, toluene, 50 °C; (c) MCPBA, CH_2Cl_2; (d) TFAA, DMF; (e) $SOCl_2$, toluene.

Scheme IV[a]



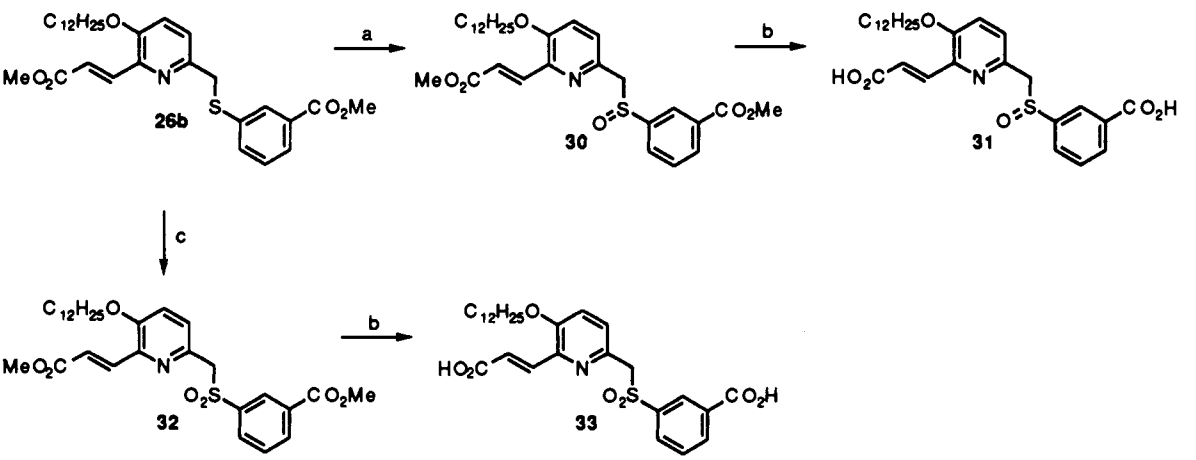
[a] (a) ArOH or ArSH, K_2CO_3 or Cs_2CO_3, DMF, 50–90 °C; (b) aq. LiOH, THF, MeOH.

Scheme V[a]



[a] (a) MCPBA, CH_2Cl_2; (b) aq. LiOH, THF, MeOH.

Scheme VI[a]

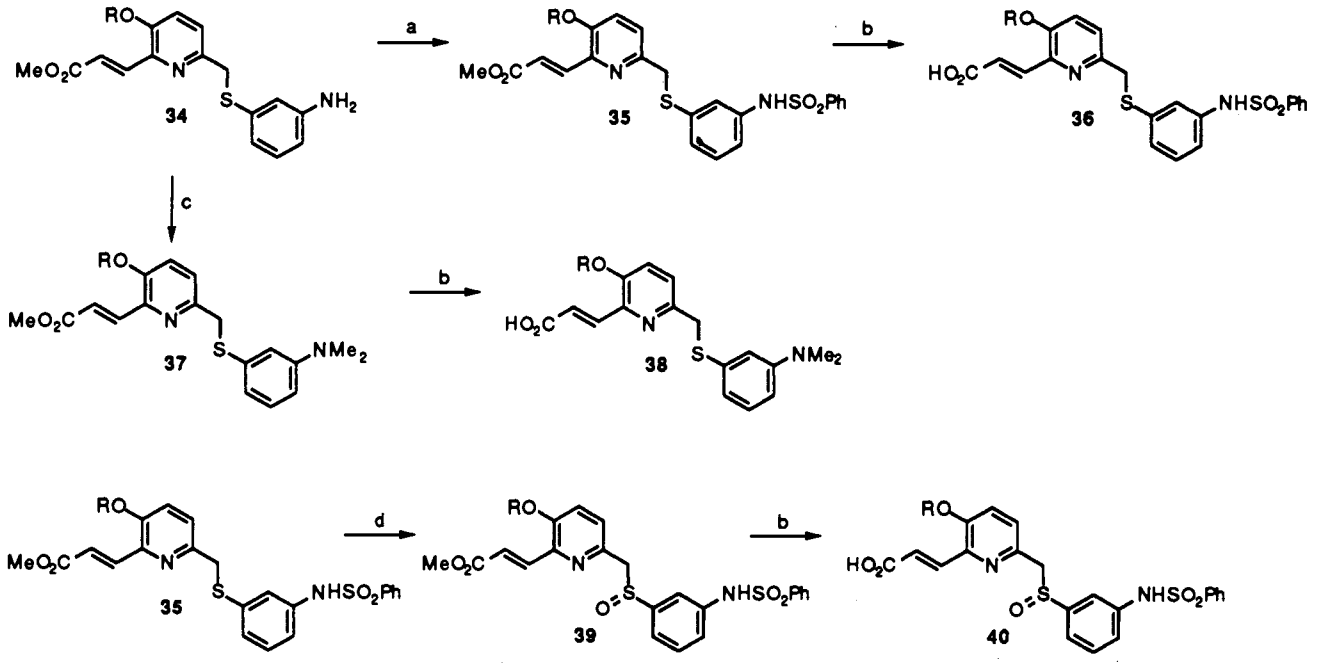


[a] (a) 1 equiv. MCPBA, CH_2Cl_2, 0 °C; (b) aq. LiOH, THF, MeOH; (c) 2 equiv. MCPBA, CH_2Cl_2, 0 °C.

mobilization assay using human PMNs and U-937 cells. To assess the presence of agonist activity, the highly sensitive human PMNs were used. Since LTB_4 is more effectively coupled to calcium mobilization in these cells, a much greater response is obtained than with human U-937 cells. All compounds were tested for agonist activity up to 10 μM using human PMNs. For antagonist activity, the ability of the compounds to inhibit the more stable and reproducible calcium mobilization response in human U-937 cells was used. In this assay, the IC_{50} is determined which corresponds to the concentration of compound that inhibits the LTB_4-induced calcium mobilization by 50%. For the present study, the whole-cell human PMN binding assay served as our primary test system to determine structure–activity relationships while the calcium functional assay was used to assess agonist activity (PMNs) and potency (U-937) of the test compounds. The data for the human PMN binding and the U-937 calcium mobilization assays are presented in Tables I–III. All compounds in this series were free of LTB_4 receptor agonist activity at concentrations up to 10 μM.

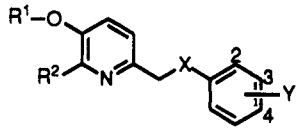
Our initial compound design utilized a structural template based upon the solution conformation of LTB_4 (1, Figure 1).[12] This approach led to the synthesis of compounds possessing high affinity for the LTB_4 receptor,[1] the most potent of which was the disubstituted pyridine 2 (K_i = 1 nM). However, these compounds demonstrated agonist activity at the LTB_4 receptor. This previous work, as well as work reported by Upjohn,[13] led us to believe that the agonist activity may be triggered by a combination of the C-12 allylic alcohol (LTB_4 numbering) and the lipophilic tail. As we have reported,[1] the removal of the

Scheme VII[a]



[a] (a) RSO_2Cl, CH_2Cl_2, 0 °C; (b) aq. LiOH, THF, MeOH; (c) formaldehyde, $NaCNBH_3$, HOAc, MeCN; (d) 1 equiv. MCPBA, CH_2Cl_2, 0 °C. R = 4-$MeOC_6H_4(CH_2)_8$-

Table I. Inhibition of [^{3}H]LTB_4 Binding to Neutrophils and Inhibition of LTB_4-Induced Ca^{2+} Mobilization



compd	R^1	R^2	X	Y	whole cell binding (PMN) K_i, μM[a]	Ca^{2+} mobilization (U-937) IC_{50}, μM[a]
2					0.001	
4	$C_{10}H_{21}$	$CH{=}CHCO_2H$	CHOH	3-CO_2H	0.282	3.3 ± 0.7
20	$C_{10}H_{21}$	$CH_2CH_2CO_2H$	CHOH	3-CO_2H	0.429	3.4
41	*p*-$MeOC_6H_4(CH_2)_6$	$CH{=}CHCO_2H$	CHOH	3-CO_2H	0.165	4.0
27a	$C_{12}H_{25}$	$CH{=}CHCO_2H$	O	3-CO_2H	1.13	0.58
29	$C_{12}H_{25}$	$CH{=}CHCO_2H$	O	3-CO_2H	0.338	1.01 ± 0.07
42	*p*-$MeOC_6H_4(CH_2)_8$	$CH{=}CHCO_2H$	*N*-oxide O	3-CO_2H	0.150	0.89 ± 0.04
31	$C_{12}H_{25}$	$CH{=}CHCO_2H$	*N*-oxide S=O	3-CO_2H	0.129 ± 0.014	0.93 ± 0.05
33	$C_{12}H_{25}$	$CH{=}CHCO_2H$	SO_2	3-CO_2H	0.148	1.06
43	$C_{12}H_{25}$	$CH{=}CHCO_2H$	S=O	4-CO_2H	0.252	1.3
44	$C_{12}H_{25}$	$CH{=}CHCO_2H$	S=O	2-CO_2H	0.478	1.5

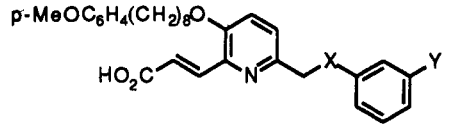
[a] The K_i and IC_{50} values are stated as the mean of at least three determinations ± standard error. All other values were obtained from one or two concentration response curves.

C-5 hydroxyl, the reduction of the C-10,11 olefin, and the replacement of the ring nitrogen with carbon had little or no effect on the agonist activity of the compounds. Likewise, the Upjohn workers have shown that replacement of the C-1 carboxylic acid with a primary alcohol also resulted in compounds with high affinity for the LTB_4 receptor but which also demonstrated agonist activity.[13]

Compound **3**, prepared in our earlier study, revealed that the lipophilic binding pocket may be capable of accommodating changes in the lipid chain. Therefore, it was decided to separate the lipophilic section from the polar C-12 hydroxyl portion of the tail. Maintaining the pyridine nucleus, the lipophilic chain was moved to the 3-position of the pyridine ring and attached via an ether linkage. The alkyl chain length was chosen to maintain an overall length consistent with that of LTB_4. In addition, the corresponding C-12 alcohol was replaced by a carboxylic acid. This change in oxidation state was performed to enhance synthetic accessibility and to increase the water solubility of the final compounds. The resulting compound **4** became our first synthetic target in this new series of compounds.

Compound **4** showed a large decrease (ca. 300-fold) in LTB_4 receptor affinity compared to the most potent compound of the disubstituted pyridine series (**2**, Table I). This substantial loss in affinity was, however, accompanied by a complete loss of LTB_4 agonist activity. Thus, the transformation from disubstituted to trisubstituted pyridine provided a compound with LTB_4 receptor antagonist activity, albeit with greatly reduced receptor affinity. Structural modifications were then performed in an attempt to build high receptor affinity back into the compound while preserving the antagonist activity. *All subsequent compounds prepared in this series were found to be free of LTB_4 receptor agonist activity as determined*

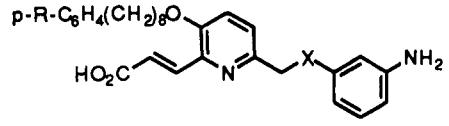
Table II. Inhibition of [^{3}H]LTB$_4$ Binding to Neutrophils and Inhibition of LTB$_4$-Induced Ca^{2+} Mobilization



compd	X	Y	whole cell binding (PMN) K_i, μM[a]	Ca^{2+} mobilization (U-937) IC_{50}, μM[a]
45	S=O	CO_2H	0.151	1.1
46	S	CO_2H	0.080 ± 0.018	0.39 ± 0.01
47	S	$NHSO_2CF_3$	0.284	0.34
48	S=O	$CHSO_2CF_3$	0.225	0.55 ± 0.04
36	S	$NHSO_2Ph$	0.609	0.24
40	S=O	$NHSO_2Ph$	0.147	0.15
49	S	NH_2	0.034 ± 0.004	0.054 ± 0.003
50	S=O	NH_2	0.0047 ± 0.0004	0.074 ± 0.005
51	SO_2	NH_2	0.036	0.15
52	S	OMe	0.192	0.29
53	S=O	OMe	0.232	0.30
54	S	H	0.074	0.11 ± 0.02
5	S=O	H	0.037	0.28
38	S	NMe_2	0.789	0.46 ± 0.04
56	S=O	NMe_2	0.245	0.82
57	S	$NHCOCO_2H$	0.072	0.48

[a] See footnote *a*, Table I.

Table III. Inhibition of [^{3}H]LTB$_4$ Binding to Neutrophils and Inhibition of LTB$_4$-Induced Ca^{2+}-Mobilization



compd	X	R	whole cell binding (PMN) K_i, μM[a]	Ca^{2+} mobilization (U-937) IC_{50}, μM[a]
50	S=O	MeO	0.0047	0.074 ± 0.005
58	S	H	0.036	0.06
59	S=O	H	0.011	0.16
60	S	CF_3	0.043	0.078
61	S=O	CF_3	0.014	0.054
62	S=O	F	0.012	0.11

[a] See footnote *a*, Table I.

by the calcium mobilization functional assay using human PMNs at concentrations up to 10 μM.

Saturation of the acrylate side chain (**20**) had no effect on receptor affinity. Incorporation of the (*p*-methoxyphenyl)hexyl lipid chain (**41**), likewise, had little effect on the receptor binding. Replacing the hydroxymethylene (X = CHOH) unit with either an oxygen or a sulfur (X = O, S) and exploring the effect of the carboxylic acid (Y = CO_2H) with respect to position gave the remaining compounds of Table I. Ether **27a** displayed a reduction in binding affinity compared to the hydroxy-containing compounds; however, conversion to the pyridine *N*-oxide **29** returned affinity to that comparable to **4**. Replacing the alkyl lipid chain with a (*p*-methoxyphenyl)octyl chain provided compound **42**, which showed a small increase in receptor affinity with respect to compound **4**. An examination of compounds **31**, **33**, **43**, and **44** revealed a preference for the meta-substituted benzoic acid moiety. However, there appeared to be little difference between a sulfoxide and a sulfone linking group.

Remaining within the sulfur-containing series and utilizing the (*p*-methoxyphenyl)octyl lipid chain, the compounds in Table II were prepared. With acidic Y groups, minor difference were observed between the sulfide and sulfoxide analogs: In the sulfonamide series, a slight preference was indicated for the sulfoxide linking group (e.g., **36** vs **40**) whereas in the carboxylic acid series, a small preference was shown for the sulfide linking group (e.g., **45** vs **46**).

Since all of the compounds prepared thus far contained ionizable Y groups, the activity of a compound possessing a Y group that was capable of interacting in a similar fashion to that of a carboxylic acid but would not be charged was of interest. An aniline was chosen as the head group since the pK_b of the free amine form is similar to that of the benzoate anion. Therefore, at physiological pH, it is likely that the aniline will not be protonated. To this end, anilines **49–51** were prepared. This change resulted in compounds with substantially improved receptor affinity. In particular, the sulfoxide **50** being more potent than either the sulfide **49** or the sulfone **51**. Replacement of the aniline with anisole (**52** and **53**) caused a large drop in receptor affinity. Similarly, the *N,N*-dimethylanilines (**38** and **56**) were substantially less active than the corresponding aniline compounds. Interestingly, the compounds lacking any substituent on the phenyl ring (Y = H, e.g., **54** and **55**) had higher receptor affinities than the other non-aniline analogs. Thus, an aniline imparts a unique interaction at the receptor that the other Y functional groups are not capable of and, in fact, other Y groups actually decrease receptor affinities compared to those compounds lacking a substituent. Finally, the oximate **57** was prepared. The activity of this compound was essentially identical to that of sulfide **46**.

Several compounds within the aniline series were prepared having different groups terminating the lipid chain. These compounds are shown in Table III. Due to the similarity of the binding affinities of the compounds, it is apparent that these particular terminating groups play a minor role in the *in vitro* receptor binding of the series. Once again, the sulfoxide linking group provided the more potent set of compounds.

In summary, all of the compounds reported in this study demonstrate competitive LTB$_4$ receptor antagonist activity in binding to human PMNs with no detectable agonist activity in the human PMN calcium mobilization functional assay. This work has led to the discovery of novel, high-affinity LTB$_4$ receptor antagonists such as aniline **50** (SB 201146).[14] This compound will be evaluated further using *in vivo* models of inflammation, and the results of these studies will be reported in due course. These studies will help ascertain the therapeutic potential of a LTB$_4$ receptor antagonist in human inflammatory diseases.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brucker AM-250 instrument with the solvents indicated. All ^{1}H chemical shifts are reported in δ relative to tetramethylsilane (TMS, δ 0.00) as the internal standard. Elemental analyses were performed by the Analytical and Physical Chemistry Department of SmithKline Beecham. Where analyses are indicated by symbols of the elements, results obtained were within ±0.40%. Mass spectra were determined by the Physical and Structural Chemistry Department of SmithKline Beecham. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F-254 glass backed plates or Whatman KC 18 F reversed-phase RP-18 glass-backed plates with the solvent systems indicated. High-performance liquid chromatography (HPLC)

was conducted using an Altex Model 110 gradient liquid chromatograph with a UV wavelength detector set at 254 nM. Flash column chromatography was carried out using silica gel with the solvents as indicated. Carboxylic acid salts were purified by reversed-phase medium-pressure liquid chromatography (MPLC) using Altec columns packed with Merck Licroprep RP-18 (25–40 μm) at a maximum pressure of 60 psi. All final compounds were homogeneous as determined chromatographically (TLC) and spectroscopically (^{1}H NMR, UV). Compound names were determined using the computer program Autonam.[15] All sulfoxide-containing compounds were prepared in racemic form.

Preparation of 1-Iodo-8-(4-methoxyphenyl)octane (10): 7-Octyn-1-ol (6). Potassium hydride (35%) in mineral oil (27 g, 240 mmol) under an argon atmosphere was washed with hexane and treated dropwise with 1,3-diaminopropane. The mixture was stirred at room temperature until it became homogeneous. The flask was cooled to 0 °C, and 3-octyn-1-ol (5; 10 g, 79 mmol) was slowly added. The reaction mixture was then stirred at room temperature for 18 h. The reaction was quenched with H_2O (50 mL), and the product was extracted into Et_2O. The organic layer was washed with 10% HCl and brine and dried ($MgSO_4$). Evaporation gave 9.73 g (97%) of 6 as a colorless oil which was used without further purification: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.65 (t, J = 5 Hz, 2H, OCH_2), 2.23 (m, 2H, CH_2), 2.0 (m, 1H, acetylenic), 1.7–1.2 (m, 8H, $(CH_2)_4$); IR (neat) ν_{max} 3350, 2930, 2125 cm^{-1}.

7-Octyn-1-yl *tert*-Butyldiphenylsilyl Ether (7). To a cooled (0 °C) solution of 6 (9.3 g, 73.7 mmol) in DMF (70 mL) under an argon atmosphere was added imidazole (7.5 g, 110 mmol) followed by the dropwise addition of *tert*-butylchlorodiphenylsilane (21 mL, 81 mmol). The reaction mixture was then stirred at room temperature for 2 h. The reaction solution was diluted with Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). Purification by flash column chromatography (3% EtOAc in hexane) provided 24.9 g (93%) of 7 as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.63 (t, 2H, OCH_2), 2.23 (m, 2H, CH_2), 1.97 (t, 1H, acetylenic), 1.6–1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *tert*-butyl); IR (film) ν_{max} 3321, 2940, 2125 cm^{-1}.

8-(4-Methoxyphenyl)-7-octyn-1-yl *tert*-Butyldiphenylsilyl Ether (8). To a flame-dried flask containing Et_3N (140 mL) under an argon atmosphere was added 4-iodoanisole (13.3 g, 56.9 mmol), 7 (24.9 g, 68.3 mmol), $(Ph_3P)_2PdCl_2$ catalyst (793 mg, 1.13 mmol), and CuI (431 mg, 2.27 mmol). The resulting mixture was heated at 50 °C for 4 h. Upon cooling to room temperature, the reaction mixture was filtered, the solids were washed with Et_2O, and the solvent was evaporated. The residue was diluted with Et_2O, washed with 5% HCl, H_2O, $NaHCO_3$, and brine, and dried ($MgSO_4$). Purification by flash column chromatography (2% EtOAc in hexane) gave 30 g (93%) of 8 as an orange oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.7 (t, 2H, OCH_2), 2.4 (t, 2H, CH_2), 1.7–1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *tert*-butyl).

8-(4-Methoxyphenyl)octan-1-ol (9). Alkyne 8 (30 g, 63.7 mmol) was dissolved in EtOH (125 mL) and EtOAc (125 mL) and treated with 5% Pd–C catalyst (3 g). The reaction mixture was vigorously stirred under an H_2 atmosphere (balloon pressure) for 4 h. The reaction mixture was filtered through a pad of Celite, and the solvent was evaporated. The resulting pale yellow oil was pure by NMR analysis and was used directly for the next step: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.6 (t, 2H, OCH_2), 2.5 (t, 2H, benzylic), 1.75–1.3 (m, 12H, $(CH_2)_6$), 1.0 (s, 9H, *tert*-butyl).

To a cooled (0 °C) solution of silyl ether obtained above (63 mmol) was added tetrabutylammonium fluoride (70 mL, 70 mmol; 1 M solution in THF). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 4.5 h. The solvent was evaporated, and the residue was dissolved in Et_2O. This was washed with H_2O, 5% HCl, $NaHCO_3$, and brine and dried ($MgSO_4$). Purification by flash column chromatography (30% EtOAc in hexane) gave 12.6 g (85%; two steps) of 9 as a white crystalline solid: mp 47–49 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (d, 2H, aryl), 6.86 (d, 2H, aryl), 3.85 (s, 3H, OCH_3), 3.68 (t, 2H, OCH_2), 2.62 (t, 2H, benzylic), 1.75–1.3 (m, 12H, $(CH_2)_6$); MS (CI) 254.2 (M + NH_4).

1-Iodo-8-(4-methoxyphenyl)octane (10). To a stirred solution of 9 (12.3 g, 52 mmol) in dry toluene (200 mL) under an argon atmosphere was added triphenylphosphine (17.8 g, 67.6 mmol) and imidazole (10.6 g, 156 mmol). After 5 min I_2 (17.1 g, 67.6 mmol) was added. The reaction mixture was then heated at 65 °C for 30 min. Upon cooling to room temperature, the reaction was concentrated to one-fourth volume. The remaining solution was diluted with Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). The solvent was removed, and the resulting residue was dissolved in CH_2Cl_2 and applied to a flash chromatography column; elution with 2% EtOAc in hexane provided 16.3 g (90%) of 10 as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2H, aryl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 3.78 (s, 3H, OCH_3), 3.17 (t, J = 7.4 Hz, 2H, ICH_2), 2.54 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.31 (m, 8H, aliphatic); MS (CI) 364.2 (M + NH_4).

Preparation of (*E*)-3-{2-[6-(2-Carboxyvinyl)-5-(decyloxy)pyridin-2-yl]-1-hydroxyethyl}benzoic Acid, Dilithium Salt (4): 3-Hydroxy-6-methylpyridine-2-carbaldehyde (12). A suspension of 2,6-lutidine-α^2,3-diol (11; 1.0 g, 7.18 mmol) in dry CH_2Cl_2 (40 mL) was treated with MnO_2 (6.1 g, 70 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite, and the solvent was removed *in vacuo*. The light tan amorphous solid obtained (12) was used directly in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.65 (s, 1H, OH), 10.30 (s, 1H, CHO), 7.30 (dd, 2H, 4-pyridyl, 5-pyridyl), 2.55 (s, 3H, CH_3).

[3-(Decyloxy)-6-methylpyridin-2-yl]hydrazone (13). Aldehyde 12 (1.17 g, 8.54 mmol) was dissolved in dry DMF (10 mL) and treated with 1-iododecane (2.2 mL, 10.3 mmol) and anhydrous K_2CO_3 (3.6 g, 26 mmol) under an argon atmosphere. The reaction mixture was heated at 90 °C for 1 h with vigorous stirring. Upon cooling to room temperature, the reaction mixture was poured into EtOAc; the EtOAc solution was washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product was used directly in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.40 (s, 1H, CHO), 7.30 (dd, 2H, 4-pyridyl, 5-pyridyl), 4.07 (t, 2H, OCH_2), 2.6 (s, 3H, CH_3), 1.85–0.90 (m, 19H, aliphatic).

The aldehyde obtained above (2.15 g, 7.8 mmol) was heated with hydrazine hydrate for 1 h at 95 °C. Upon cooling to room temperature, 25% NaOH was added and the mixture was extracted with EtOAc. The organic extract was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated to give 2.12 g (93%) of 13 as an amorphous solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.75 (broad singlet, 2H, NH_2), 7.55 (s, 1H, CHN), 7.10 (d, 1H, 5-pyridyl), 6.95 (d, 1H, 4-pyridyl), 3.95 (t, 2H, OCH_2), 2.55 (s, 3H, CH_3), 1.80–0.90 (m, 19H, aliphatic).

4-(Decyloxy)-7-methyl[1,2,3]triazolo[1,5-*a*]pyridine (14). To a flame-dried flask under an argon atmosphere was added 13 (2.12 g, 7.2 mmol) in dry benzene (30 mL). To the resulting solution was added NiO_2 (790 mg, 8.7 mmol). The resulting mixture was stirred at room temperature for 72 h and then filtered through Celite. The solvent was evaporated and the residue purified by flash column chromatography (10–15% EtOAc in hexanes) to give 1.3 g (62%) of 14 as a white noncrystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.2 (s, 1H, CHN), 6.68 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 4.1 (t, 2H, OCH_2), 2.8 (s, 3H, CH_3), 1.90–0.90 (m, 19H, aliphatic). Anal. ($C_{17}H_{27}N_3$) C, H, N.

2-[4-(Decyloxy)[1,2,3]triazolo[1,5-*a*]pyridin-7-yl]-1-(3-iodophenyl)ethanol (15). To a flame-dried flask under an argon atmosphere was added diisopropylamine (500 mg, 4.9 mmol) in dry Et_2O (10 mL). The resulting solution was cooled to −40 °C, and 2.5 M *n*-BuLi (1.97 mL, 4.9 mmol) was added. The mixture was stirred at −40 °C for 10 min followed by the dropwise addition of 14 (1.3 g, 4.4 mmol) in dry Et_2O (40 mL) via an addition funnel. The resulting red mixture was stirred at −40 °C for 6 h. 3-Iodobenzaldehyde (1.15 g, 4.9 mmol) in Et_2O (30 mL) was added in one portion. A color change from deep-red to yellow was observed. The mixture was allowed to warm to room temperature over a 2-h period and then stirred at room temperature for 12 h. The resulting reaction mixture was partitioned between EtOAc and H_2O, and the organic extract was washed with H_2O and brine

and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (10–30% EtOAc in hexanes) to give 500 mg (26%) of **15** as a white waxy solid: ^1H NMR (250 MHz, $CDCl_3$) δ 8.2 (s, 1H, CHN), 7.80 (s, 1H, aryl), 7.59 (d, 1H, aryl), 7.35 (d, 1H, aryl), 7.07 (t, 1H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 5.36 (m, 1H, CHO), 4.11 (t, 2H, OCH_2), 3.64 and 3.45 (dd, 2H, CH_2), 3.25 (d, 1H, OH), 1.88–0.88 (m, 19H, aliphatic).

3-[2-[4-(Decyloxy)[1,2,3]triazolo[1,5-*a*]pyridin-7-yl]-1-hydroxyethyl]benzoic Acid Methyl Ester (16). To a solution of **15** (500 mg, 0.96 mmol) in DMSO (10 mL) was added MeOH (4 mL), Et_3N (0.3 mL, 2.1 mmol), $Pd(OAc)_2$ (6.4 mg, 0.029 mmol), and bis(diphenylphosphino)propane (11.9 mg, 0.029 mmol). Carbon monoxide was bubbled through the solution for 4 min. The mixture was then heated at 85 °C under positive carbon monoxide pressure for 6 h. The mixture was cooled to room temperature and partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (5–20% EtOAc in hexanes) to give 260 mg (72%) of **16** as a white waxy solid: ^1H NMR (250 MHz, $CDCl_3$) δ 8.2 (s, 1H, CHN), 8.1 (s, 1H, aryl), 7.95 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 5.45 (m, 1H, CHO), 4.11 (t, 2H, OCH_2), 3.9 (s, 3H, CO_2CH_3), 3.70 and 3.45 (dd, 2H, CH_2), 3.25 (d, 1H, OH), 1.90–0.88 (m, 19H, aliphatic). Anal. ($C_{28}H_{35}N_3O_4$) C, H, N.

3-[2-[5-(Decyloxy)-6-(dibromomethyl)pyridin-2-yl]-1-hydroxyethyl]benzoic Acid Methyl Ester (17). Ester **16** (130 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. To this was slowly added a solution of Br_2 (46 mg, 0.28 mmol) in CH_2Cl_2 (3 mL); gas evolution was observed, and the reaction mixture was stirred at 0 °C for 1 h. The CH_2Cl_2 solution was washed with $NaHCO_3$, H_2O, and brine and dried (Na_2SO_4). The solvent was evaporated to give 150 mg (92%) of **17** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.1 (s, 1H, aryl), 7.92 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.09 (d, 1H, 3-pyridyl), 7.07 (s, 1H, $CHBr_2$), 7.0 (d, 1H, 4-pyridyl), 6.08 (d, 1H, OH), 5.25 (m, 1H, CHO), 4.05 (t, 2H, OCH_2), 3.9 (s, 3H, OMe), 3.15 (m, 2H, CH_2), 1.90–0.88 (m, 19H, aliphatic).

3-[2-[5-(Decyloxy)-6-formylpyridin-2-yl]-1-hydroxyethyl]benzoic Acid Methyl Ester (18). To a solution of **17** (150 mg, 0.26 mmol) in EtOH (3 mL) was added $AgNO_3$ (90 mg, 0.56 mmol) in H_2O (1 mL). The resulting mixture was heated at reflux for 1 h. The mixture was cooled to room temperature, concentrated HCl (1 mL) was added, and the precipitated silver salt was removed by filtration. The filtrate was evaporated and the residue treated with saturated $NaHCO_3$. The product was extracted into EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash column chromatography (10–30% EtOAc in hexanes) to give 40 mg (37%) of **18** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 10.4 (s, 1H, CHO), 8.1 (s, 1H, aryl), 7.92 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.33 (d, 1H, 3-pyridyl), 7.25 (d, 1H, 4-pyridyl), 5.25 (m, 1H, CHO), 5.0 (d, 1H, OH), 4.1 (t, 2H, OCH_2), 3.9 (s, 3H, OMe), 3.15 (m, 2H, CH_2), 1.90–0.88 (m, 19H, aliphatic); MS (CI) 277 (M + H).

(*E*)-3-[2-[5-(Decyloxy)-6-[2-(methoxycarbonyl)vinyl]pyridin-2-yl]-1-hydroxyethyl]benzoic Acid Methyl Ester (19). Aldehyde **18** (40 mg, 0.09 mmol) was dissolved in dry toluene (2 mL) under an argon atmosphere. To this was added methyl (triphenylphosphoranylidene)acetate (60 mg, 0.18 mmol), and the resulting mixture was heated at 50 °C for 1 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (15–20% EtOAc in hexanes) to give 37 mg (82%) of **19** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.1 (s, 1H, aryl), 8.1 (d, J = 16 Hz, 1H, vinyl), 7.9 (d, 1H, aryl), 7.65 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.15 (d, 1H, 5-pyridyl), 7.03 (d, 1H, 4-pyridyl), 6.95 (d, J = 16 Hz, 1H, vinyl), 5.65 (d, 1H, OH), 5.2 (m, 1H, CHO), 4.05 (t, 2H, OCH_2), 3.9 (s, 3H, OMe), 3.8 (s, 3H, OMe), 3.10 (m, 2H, CH_2), 1.90–0.88 (m, 19H, aliphatic); MS (CI) 498 (M + H).

(*E*)-3-[2-[6-(2-Carboxyvinyl)-5-(decyloxy)pyridin-2-yl]-1-hydroxyethyl]benzoic Acid, Dilithium Salt (4). Diester **19** (22 mg, 0.04 mmol) was dissolved in THF, H_2O, and MeOH (0.50 mL each) and treated with LiOH monohydrate (5 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was dissolved in H_2O and purified by reversed-phase MPLC (10–40% MeOH in H_2O). The desired fractions were lyophilized to give 15 mg (73%) of **4** as a colorless amorphous solid: ^1H NMR (250 MHz, MeOH-d_4) δ 8.01 (s, 1H, aryl), 7.80 (d, 1H, aryl), 7.76 (d, J = 16 Hz, 1H, vinyl), 7.36 (d, 1H, aryl), 7.30 (t, 1H, aryl), 7.24 (d, 1H, 5-pyridyl), 7.07 (d, J = 16 Hz, 1H, vinyl), 7.01 (d, 1H, 4-pyridyl), 5.11 (t, 1H, CHO), 4.0 (t, 2H, OCH_2), 3.1 (m, 2H, CH_2), 1.83–0.89 (m, 19H, aliphatic); FAB-MS 474.3 (M – H, monolithium salt), 468 (M – H, free acid).

Preparation of 3-{2-[6-(2-Carboxyethyl)-5-(decyloxy)pyridin-2-yl]-1-hydroxyethyl}benzoic Acid, Dilithium Salt (20). To a solution of **19** (13 mg, 0.02 mmol) in EtOH (3 mL) was added 5% Pd/C (2 mg). The mixture was subjected to 55 psi of H_2 for 1 h. The mixture was filtered through Celite, and the solvent was evaporated to give 10 mg (95%) of the saturated diester as an oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.08 (s, 1H, aryl), 7.9 (d, 1H, aryl), 7.6 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.05 (d, 1H, 5-pyridyl), 6.87 (d, 1H, 4-pyridyl), 6.0 (br s, 1H, OH), 5.15 (m, 1H, CHO), 4.01 (t, 2H, OCH_2), 3.9 (s, 3H, OMe), 3.8 (s, 3H, OMe), 3.2 (t, 2H, CH_2), 3.05 (m, 2H, CH_2), 2.8 (t, 2H, CH_2), 1.83–0.88 (m, 19H, aliphatic).

The diester obtained above (10 mg, 0.015 mmol) was dissolved in THF, H_2O, and MeOH (0.5 mL each) and treated with LiOH monohydrate (2 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was dissolved in H_2O, filtered through a nylon filter, and purified by reversed-phase MPLC (10–40% MeOH in H_2O). The desired fractions were lyophilized to give 7 mg (70%) of **20** as a colorless amorphous solid: ^1H NMR (250 MHz, MeOH-d_4) δ 8.0 (s, 1H, aryl), 7.8 (d, 1H, aryl), 7.32 (d, 1H, aryl), 7.25 (t, 1H, aryl), 7.1 (d, 1H, 5-pyridyl), 6.9 (d, 1H, 4-pyridyl), 5.1 (t, 1H, CHO), 4.0 (t, 2H, OCH_2), 3.1 (t, 2H, CH_2), 3.05 (m, 2H, CH_2), 2.5 (t, 2H, CH_2), 1.8–0.90 (m, 19H, aliphatic); FAB-MS 484 (M + H).

The following compound was prepared by the same procedure using 1-iodo-6-(4-methoxyphenyl)hexane. **(*E*)-3-{2-[6-(2-Carboxyvinyl)-5-[[6-(4-methoxyphenyl)hexyl]oxy]pyridin-2-yl]-1-hydroxyethyl}benzoic acid, dilithium salt (41):** colorless amorphous solid; ^1H NMR (250 MHz, MeOH-d_4) δ 8.05 (s, 1H, aryl), 7.8 (d, 1H, aryl), 7.75 (d, J = 16 Hz, 1H, vinyl), 7.35 (d, 1H, aryl), 7.25 (t, 1H, aryl), 7.2 (d, J = 16 Hz, 1H, vinyl), 7.0 (m, 4H, 4-pyridyl, 5-pyridyl, aryl), 6.75 (d, 2H, aryl), 5.15 (t, 1H, CHO), 4.0 (t, 2H, OCH_2), 3.7 (s, 3H, OMe), 3.1 (m, 2H, CH_2), 2.5 (t, 2H, benzylic), 1.80–1.35 (m, 8H, aliphatic); FAB-MS (+ve), 532.2 (M + H); (-ve), 524.4 (M – Li).

Preparation of (*E*)-3-[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methoxy]benzoic Acid, Dilithium Salt (27a): 3-(Dodecyloxy)-6-methylpyridine-2-carbaldehyde (21). Aldehyde **12** (975 mg, 7.12 mmol) was dissolved in dry DMF (10 mL) and treated with 1-iodododecane (2.1 mL, 8.62 mmol) and anhydrous K_2CO_3 (3.0 g, 21.7 mmol) under an argon atmosphere. The reaction was heated at 90 °C for 1 h with vigorous stirring. Upon cooling to room temperature, the reaction mixture was poured into EtOAc; the EtOAc solution was washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product (**21**) was used directly in the next step without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 10.40 (s, 1H, CHO), 7.30 (m, 2H, 4-pyridyl, 5-pyridyl), 4.07 (t, J = 6.5 Hz, 2H, OCH_2), 2.6 (s, 3H, CH_3), 1.85–0.89 (m, 23H, aliphatic).

(*E*)-3-[3-(Dodecyloxy)-6-methylpyridin-2-yl]acrylic Acid Methyl Ester (22). Aldehyde **21** obtained above was dissolved in dry toluene (12 mL) under an argon atmosphere and treated with methyl (triphenylphosphoranylidene)acetate (5.0 g, 15 mmol). The reaction mixture was heated for 1 h at 50 °C. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Purification by flash column chromatography (EtOAc in petroleum ether) gave 2.15 g (83%, three steps) of **22** as a colorless waxy solid: ^1H NMR (250 MHz, $CDCl_3$) δ 8.07 (d, J = 15.7 Hz, 1H, vinyl), 7.10 (m, 2H, 4-pyridyl, 5-pyridyl), 7.05 (d, J = 15.7 Hz, 1H, vinyl), 3.98 (t, J = 6.6 Hz, 2H, OCH_2), 3.80 (s, 3H, OMe), 2.49 (s, 3H, CH_3), 1.88–0.85 (m, 23H, aliphatic).

(*E*)-3-[3-(Dodecyloxy)-6-methylpyridin-2-yl]acrylic Acid Methyl Ester *N*-Oxide (23). Pyridine **22** (2.15 g, 5.95 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C; 85% MCPBA (1.45 g, 7.14 mmol) was added, and the reaction mixture was stirred at 0 °C for 30 min and at room temperature for 16 h. The reaction solution was poured into saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the combined CH_2Cl_2 extracts were washed with H_2O and brine and dried ($MgSO_4$). The crude pale yellow noncrystalline solid (**23**) was used directly in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.23 (d, J = 16.2 Hz, 1H, vinyl), 7.58 (d, J = 16.2 Hz, 1H, vinyl), 7.13 (d, J = 8.8 Hz, 1H, 5-pyridyl), 6.79 (d, J = 8.8 Hz, 1H, 4-pyridyl), 4.06 (t, J = 6.6 Hz, 2H, OCH_2), 3.81 (s, 3H, OMe), 2.45 (s, 3H, CH_3), 1.92–0.85 (m, 23H, aliphatic); MS (CI) 378.2 (M + H).

(*E*)-3-[3-(Dodecyloxy)-6-(hydroxymethyl)pyridin-2-yl]acrylic Acid Methyl Ester (24). Pyridine *N*-oxide **23** obtained above was suspended in dry DMF (20 mL) and cooled to 0 °C under an argon atmosphere. To this was slowly added trifluoroacetic anhydride (8.5 mL, 60.2 mmol). The reaction was stirred at 0 °C for 10 min and then at room temperature for 16 h; TLC indicated that two reaction products were present (alcohol and trifluoroacetate). The reaction solution was slowly added to a cooled (0 °C) saturated aqueous Na_2CO_3 solution and vigorously stirred for 2 h at room temperature. The product was extracted into EtOAc, and the combined EtOAc extracts were washed with H_2O and brine and dried ($MgSO_4$); the solvent was removed *in vacuo*. Purification by flash column chromatography (25% EtOAc in petroleum ether) gave 1.07 g (49%, three steps) of **24** as a pale orange semisolid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 (d, J = 15.8 Hz, 1H, vinyl), 7.24 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.16 (d, J = 8.6 Hz, 1H, 4-pyridyl), 7.03 (d, J = 15.8 Hz, 1H, vinyl), 4.69 (d, J = 4.2 Hz, 2H, CH_2), 4.03 (t, J = 6.6 Hz, 2H, OCH_2), 3.82 (s, 3H, OMe), 3.61 (t, J = 4.2 Hz, 1H, OH), 1.91–0.85 (m, 23H, aliphatic); MS (CI) 378.3 (M + H).

(*E*)-3-[6-(Chloromethyl)-3-(dodecyloxy)pyridin-2-yl]acrylic Acid Methyl Ester Hydrochloride (25). Compound **24** (250 mg, 0.662 mmol) was dissolved in dry toluene (10 mL) under an argon atmosphere and cooled to 0 °C. Thionyl chloride (0.50 mL, 6.85 mmol) was slowly added, and the solution was stirred at 0 °C for 30 min followed by 1 h at room temperature. The solvent and excess thionyl chloride were removed at reduced pressure. The crude hydrochloride salt (**25**) was used directly in the next step without further purification.

(*E*)-3-[[5-(Dodecyloxy)-6-[2-(methoxycarbonyl)vinyl]pyridin-2-yl]methoxy]benzoic Acid Methyl Ester (26a). Chloride **25** obtained above was dissolved in dry DMF (2 mL) and treated with methyl 3-hydroxybenzoate (152 mg, 1.00 mmol) and anhydrous K_2CO_3 (500 mg, 3.62 mmol) under an argon atmosphere. The reaction was heated at 90 °C for 1 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Purification by flash column chromatography (CH_2Cl_2–petroleum ether–EtOAc, 50:48:2) gave 218 mg (64%, two steps) of **26a** as a colorless noncrystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 (d, J = 15.8 Hz, 1H, vinyl), 7.69 (s, 1H, 2-phenyl), 7.65 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.44 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.34 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.22 (d, J = 8.6 Hz, 1H, 4-pyridyl), 7.16 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.07 (d, J = 15.8 Hz, 1H, vinyl), 5.18 (s, 2H, CH_2), 4.02 (t, J = 6.6 Hz, 2H, OCH_2), 3.91 (s, 3H, OMe), 3.82 (s, 3H, OMe), 1.90–0.88 (m, 23H, aliphatic); MS (CI) 512.4 (M + H). Anal. ($C_{30}H_{41}NO_6 \cdot {}^1/_8C_6H_5CH_3$) C, H, N.

(*E*)-3-[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methoxy]benzoic Acid, Dilithium Salt (27a). Diester **26a** (80 mg, 0.156 mmol) was dissolved in THF (1.34 mL) and MeOH (0.50 mL) and treated with 1 M LiOH (0.50 mL, 0.50 mmol). The reaction mixture was stirred at room temperature for 20 h. The THF and MeOH were removed at reduced pressure, and the product was purified by reversed-phase MPLC (10–65% MeOH in H_2O) and isolated by lyophilization to give 61 mg (79%) of **27a** as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.81 (d, J = 15.7 Hz, 1H, vinyl), 7.62 (s, 1H, 2-phenyl), 7.56 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.44 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.40 (d, J = 8.6 Hz, 1H, 4-pyridyl), 7.26 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.07 (d, J = 15.7 Hz, 1H, vinyl), 7.05 (d, J = 7.9 Hz, 1H, 6-phenyl), 5.13 (s, 2H, CH_2), 4.07 (t, J = 6.5 Hz, 2H, OCH_2), 1.89–0.89 (m, 23H, aliphatic); FAB-MS (+ve), 502.3 (M + Li); (-ve), 488.2 (M–Li). Anal. ($C_{28}H_{35}NO_6Li_2 \cdot 2{}^1/_2H_2O$) C, H, N.

Preparation of (*E*)-3-[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methoxy]benzoic Acid *N*-Oxide, Dilithium Salt (29): (*E*)-3-[[5-(Dodecyloxy)-6-[2-(methoxycarbonyl)vinyl]pyridin-2-yl]methoxy]benzoic Acid Methyl Ester *N*-Oxide (28). Diester **26a** (130 mg, 0.254 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL), cooled to 0 °C, and treated with 85% MCPBA (57 mg, 0.28 mmol). The reaction mixture was stirred at 0 °C for 10 min and then for 20 h at room temperature. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and dried ($MgSO_4$). The product was purified by flash column chromatography (CH_2Cl_2–petroleum ether–EtOAc, 50:40:10) to give 111 mg (83%) of **28** as a colorless noncrystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (d, J = 16.2 Hz, 1H, vinyl), 7.71 (d, J = 8.0 Hz, 1H, 4-phenyl), 7.68 (s, 1H, 2-phenyl), 7.60 (d, J = 16.2 Hz, 1H, vinyl), 7.46 (d, J = 9.0 Hz, 1H, 5-pyridyl), 7.38 (dd, J = 8.0 Hz, 1H, 5-phenyl), 7.22 (d, J = 8.0 Hz, 1H, 6-phenyl), 6.9 (d, J = 9.0 Hz, 1H, 4-pyridyl), 5.32 (s, 2H, CH_2), 4.10 (t, J = 6.6 Hz, 2H, OCH_2), 3.92 (s, 3H, OMe), 3.83 (s, 3H, OMe), 1.94–0.88 (m, 23H, aliphatic); MS (CI) 528.3 (M + H). Anal. ($C_{30}H_{41}NO_7$) C, H, N.

(*E*)-3-[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methoxy]benzoic Acid *N*-Oxide, Dilithium Salt (29). *N*-Oxide **28** (110 mg, 0.208 mmol) was dissolved in THF (2 mL) and MeOH (0.65 mL) and treated with 1 M LiOH (0.65 mL). The reaction was stirred at room temperature for 20 h. The THF and MeOH were removed under reduced pressure, and the product was purified by reversed-phase MPLC (10–65% MeOH in H_2O) and isolated by lyophilization to give 88 mg (83%) of **29** as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.99 (d, J = 16.2 Hz, 1H, vinyl), 7.64 (s, 1H, 2-phenyl), 7.60 (d, J = 8.0 Hz, 1H, 4-phenyl), 7.52 (d, J = 9.0 Hz, 1H, 5-pyridyl), 7.45 (d, J = 16.2 Hz, 1H, vinyl), 7.30 (d, J = 9.0 Hz, 1H, 4-pyridyl), 7.29 (dd, J = 8.0 Hz, 1H, 5-phenyl), 7.08 (d, J = 8.0 Hz, 1H, 6-phenyl), 5.30 (s, 2H, CH_2), 4.17 (t, J = 6.6 Hz, 2H, OCH_2), 1.95–0.86 (m, 23H, aliphatic); FAB-MS (+ve), 512.2 (M + H); (-ve), 504.5 (M – Li). Anal. ($C_{28}H_{35}NO_7Li_2 \cdot 3H_2O$) C, H, N.

The following compound was prepared by the same procedure using 1-iodo-8-(4-methoxyphenyl)octane. **(*E*)-3-[[6-(2-Carboxyvinyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]methoxy]benzoic Acid *N*-oxide, dilithium salt (42):** colorless amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.0 (d, J = 16.3 Hz, 1H, vinyl), 7.64 (s, 1H, 2-phenyl), 7.57 (d, J = 7.4 Hz, 1H, aryl), 7.51 (d, J = 9.0 Hz, 1H, pyridyl), 7.45 (d, J = 16.3 Hz, 1H, vinyl), 7.29 (m, 2H, pyridyl, aryl), 7.08 (m, 1H, aryl), 7.04 (d, J = 8.6 Hz, 2H, aryl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 5.30 (s, 2H, OCH_2), 4.16 (t, J = 6.5 Hz, 2H, OCH_2), 3.73 (s, 3H, OMe), 2.52 (t, J = 7.4 Hz, 2H, benzylic), 1.78 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); FAB-MS (+ve), 562.1 (M + H). Anal. ($C_{31}H_{33}NO_6Li_2 \cdot 2{}^1/_8H_2O$) C, H, N.

Preparation of (*E*)-3-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfinyl]benzoic Acid, Dilithium Salt (31): (*E*)-3-[[[5-(Dodecyloxy)-6-[2-(methoxycarbonyl)vinyl]pyridin-2-yl]methyl]sulfanyl]benzoic Acid Methyl Ester (26b). Chloride **25** (0.662 mmol) was dissolved in dry DMF (1 mL) and sequentially treated with methyl 3-mercaptobenzoate (167 mg, 0.993 mmol) and anhydrous Cs_2CO_3 (970 mg, 2.98 mmol) under an argon atmosphere. The reaction mixture was heated at 65 °C for 45 min. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Purification by flash column chromatography (petroleum ether–CH_2Cl_2–EtOAc, 70:25:5) gave 323 mg (92%) of **26b** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (s, 1H, 2-phenyl), 8.03 (d, J = 15.7 Hz, 1H, vinyl), 7.81 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.52 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.31 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.29 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.12 (d, J = 8.6 Hz, 1H, 4-pyridyl), 6.98 (d, J = 15.7 Hz, 1H, vinyl), 4.26 (s, 2H, CH_2S), 3.97 (t, J = 6.6 Hz, 2H, OCH_2), 3.90 (s, 3H, OMe), 3.81 (s, 3H, OMe), 1.85–0.85 (m, 23H, aliphatic).

(*E*)-3-[[[5-(Dodecyloxy)-6-(2-(methoxycarbonyl)vinyl)pyridin-2-yl]methyl]sulfinyl]benzoic Acid Methyl Ester (30). Sulfide **26b** (320 mg, 0.606 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and cooled to 0 °C. MCPBA (85%, 130 mg, 0.64 mmol)

was added, and the solution was stirred for 10 min at 0 °C. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Purification by flash column chromatography (CH_2Cl_2–petroleum ether–EtOAc, 50:25:25) gave 247 mg (75%) of **30** as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.11 (d, J = 7.9 Hz, 1H, 4-phenyl), 8.10 (s, 1H, 2-phenyl), 7.94 (d, J = 15.7 Hz, 1H, vinyl), 7.67 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.53 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.19 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.14 (d, J = 8.6 Hz, 1H, 4-pyridyl), 6.68 (d, J = 15.7 Hz, 1H, vinyl), 4.21 and 4.15 (d, J = 12.5 Hz, 2H, CH_2SO), 3.99 (t, J = 6.6 Hz, 2H, OCH_2), 3.93 (s, 3H, OMe), 3.81 (s, 3H, OMe), 1.87–0.85 (m, 23H, aliphatic); MS (CI) 544.3 (M + H). Anal. ($C_{31}H_{41}NO_6S$) C, H, N.

(*E*)-3-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfinyl]benzoic Acid, Dilithium Salt (31). Sulfoxide **30** (120 mg, 0.221 mmol) was dissolved in THF (1.3 mL) and MeOH (0.66 mL) under an argon atmosphere and treated with 1 M LiOH (0.66 mL, 0.66 mmol). The reaction was stirred at room temperature for 18 h. The THF and MeOH were removed under reduced pressure, and the product was purified by reversed-phase MPLC (10–65% MeOH in H_2O) and isolated by lyophilization to give 105 mg (90%) of **31** as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 8.27 (s, 1H, 2-phenyl), 8.11 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.77 (d, J = 15.7 Hz, 1H, vinyl), 7.60 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.58 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.27 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 7.01 (d, J = 8.6 Hz, 1H, 4-pyridyl), 4.33 and 4.25 (d, J = 12.5 Hz, 2H, CH_2SO), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 1.88–0.86 (m, 23H, aliphatic); FAB-MS (+ve), 528.5 (M + H). Anal ($C_{28}H_{35}NO_6SLi_2 \cdot 2H_2O$) C, H, N.

The following compounds were prepared by the same procedure using the appropriate thiophenol. **(*E*)-4-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfinyl]benzoic acid, dilithium salt (43):** colorless amorphous solid; mp 205–207 °C dec; ^{1}H NMR (250 MHz, MeOH-d_4) δ 8.09 (d, J = 8.5 Hz, 2H, aryl), 7.78 (d, J = 15.7 Hz, 1H, vinyl), 7.59 (d, J = 8.5 Hz, 2H, aryl), 7.26 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.07 (d, J = 15.7 Hz, 1H, vinyl), 6.98 (d, J = 8.6 Hz, 1H, 4-pyridyl), 4.33 and 4.22 (d, J = 12.5 Hz, 2H, CH_2SO), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 1.88–0.86 (m, 23H, aliphatic); FAB-MS (+ve), 528.5 (M + H). Anal. ($C_{28}H_{35}NO_6SLi_2 \cdot 1^1/_2H_2O$) C, H, N.

(*E*)-2-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfinyl]benzoic acid, dilithium salt (44): colorless amorphous solid; mp 235 °C dec; ^{1}H NMR (250 MHz, MeOH-d_4) δ 8.07 (d, J = 7.8 Hz, 1H, 3-phenyl), 7.76 (d, J = 7.8 Hz, 1H, 6-phenyl), 7.71 (d, J = 15.7 Hz, 1H, vinyl), 7.53 (m, 2H, aryl), 7.31 (s, 2H, pyridyl), 6.92 (d, J = 15.7 Hz, 1H, vinyl), 4.72 and 4.12 (d, J = 12.6 Hz, 2H, CH_2SO), 4.05 (t, J = 6.5 Hz, 2H, OCH_2), 1.88–0.86 (m, 23H, aliphatic); FAB-MS (+ve), 528.3 (M + H).

(*E*)-3-[[[6-(2-Carboxyvinyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]methyl]sulfinyl]benzoic acid, dilithium salt (45): colorless amorphous solid; mp 255 °C dec; ^{1}H NMR (250 MHz, MeOH-d_4) δ 8.30 (s, 1H, 2-phenyl), 8.11 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.72 (d, J = 15.8 Hz, 1H, vinyl), 7.55 (m, 2H, aryl), 7.22 (d, J = 8.6 Hz, 1H, pyridyl), 7.04 (m, 4H, vinyl, pyridyl, aryl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.33 and 4.22 (d, J = 12.5 Hz, 2H, CH_2SO), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 3.73 (s, 3H, OMe), 2.54 (t, J = 7.6 Hz, 2H, benzylic), 1.86 (m, 2H, CH_2), 1.58 (m, 4H, aliphatic), 1.38 (m, 6H, aliphatic); FAB-MS (+ve), 578.2 (M + H). Anal. ($C_{31}H_{33}NO_7SLi_2 \cdot 1^1/_2H_2O$) C, H, N.

(*E*)-3-[[[6-(2-Carboxyvinyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]methyl]sulfanyl]benzoic acid, dilithium salt (46): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.98 (s, 1H, 2-phenyl), 7.76 (d, J = 15.8 Hz, 1H, vinyl), 7.74 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.38 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.22 (m, 2H, pyridyl, 5-phenyl), 7.06 (d, J = 15.8 Hz, 1H, vinyl), 7.04 (d, J = 8.6 Hz, 2H, aryl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.22 (s, 2H, SCH_2), 3.99 (t, J = 6.5 Hz, 2H, OCH_2), 3.73 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.82 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.48 (m, 6H, aliphatic); FAB-MS (+ve), 562.4 (M + H). Anal. ($C_{31}H_{33}NO_6SLi_2 \cdot 3^3/_8H_2O$) C, H, N.

(*E*)-3-[6-[[(3-Aminophenyl)sulfanyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]acrylic acid, lithium salt (49): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.76 (d, J = 15.7 Hz, 1H, vinyl), 7.25 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.24 (d, J = 8.6 Hz, 1H, 4-pyridyl), 7.09 (d, J = 8.6 Hz, 2H, phenyl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.97 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 6.80 (d, J = 8.6 Hz, 2H, phenyl), 6.72 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.67 (ddd, J = 8.0, 1.9 Hz, 1H, 4′-phenyl), 6.51 (ddd, J = 8.0, 1.9 Hz, 1H, 6′-phenyl), 4.16 (s, 2H, CH_2-S), 4.00 (t, J = 6.5 Hz, 2H, OCH_2), 3.74 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.80 (m, 2H, CH_2), 1.49 (m, 4H, aliphatic), 1.33 (m, 6H, aliphatic); MS (FAB) 527 (M + H), 521 (M + H; free acid). Anal. ($C_{30}H_{35}N_2O_4SLi \cdot 2^1/_2H_2O$) C, H, N.

(*E*)-3-[6-[[(3-Aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]acrylic acid, lithium salt (50): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.28 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.15 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 7.03 (m, 4H, 4-pyridyl, vinyl, phenyl), 6.86 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.75 (m, 4H, 4′,6′-phenyl, phenyl), 4.30 and 4.20 (d, J = 13 Hz, 2H, CH_2-S), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 3.72 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.53 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); MS (FAB) 543 (M + H), 537 (M + H; free acid). Anal. ($C_{30}H_{35}N_2O_5SLi \cdot 2H_2O$) C, H, N.

Preparation of (*E*)-3-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfonyl]benzoic Acid, Dilithium Salt (33): (*E*)-3-[[[5-(Dodecyloxy)-6-[2-(methoxycarbonyl)vinyl]pyridin-2-yl]methyl]sulfonyl]benzoic Acid Methyl Ester (32). Sulfide **26b** (103 mg, 0.197 mmol) was dissolved in dry CH_2Cl_2 (2 mL), cooled to 0 °C, and treated with 85% MCPBA (88 mg, 0.433 mmol). The reaction was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$). The product was purified by flash column chromatography (CH_2Cl_2–EtOAc, 60:25:15) to give 105 mg (95%) of **32** as a colorless noncrystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.30 (s, 1H, 2-phenyl), 8.26 (d, J = 7.7 Hz, 1H, 4-phenyl), 7.83 (d, J = 7.7 Hz, 1H, 6-phenyl), 7.82 (d, J = 15.7 Hz, 1H, vinyl), 7.55 (dd, J = 7.7 Hz, 1H, 5-phenyl), 7.42 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.21 (d, J = 8.6 Hz, 1H, 4-pyridyl), 6.28 (d, J = 15.7 Hz, 1H, vinyl), 4.52 (s, 2H, CH_2SO_2), 4.00 (t, J = 6.6 Hz, 2H, OCH_2), 3.92 (s, 3H, OMe), 3.78 (s, 3H, OMe), 1.87–0.85 (m, 23H, aliphatic); MS (CI) 560.3 (M + H). Anal. ($C_{30}H_{41}NO_7S$) C, H, N.

(*E*)-3-[[[6-(2-Carboxyvinyl)-5-(dodecyloxy)pyridin-2-yl]methyl]sulfonyl]benzoic Acid, Dilithium Salt (33). Sulfone **32** (170 mg, 0.303 mmol) was dissolved in THF (3.0 mL) and MeOH (1.0 mL) and treated with 1 M LiOH (1.0 mL, 1.0 mmol). The reaction mixture was stirred at room temperature for 24 h. The THF and MeOH were removed under reduced pressure, and the product was purified by reversed-phase MPLC (10–65% MeOH in H_2O) and isolated by lyophilization to give 148 mg (90%) of **33** as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 8.40 (s, 1H, 2-phenyl), 8.22 (d, J = 7.9 Hz, 1H, 4-phenyl), 7.69 (d, J = 7.9 Hz, 1H, 6-phenyl), 7.67 (d, J = 15.7 Hz, 1H, vinyl), 7.53 (dd, J = 7.9 Hz, 1H, 5-phenyl), 7.30 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.18 (d, J = 8.6 Hz, 1H, 4-pyridyl), 6.85 (d, J = 15.7 Hz, 1H, vinyl), 4.62 (s, 2H, CH_2SO_2), 4.03 (t, J = 6.5 Hz, 2H, OCH_2), 1.87–0.86 (m, 23H, aliphatic); FAB-MS (+ve), 544.3 (M + H); (-ve), 536.2 (M – Li). Anal. ($C_{28}H_{35}NO_7SLi_2 \cdot 1^3/_4H_2O$) C, H, N.

The following compound was prepared by the same procedure. **(*E*)-3-[6-[[(3-Aminophenyl)sulfonyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]acrylic acid, lithium salt (51):** colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.65 (d, J = 15.7 Hz, 1H, vinyl), 7.26 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.24 (d, J = 8.6 Hz, 1H, 4-pyridyl), 7.17 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 7.06 (d, J = 8.6 Hz, 2H, phenyl), 6.97 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.85 (m, 2H, 4′,6′-phenyl), 6.78 (d, J = 8.6 Hz, 2H, phenyl), 6.75 (d, J = 15.7 Hz, 1H, vinyl), 4.55 (s, 2H, CH_2S), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 3.74 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.86 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); MS (FAB) 559 (M + H), 553 (M + H; free acid).

Preparation of (*E*)-3-[6-[[[3-[(Phenylsulfonyl)amino]phenyl]sulfanyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl]acrylic Acid, Dilithium Salt (36). Aniline **34** (204 mg, 0.38 mmol) was dissolved in dry CH_2Cl_2 (3 mL) under an argon atmosphere and treated with Et_3N (0.11 mL, 0.76 mmol). The solution was cooled to 0 °C and benzenesulfonyl chloride (100 mg, 0.57 mmol) was added. The reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with H_2O and the

product extracted into EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Purification by flash column chromatography (20% EtOAc in hexane) gave 243 mg (95%) of sulfonamide **35** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, J = 15.7 Hz, 1H, vinyl), 7.94 (d, J = 7.9 Hz, 2H, aryl), 7.68 (t, J = 7.9 Hz, 1H, aryl), 7.55 (dd, J = 7.9 Hz, 2H, aryl), 7.46 (s, 1H, 2-phenyl), 7.20 (m, 5H, aryl, pyridyl), 7.12 (d, J = 8.6 Hz, 2H, aryl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.91 (s, 1H, NH), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.10 (s, 2H, SCH_2), 3.95 (t, J = 6.5 Hz, 2H, OCH_2), 3.81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 2.53 (t, J = 7.6 Hz, 2H, benzylic), 1.79 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 1.31 (m, 6H, aliphatic); MS (CI) 675 (M + H).

Sulfonamide **35** was hydrolyzed with LiOH by methods already described to give **36** as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.76 (d, J = 15.7 Hz, 1H, vinyl), 7.72 (d, J = 7.9 Hz, 2H, aryl), 7.43 (m, 3H, aryl), 7.18–6.85 (m, 9H, aryl, pyridyl, vinyl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.08 (s, 2H, SCH_2), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 3.73 (s, 3H, OMe), 2.51 (t, J = 7.6 Hz, 2H, benzylic), 1.80 (m, 2H, CH_2), 1.57 (m, 4H, aliphatic), 1.34 (m, 6H, aliphatic); FAB-MS (+ve), 673.3 (M + H).

Preparation of (*E*)-3-{6-[[[3-[9Phenylsulfonyl)amino]-phenyl]sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}acrylic Acid, Monolithium Salt (40). Prepared by MCPBA oxidation of **35** followed by hydrolysis using methods analogous to those previously described: colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.92 (m, 2H, aryl), 7.79 (d, J = 15.7 Hz, 1H, vinyl), 7.44 (m, 3H, aryl), 7.32 (s, 1H, NH), 7.15 (m, 6H, aryl, pyridyl), 7.08 (d, J = 15.7 Hz, 1H, vinyl), 6.82 (m, 4H, aryl), 4.22 and 4.08 (d, J = 13 Hz, 2H, CH_2-SO), 4.05 (t, J = 6.5 Hz, 2H, OCH_2), 3.78 (s, 3H, OMe), 2.56 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.38 (m, 6H, aliphatic); FAB-MS (+ve), 683.2 (M + H).

The following compounds were prepared by methods similar to those reported for the preparation of **36** and **40**.

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[[[3-[[(trifluoromethyl)sulfonyl]amino]phenyl]sulfanyl]methyl]pyridin-2-yl}acrylic acid, dilithium salt (47):colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.19 (d, J = 8.6 Hz, 1H, pyridyl), 7.18 (s, 1H, 2-phenyl), 7.17 (d, J = 8.6 Hz, 1H, pyridyl), 7.08 (d, J = 8.6 Hz, 2H, aryl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.97 (m, 2H, aryl), 6.80 (m, 1H, aryl), 6.79 (d, J = 8.6 Hz, 2H, aryl), 4.17 (s, 2H, SCH_2), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 3.75 (s, 3H, OMe), 2.53 (t, J = 7.6 Hz, 2H, benzylic), 1.80 (m, 2H, CH_2), 1.52 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); FAB-MS (+ve), 665.3 (M + H); (ES+), 653.0 (M + H, free acid).

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[[[3-[[(trifluoromethyl)sulfonyl]amino]phenyl]sulfinyl]methyl]pyridin-2-yl}acrylic acid, dilithium salt (48):colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.78 (d, J = 15.7 Hz, 1H, vinyl), 7.44 (s, 1H, 2-phenyl), 7.26 (dd, J = 8.0 Hz, 2H, pyridyl), 7.21 (d, J = 8.4 Hz, 1H, 4-phenyl), 7.09 (m, 4H, aryl, vinyl), 6.92 (d, J = 8.4 Hz, 1H, 6-phenyl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.33 and 4.15 (d, J = 13 Hz, 2H, CH_2SO), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 3.74 (s, 3H, OMe), 2.53 (t, J = 7.6 Hz, 2H, benzylic), 1.83 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); FAB-MS (+ve), 681.4 (M + H).

(*E*)-3-{6-[[[3-[(Carboxycarbonyl)amino]phenyl]sulfanyl]-methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}-acrylic acid, dilithium salt (57):colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.86 (s, 1H, 2-phenyl), 7.78 (d, J = 15.7 Hz, 1H, vinyl), 7.42 (d, J = 8.4 Hz, 1H, aryl), 7.27 (s, 2H, pyridyl), 7.20 (dd, J = 8.4 Hz, 1H, 5-phenyl), 7.09 (d, J = 8.4 Hz, 1H, aryl), 7.06 (d, J = 8.6 Hz, 2H, aryl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.25 (s, 2H, SCH_2), 4.01 (t, J = 6.5 Hz, 2H, OCH_2), 3.76 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.58 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); FAB-MS (+ve), 605.3 (M + H).

Preparation of (*E*)-3-{6-[[[3-(Dimethylamino)phenyl]sulfanyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}acrylic Acid, Lithium Salt (38): (*E*)-3-{6-[[3-(Dimethylamino)phenyl]sulfanyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}acrylic Acid Methyl Ester (37). To a solution of **34** (75 mg, 0.14 mmol) in MeCN (1 mL) was added formaldehyde (0.25 mL, 3.1 mmol; 37% aqueous solution) and $NaCNBH_3$ (50 mg, 0.80 mmol). The reaction mixture was stirred at room temperature for 15 min. The reaction solution was made neutral by the addition of glacial HOAc and stirred for an additional 2 h. The reaction mixture was diluted with H_2O and the product extracted into EtOAc. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (20% EtOAc in hexane) gave 56 mg (72%) of **37** as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 (d, J = 15.7 Hz, 1H, vinyl), 7.35 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.08 (m, 4H, 4-pyridyl, 5′-phenyl, phenyl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.83 (d, J = 8.6 Hz, 2H, phenyl), 6.74 (m, 2H, 2′,4′-phenyl), 6.52 (dd, J = 8.0, 1.9 Hz, 1H, 6′-phenyl), 4.23 (s, 2H, CH_2-S), 4.00 (t, J = 6.5 Hz, 2H, OCH_2), 3.82 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.89 (s, 6H, Me_2), 2.55 (t, J = 7.6 Hz, 2H, benzylic), 1.83 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 6H, aliphatic); MS (CI) 563 (M + H).

(*E*)-3-{6-[[[3-(Dimethylamino)phenyl]sulfanyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}acrylic Acid, Lithium Salt (38). Dimethylaniline **37** was hydrolized by methods previously described to give **38** (64%) as a colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.78 (d, J = 15.7 Hz, 1H, vinyl), 7.25 (s, 2H, 4,5-pyridyl), 7.07 (m, 4H, phenyl, vinyl, 5′-phenyl), 6.80 (d, J = 8.6 Hz, 2H, phenyl), 6.72 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.67 (ddd, J = 8.0, 1.9 Hz, 1H, 4′-phenyl), 6.55 (ddd, J = 8.0, 1.9 Hz, 1H, 6′-phenyl), 4.20 (s, 2H, CH_2-S), 4.00 (t, J = 6.5 Hz, 2H, OCH_2), 3.76 (s, 3H, OMe), 2.85 (s, 6H, Me_2), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.33 (m, 6H, aliphatic); MS (FAB) 555.2 (M + H). Anal. ($C_{32}H_{39}N_2O_4SLi\cdot1^1/_4H_2O$) C, H, N.

(*E*)-3-{6-[[[3-(Dimethylamino)phenyl]sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]pyridin-2-yl}acrylic acid, lithium salt (56) was prepared from **37** according to procedures already described: colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.31 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 7.24 (d, J = 8.6 Hz, 1H, 5-pyridyl), 7.03 (m, 3H, 4-pyridyl, phenyl), 6.95 (d, J = 15.7 Hz, 1H, vinyl), 6.80 (m, 4H, aryl), 6.70 (m, 1H, aryl), 4.25 and 4.15 (d, J = 13 Hz, 2H, CH_2S), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 3.74 (s, 3H, OMe), 2.84 (s, 6H, Me_2), 2.56 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.53 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); MS (FAB): 571.3 (M + H).

The following compounds were prepared using methods similar to those already described. **(*E*)-3-{6-[[(3-Aminophenyl)sulfanyl]methyl]-3-[[8-[4-(trifluoromethyl)phenyl]octyl]oxy]-pyridin-2-yl}acrylic acid, lithium salt (60)**:colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.78 (d, J = 15.7 Hz, 1H, vinyl), 7.53 (d, J = 8.6 Hz, 2H, phenyl), 7.34 (d, J = 8.6 Hz, 2H, phenyl), 7.25 (d, J = 8.6 Hz, 1H, pyridyl), 7.24 (d, J = 8.6 Hz, 1H, pyridyl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.97 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 6.72 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.67 (ddd, J = 8.0, 1.9 Hz, 1H, 4′-phenyl), 6.51 (ddd, J = 8.0, 1.9 Hz, 1H, 6′-phenyl), 4.16 (s, 2H, CH_2S), 4.01 (t, J = 6.5 Hz, 2H, OCH_2), 2.68 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.68 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.37 (m, 6H, aliphatic); MS (ES+) 559.0 (M + H; free acid), (ES−) 557.0 (M − H; free acid). Anal. ($C_{30}H_{32}F_3N_2O_3SLi\cdot1^1/_2H_2O$) C, H, N.

(*E*)-3-{6-[[(3-Aminophenyl)sulfinyl]methyl]-3-[[8-[4-(trifluoromethyl)phenyl]octyl]oxy]pyridin-2-yl}acrylic acid, lithium salt (61):colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.53 (d, J = 8.6 Hz, 2H, phenyl), 7.34 (d, J = 8.6 Hz, 2H, phenyl), 7.24 (d, J = 8.6 Hz, 1H, pyridyl), 7.18 (d, J = 8.6 Hz, 1H, pyridyl), 7.04 (d, J = 8.0 Hz, 1H, 4′-phenyl), 7.02 (d, J = 15.7 Hz, 1H, vinyl), 6.89 (s, 1H, 2′-phenyl), 6.78 (m, 2H, 5′,6′-phenyl), 4.25 and 4.15 (d, J = 13 Hz, 2H, CH_2SO), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.39 (m, 6H, aliphatic); MS (ES+): 575.2 (M + H; free acid). Anal. ($C_{30}H_{32}F_3N_2O_4SLi\cdot1^3/_4H_2O$) C, H, N.

(*E*)-3-{6-[[(3-Aminophenyl)sulfanyl]methyl]-3-[(8-phenyloctyl)oxy]pyridin-2-yl}acrylic acid, lithium salt (58): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.72 (d, J = 15.7 Hz, 1H, vinyl), 7.20 (m, 7H, pyridyl, phenyl), 7.04 (d, J = 15.7 Hz, 1H, vinyl), 6.97 (dd, J = 8.0 Hz, 1H, 5′-phenyl), 6.72 (dd, J = 1.9 Hz, 1H, 2′-phenyl), 6.67 (ddd, J = 8.0, 1.9 Hz, 1H, 4′-phenyl), 6.51 (ddd, J = 8.0, 1.9 Hz, 1H, 6′-phenyl),

4.16 (s, 2H, CH_2-S), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.83 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.37 (m, 6H, aliphatic); MS (ES+): 491.0 (M + H; free acid), (ES−) 489.0 (M − H; free acid).

(*E*)-3-{6-[[(3-Aminophenyl)sulfinyl]methyl]-3-[(8-phenyloctyl)oxy]pyridin-2-yl}acrylic acid, lithium salt (59): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.20 (m, 7H, pyridyl, phenyl), 7.04 (d, J = 8.0 Hz, 1H, 4′-phenyl), 7.02 (d, J = 15.7 Hz, 1H, vinyl), 6.89 (s, 1H, 2′-phenyl), 6.78 (m, 2H, 5′,6′-phenyl), 4.25 and 4.13 (d, J = 13 Hz, 2H, CH_2SO), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.39 (m, 6H, aliphatic); MS (ES+) 507.0 (M + H; free acid), (ES−) 505.0 (M − H; free acid). Anal. ($C_{29}H_{33}N_2O_4SLi\cdot H_2O$) C, H, N.

(*E*)-3-{6-[[(3-Aminophenyl)sulfinyl]methyl]-3-[[8-(4-fluorophenyl)octyl]oxy]pyridin-2-yl}acrylic acid, lithium salt (62):colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.30–6.90 (multiplet, 8H, pyridyl, phenyl, vinyl, 4′-phenyl), 6.89 (s, 1H, 2′-phenyl), 6.78 (m, 2H, 5′,6′-phenyl), 4.25 and 4.15 (d, J = 13 Hz, 2H, CH_2SO), 4.02 (t, J = 6.5 Hz, 2H, OCH_2), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.39 (m, 6H, aliphatic); MS (ES+) 525.2 (M + H; free acid), (ES−) 523.0 (M − H; free acid).

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[[(3-methoxyphenyl)sulfanyl]methyl]pyridin-2-yl}acrylic acid, lithium salt (52):colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.48 (d, J = 15.7 Hz, 1H, vinyl), 7.45 (d, J = 8.0 Hz, 1H, 4-phenyl), 7.38 (s, 1H, 2-phenyl), 7.22 (dd, J = 8.0 Hz, 1H, 5-phenyl), 7.17 (d, J = 8.6 Hz, 2H, aryl), 7.02 (d, J = 8.6 Hz, 2H, pyridyl), 6.90 (d, J = 15.7 Hz, 1H, vinyl), 6.86 (d, J = 8.6 Hz, 2H, aryl), 4.37 (s, 2H, SCH_2), 4.08 (t, J = 6.5 Hz, 2H, OCH_2), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.58 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.35 (m, 6H, aliphatic); FAB-MS (+ve) 542 (M + H).

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[[(3-methoxyphenyl)sulfinyl]methyl]pyridin-2-yl}acrylic acid, lithium salt (53):colorless amorphous solid: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.71 (d, J = 15.7 Hz, 1H, vinyl), 7.38 (m, 1H, aryl), 7.29 (d, J = 8.0 Hz, 1H, aryl), 7.08 (m, 6H, aryl, pyridyl), 6.93 (d, J = 15.7 Hz, 1H, vinyl), 6.82 (d, J = 8.6 Hz, 2H, aryl), 4.28 and 4.17 (d, J = 13 Hz, 2H, CH_2SO), 4.03 (t, J = 6.5 Hz, 2H, OCH_2), 3.77 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.52 (t, J = 7.6 Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.54 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); FAB-MS (+ve) 558 (M + H). Anal. ($C_{31}H_{36}NO_6SLi\cdot 2H_2O$) C, H, N.

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[(phenylsulfanyl)methyl]pyridin-2-yl}acrylic acid, lithium salt (54): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.75 (d, J = 15.7 Hz, 1H, vinyl), 7.38–7.13 (m, 7H, aryl, pyridyl), 7.08 (d, J = 8.6 Hz, 2H, aryl), 7.03 (d, J = 15.7 Hz, 1H, vinyl), 6.78 (d, J = 8.6 Hz, 2H, aryl), 4.21 (s, 2H, SCH_2), 4.04 (d, J = 6.5 Hz, 2H, OCH_2), 3.73 (s, 3H, OMe), 2.51 (t, J = 7.6 Hz, 2H, benzylic), 1.82 (m, 2H, CH_2), 1.52 (m, 4H, aliphatic), 1.34 (m, 6H, aliphatic); FAB-MS (+ve) 512 (M + H).

(*E*)-3-{3-[[8-(4-Methoxyphenyl)octyl]oxy]-6-[(phenylsulfinyl)methyl]pyridin-2-yl}acrylic acid, lithium salt (55): colorless amorphous solid; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.72 (d, J = 15.7 Hz, 1H, vinyl), 7.56 (m, 5H, aryl), 7.30 (d, J = 8.6 Hz, 1H, pyridyl), 7.08 (m, 3H, aryl, pyridyl), 6.92 (d, J = 15.7 Hz, 1H, vinyl), 6.78 (d, J = 8.6 Hz, 2H, aryl), 4.37 and 4.22 (d, J = 13 Hz, 2H, CH_2SO), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 3.74 (s, 3H, OMe), 2.54 (t, J = 7.6 Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.38 (m, 6H, aliphatic); FAB-MS (+ve) 528 (M + H).

Biological Evaluation. [^{3}H]LTB_4 Binding Assays. [^{3}H]-LTB_4 with specific activity of 140–210 Ci/mmol was obtained from New England Nuclear (Boston, MA). Unlabeled LTB_4 was synthesized by the Medicinal Chemistry Prep Group at Smith-Kline Beecham.

Human peripheral blood from healthy aspirin-free donors was phlebotomized into sterile heparinized syringes. PMNs were isolated by the standard Ficoll-Hypaque centrifugation, dextran 70 sedimentation and hypotonic lysis procedure.[16] Cell preparations were >90% neutrophils and >95% viable.

Test compounds were evaluated for the ability to compete with [^{3}H]LTB_4 for receptors on intact human PMNs utilizing methods described previously.[17,18] Equilibrium binding for washed PMNs (10^6 cells) was performed at 0 °C for 20 min in Hanks balanced salt solution with 0.1% ovalbumin and 0.2 nM [^{3}H]LTB_4 in a total volume of 500 μL. Total and nonspecific binding of [^{3}H]LTB_4 were determined in the absence and presence of 1 μM unlabeled LTB_4, respectively. For radioligand competition experiments increasing concentrations of LTB_4 (0.05–10 nM) or test compound (0.1 nM–10 μM) were included. Unbound radioligand and competing compounds were separated from cell-bound ligand by vacuum filtration through Whatman GF/C filters. Cell bound radioactivity was determined by liquid scintillation spectrometry. The percent inhibition of specific [^{3}H]LTB_4 binding was determined for each concentration, and the IC_{50} is defined as the concentration of test compound required to inhibit 50% of the specific [^{3}H]LTB_4 binding. Concentration response curves (five to eight concentrations) for all compounds were run in duplicate and tested in at least two assays. Values presented are the mean K_i values which were determined from the mean IC_{50} as described by Cheng and Prusoff[19] using the following equation:

$$K_i = \frac{IC_{50}}{[1 + [L]/K_d]}$$

where [L] is the concentration of added ligand and the K_d, as determined from saturation studies, is 0.15 nM.

LTB_4-Induced Calcium Mobilization. The functional assay used to determine agonist/antagonist activity of test compounds was LTB_4-induced calcium mobilization in human PMNs and U-937 cells.[20] U-937 cells were obtained from American Type Culture Collection and grown in RPMI-1640 media supplemented with 10% (v/v) heat-inactivated fetal calf serum in spinner culture in a humidified environment of 5% CO_2, 95% air at 37 °C. U-937 cells were differentiated with 1.3% DMSO for 3–4 days, grown to a density of 10^6 cells/mL, and then harvested by centrifugation. Cells were washed with 50 mM Tris, pH 7.4, containing 1 mM EDTA. Washed PMN and U-937 cells (described above) were utilized for calcium mobilization studies. The $[Ca^{2+}]_i$ was estimated with the calcium fluorescent probe fura 2.[21] Isolated PMNs were suspended in Krebs Ringer Hensilet at 2×10^6 cells/mL containing 0.1% BSA, 1.1 mM $MgCl_2$ and 5 mM HEPES, pH 7.4 (buffer A). The diacetoxymethoxy ester of fura 2 (fura 2/AM) was added at a concentration of 2 μM and incubated for 45 min at 37 °C. Cells were centrifuged at 225g for 5 min and resuspended at 2×10^6 cells/mL in buffer A and incubated an additional 20 min to allow complete hydrolysis of the entrapped ester. Cells were centrifuged as above and resuspended at 10^6 cells/mL in buffer A containing 1 mM $CaCl_2$. The cells were maintained at room temperature until used in the fluorescent assay which was performed within 3 h for PMN and 5 h for U-937 cells.

The fluorescence of fura 2 containing cells was measured with a fluorometer designed by the Johnson Foundation Biomedical Instrumentation Group. The fluorometer was equipped with a temperature control and a magnetic stirrer under the cuvette holder. Wavelengths were set at 340 nm (10-nm band width) for excitation and 510 nm (20-nm band width) for emission. All experiments were performed at 37 °C with constant stirring. For compound studies, fura 2 loaded cells were centrifuged and resuspended in buffer A containing 1 mM $CaCl_2$ minus BSA at 10^6 cells/mL. For agonist activity, a 2-mL aliquot of PMNs was added to a cuvette and warmed in a water bath to 37 °C. The 1-cm^2 cuvette was transferred to the fluorometer, and fluorescence was recorded for 15 s to ensure a stable baseline before addition of compound. Fluorescence was recorded continuously for up to 2 min after addition of compounds to monitor for the presence of any agonist activity. None of the compounds from the present study demonstrated agonist activity up to 10 μM.

For antagonist studies, varying concentrations of antagonists or vehicle were added to the fura 2 loaded U-937 cells and monitored for 1 min to ensure that there was no change in baseline fluorescence followed by the addition of 1 nM LTB_4. The maximal $[Ca^{2+}]$/fura 2 fluorescence was then determined for each

sample. The $[Ca^{2+}]_i$ was calculated using the following formula as previously described:[17]

$$[Ca^{2+}]_i = 224\ (nM)\ \frac{F - F_{min}}{F_{max} - F}$$

The percent of maximal LTB_4 (1 nM) induced $[Ca^{2+}]_i$ was determined for each concentration of compound and the IC_{50} defined as the concentration of test compound that inhibits 50% of the maximal LTB_4 response. The dose–response curve for each compound (five to seven concentrations) was run in two different assays.

References

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