Synthesis of Potent Leukotriene A_4 Hydrolase Inhibitors. Identification of 3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanoic Acid

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Leukotriene B_4 (LTB_4) is a potent, proinflammatory mediator involved in the pathogenesis of a number of diseases including inflammatory bowel disease, psoriasis, rheumatoid arthritis, and asthma. The enzyme LTA_4 hydrolase represents an attractive target for pharmacological intervention in these disease states, since the action of this enzyme is the rate-limiting step in the production of LTB_4. Our previous efforts focused on the exploration of a series of analogues related to screening hit SC-22716 (**1**, 1-[2-(4-phenylphenoxy)ethyl]pyrrolidine) and resulted in the identification of potent, orally active inhibitors such as **2**. Additional structure−activity relationship studies around this structural class resulted in the identification of a series of α-, *β*-, and *γ*-amino acid analogues that are potent inhibitors of the LTA_4 hydrolase enzyme and demonstrated good oral activity in a mouse ex vivo whole blood LTB_4 production assay. The efforts leading to the identification of clinical candidate SC-57461A (**8d**, 3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanoic acid) are described.

Introduction

Leukotriene B_4 (LTB_4) is a 5-lipoxygenase (5-LO)-derived metabolite of arachidonic acid that is synthesized by a number of cell types, including eosinophils, neutrophils (PMNs), and macrophages.[1] LTB_4 is a potent proinflammatory mediator that plays a significant role in the amplification of many inflammatory disease states[2] including inflammatory bowel disease (IBD),[3] psoriasis,[4] rheumatoid arthritis,[5] gout,[6] and asthma.[7] LTB_4 also stimulates the production of various cytokines and may play a role in immunoregulation.[8−11] In addition, LTB_4 is a mediator of inflammatory pain[12] and binds to peroxisome proliferator-activated receptor (PPARα), which could affect the duration of an inflammatory response to LTB_4.[13]

Leukotriene A_4 (LTA_4) hydrolase is a zinc-containing enzyme[14] that stereospecifically catalyzes the hydrolysis of the unstable epoxide LTA_4 to LTB_4, the rate-limiting step in the biosynthesis of LTB_4. LTA_4 hydrolase is a cytosolic, monomeric enzyme that is ubiquitously distributed in mammalian tissues.[15] Selective inhibitors of LTA_4 hydrolase would preferentially block the formation of LTB_4 (vs the cysteinyl leukotrienes LTC_4, LTD_4, and LTE_4) and thus would be an attractive pharmacological target.

A variety of inhibitors of LTA_4 hydrolase have been reported over the past several years, a topic that has recently been reviewed.[16] Our previously described efforts[17] focused on the exploration of a series of analogues related to screening hit SC-22716 (**1**), an early lead that inhibited LTA_4 hydrolase with an IC_{50} of 0.20 *μ*M and demonstrated good cellular activity in a calcium ionophore-stimulated human whole blood assay, inhibiting the production of LTB_4 with an IC_{50} of 0.79 *μ*M. However, **1** demonstrated poor oral activity in a mouse ex vivo whole blood LTB_4 production assay (9% inhibition at 10 mg/kg). These efforts resulted in the identification of potent, orally active analogues such as **2**, which had IC_{50} values of 0.043 and 0.055 *μ*M in the enzyme and whole blood assays and demonstrated good oral activity in the mouse ex vivo assay (93% inhibition at 10 mg/kg). In the present study, we describe our efforts on a unique series of α-, *β*-, and *γ*-amino acid analogues developed from these earlier leads in an effort to further optimize the oral efficacy of this class. A number of these analogues were potent inhibitors of LTA_4 hydrolase and showed excellent oral activity in the mouse ex vivo assay, resulting in the identification of clinical candidate SC-57461A (**8d**).

Chemistry

Our previous report described a detailed structure−activity study of initial lead **1**, which included numerous modifications of the amino functional group. In the present study, we sought to broaden the scope of this work by investigating a series of acyclic amino acid analogues. The initial series shown in Table 1 maintained the diphenylmethane functionality while varying the length of the linkers between the oxygen and nitrogen atoms (*x* linker) and the nitrogen and carboxylate functionality (*y* linker). Secondary amines, as well as methyl-substituted tertiary amines, were also explored. A second series (Table 2) varied the aryl functionality while maintaining an optimized right-hand-side amino acid moiety. The third series shown in Table

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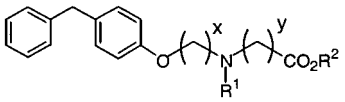
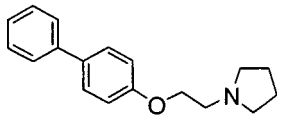
Table 1. Amino Acid Modifications

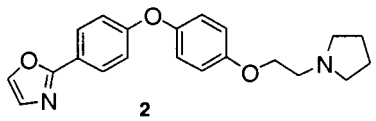


compd	*x*	*y*	R^1	R^2	IC_{50}[a] (μM) rhLTA$_4$ hydrolase	IC_{50}[a] (μM) human whole blood	ED_{90} (mg/kg) mouse ex vivo
1 (SC-22716)					0.2 (2)	0.79	9% @ 10 mg/kg
2					0.043	0.055	93% @ 10 mg/kg
3a	2	1	H	Et	2.5 (2)	>30(2)	*b*
4a	2	2	H	Me	0.22 (1)	0.59	62% @ 10 mg/kg
5a	2	3	H	Et	3.7	2.5 (2)	*b*
6a	2	4	H	Et	10.7 (2)	2.5 (2)	*b*
7a	3	1	H	Et	3.0 (2)	1.1	22% @ 10 mg/kg
8a	3	2	H	Et	0.084	0.45	54% @ 10 mg/kg
8b	3	2	H	H	0.14 (2)	0.28	≥10
9a	4	1	H	Et	0.014	0.35	≥10
9b	4	1	H	H	0.0013	0.23	≥10
10a	4	2	H	Et	0.007	0.076	3
10b	4	2	H	H	0.018	0.49	70% @ 10 mg/kg
11a	5	1	H	Et	0.25	0.42	10
5c	2	3	Me	Me	0.45	0.46	≥10
8c	3	2	Me	Et	0.19	0.11	3−10
8d (SC-57461A)	3	2	Me	H	0.0025	0.049	1−3
9c	4	1	Me	Et	6.6	3.3 (2)	*b*
9d	4	1	Me	H	0.11	0.45	*b*
10c	4	2	Me	Et	>10	0.52	*b*

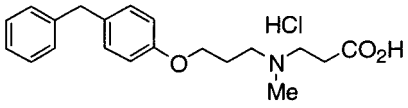
[a] Average of at least three determinations except where noted in parentheses. [b] Not determined.



1 (SC-22716)



2



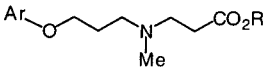
8d (SC-57461A)

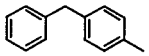
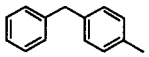
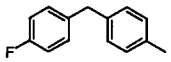
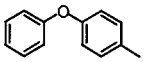
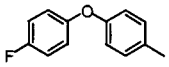
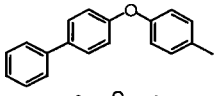
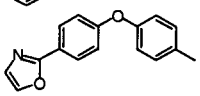
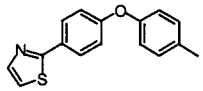
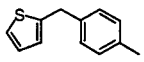
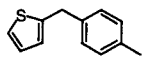
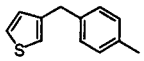
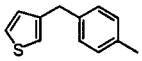
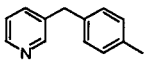
3 explored isosteric replacements for the carboxylate functional group. Scheme 1 details the various synthetic routes utilized in the synthesis of these analogues. In general, all phenol starting materials either were commercially available or could be easily prepared as previously described.[17,18] These phenols were alkylated using a bromochloroalkane to give chloride **21**.[17] Alkylation of an amino ester **22** in the presence of potassium carbonate and sodium iodide in DMF at 80 °C then provided the desired amino esters. Similarly, the phenols could be converted to tosylate **23** (alkylation with bromo *tert*-butylacetate, reduction, tosylation)[18] and combined with **22** to give the amino esters. Alternatively, chloride **21** was reacted with methylamine to give **24**, followed by 1,4-conjugate addition to an acrylate ester, to provide an *N*-methylamino ester. A phenol could also be alkylated with bromoacetaldehyde diethyl acetal to give, after hydrolysis of the acetal, aldehyde **25**. Reductive amination with the appropriate amino ester provided the desired amino esters. Alkylation of a phenol with chloronitrile **26** (prepared from 1-bromo-3-chloropropane and *N*-methyl-β-alaninenitrile) gave, after hydrolysis of the nitrile, the target amino acid. In cases where a secondary amino ester was produced, the amine was methylated under reductive amination conditions using aqueous formaldehyde and sodium cyanoborohydride to provide the *N*-methylamino ester. All esters were converted to their respective carboxylic acids either under acidic conditions for methyl and ethyl esters or under catalytic hydrogenolysis conditions for benzyl esters.

Results and Discussion

Table 1 details an extensive structure−activity effort in which the length of the linkers between the oxygen and nitrogen atoms (*x* linker) and between the nitrogen and carboxylate moiety (*y* linker) was explored while maintaining the diphenylmethane functionality. In addition, substitution at nitrogen and potential differences between acids and esters were also explored. In the NH series of analogues with a two-carbon *x* linker, the analogue with a two-carbon *y* linker (**4a**) was optimal, with an IC_{50} of 0.22 and 0.59 μM in the LTA_4 hydrolase enzyme and human whole blood assays, respectively. One-, three-, and four-carbon *y* linkers all had significantly reduced potency. In the series where the *x* linker is three carbons, an analogue with a two-carbon *y* linker was optimal (**8a**) with an IC_{50} of 0.084 and 0.45 μM in the enzyme and whole blood assays. In the four-carbon *x* linker series, both one- and two-carbon *y* linker analogues (**9a** and **10a**) showed excellent potency in the enzyme assay (IC_{50} = 0.014 and 0.007 μM). A five-carbon *x* linker analogue **11a** showed slightly diminished enzyme potency. Although in general the acids did show a trend toward increased potency over the esters in the enzyme assay, this was not reflected in either the whole blood or mouse ex vivo assays, where the

Table 2. Aryl Modifications



compd	Ar	R	IC50 (μM)[a] rhLTA4 hydrolase	IC50 (μM)[a] human whole blood	mouse ex vivo ED90 (mg/kg)
8c		Et	0.19	0.11	3-10
8d		H	0.0025	0.049	1-3
12d		H	0.031	0.19	≥10
13d		H	0.019	0.23	3
14d		H	0.16	0.21	3
15d		H	<0.0005	0.19	10
16d		H	0.027	0.19	≥10
17d		H	0.95 (1)	0.072	87% @ 10 mg/kg
18c		Me	0.016	0.095	3-10
18d		H	0.0047	0.12	3-10
19c		Me	0.87	0.25	1-3
19d		H	0.002	0.19	3-10
20c		Me	0.82	0.3	58% @ 10 mg/kg

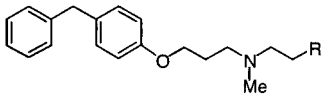
[a] Average of at least three determinations except where noted in parentheses.

esters and acids demonstrated similar potency. It is likely that the esters are simply converted to the corresponding acids in the ex vivo assay, although we currently have no data to support this. Overall, within the NH− series, **9a**,**b** and **10a**,**b** were the most potent inhibitors of LTA_4 hydrolase, with IC_{50} values down to 1.3 nM for **9b**. Good potencies were also seen in the whole blood assay for these analogues. However, within the NH− series, only **10a** showed the potency that we desired in the mouse ex vivo assay, with an ED_{90} of 3 mg/kg. A similar series of analogues was synthesized in the *N*-methyl series, resulting in the identification of **8d** as the most potent inhibitor of the enzyme (IC_{50} = 0.0025 μM) and whole blood LTB_4 production (IC_{50} = 0.049 μM). In addition, this analogue demonstrated excellent oral activity in the mouse ex vivo assay, with an ED_{90} in the 1−3 mg/kg range. All other analogues in the *N*-methyl series showed significantly reduced potency.

Because of the excellent in vitro and ex vivo potency of **8d**, the amino acid portion of this analogue was maintained in further optimization efforts focusing on the left-hand side of the molecule. The results of this study are detailed in Table 2. On the basis of the results of some of our previous work, biaryls and heterocycles were a major focus of this effort. The majority of these analogues demonstrated significant potency in the enzyme assay, with several showing outstanding potency, including **15d**, **18d**, and **19d** with IC_{50} values of <0.0005, 0.0047, and 0.002 μM, respectively. As demonstrated before, there was a trend toward increased enzyme potency with the free carboxylic acids. Within this series, those demonstrating the best oral activity in the mouse ex vivo assay were **19c** with an ED_{90} of 1−3 mg/kg and **13d** and **14d**, each with an ED_{90} value of 3 mg/kg.

In the final study shown in Table 3, we explored isosteric replacements for the carboxylate moiety using

Table 3. Carboxylate Surrogates



compd	R	IC_{50}[a] (μM) rhLTA$_4$ hydrolase	IC_{50}[a] (μM) human whole blood	ED_{90} (mg/kg) mouse ex vivo
8c	$-CO_2Et$	0.25 (2)	0.11	72% @ 10 mg/kg
8d	$-CO_2H$	0.0025	0.049	1-3
8e	$-CONH_2$	0.007	0.11	98% @ 10 mg/kg
8f	−tetrazole	1.65 (2)	0.56 (2)	*b*
8g	$-CONHSO_2Me$	0.0013	0.07	≤1
8h	$-CONHSO_2Ph$	0.001	0.075	3
8i	$-SO_3H$	0.22	5.2 (2)	*b*
8j	$-SO_2NH_2$	0.004	0.74	84% @ 10 mg/kg

[a] Average of at least three determinations except where noted in parentheses. [b] Not determined.

the **8d** scaffold. Primary amide **8e** showed potency similar to that of the acid in both in vitro and ex vivo assays, while tetrazole **8f** showed significant reduction in potency. Acyl sulfonamides **8g** and **8h** also were very potent inhibitors of the enzyme, with IC_{50} values of 1.3 and 1.0 nM, respectively. In addition, **8g** demonstrated the best ex vivo potency that we had seen to date, with $ED_{90} \leq 1$ mg/kg. Sulfonic acid **8i** and sulfonamide **8j** were reasonably potent in the enzyme assay but showed diminished potency in the whole blood and ex vivo assays.

Many of these acyclic amino acid analogues were among the most potent inhibitors of LTA_4 hydrolase described to date, with IC_{50} values in the subnanomolar to low nanomolar range. In addition, many demonstrated excellent oral activity in the mouse ex vivo assay. On the basis of its overall profile and ease of synthesis, **8d** was selected for further development. An overview of the in vitro and in vivo studies with **8d** has been recently reported.[19,20] In summary, **8d** demonstrated excellent potency against LTA_4 hydrolase (IC_{50} = 0.0025 μM) and in a human whole blood LTB_4 production assay (IC_{50} = 0.049 μM).[19] It also showed excellent potency when dosed orally in the mouse ex vivo assay, inhibiting the production of LTB_4 with an ED_{50} of 0.2 mg/kg and an ED_{90} of 1−3 mg/kg.[20] In addition, **8d** was orally efficacious in a rat peritoneal LTB_4 production model (ED_{50} = 1 mg/kg) and in a rat reversed passive dermal arthus model (ED_{50} = 0.3 mg/kg and ED_{90} = 3−10 mg/kg) and demonstrated both oral (ED_{50} < 0.8 mg/kg) and topical (ED_{50} = 0.11 mg/ear) efficacy in a mouse arachidonic acid-induced ear edema model.[20] In a phase II animal efficacy study in cotton-top tamarins,[21,22] **8d** showed excellent efficacy when given orally for 8 weeks at a dose of 10 mg/kg, b.i.d. In this model of spontaneous colitis, which is similar to ulcerative colitis in humans, **8d** significantly reduced LTB_4 levels (>90% at mid-treatment) in rectal dialysates, as well as improved stool consistency scores and histology scores in colonic biopsies of these animals. These data provided the impetus for the advancement of this compound into human clinical trials for the treatment of inflammatory bowel disease. Unfortunately, in preclinical safety studies, accumulation of a long-lived metabolite in adipose tissue along with some mild hepatic toxicity precluded **8d** from further development.[23,24]

It was assumed that this class of α-, β-, and γ-amino acid inhibitors was distinct from previously described classes of inhibitors containing a known zinc-binding moiety such as a hydroxamic acid, hydroxyurea, and thiol. This new amino acid class is distinguished from these previous classes not only structurally but also in their apparent mode of binding to the enzyme, primarily in the lack of an obvious zinc-binding functional group. Supporting evidence of this was obtained from preliminary extended X-ray absorption fine structure (EXAFS) spectroscopy. EXAFS spectroscopy of the zinc-containing LTA_4 hydrolase enzyme carried out in either the presence or absence of **8d** was similar within the first coordination shell of the zinc atom. This provided good evidence of a lack of interaction of this class of inhibitors with the zinc atom of the enzyme. In addition, it appears that the carboxylate moiety does not play a major role in these inhibitors' interactions with the enzyme, since amide, ester, and acid analogues, as well as many of our previously described[17] analogues lacking the carboxylate functionality, all have similar potencies against the enzyme. Likewise, the carboxylate group does not play a major role in cell penetration, as evidenced by analogous human whole blood data. Rather, the carboxylate group seems to play a significant role in the optimization of the in vivo properties of this class of inhibitors, presumably by improved oral absorption. However, at this time no detailed comparative pharmacokinetic studies have been carried out to confirm this.

Conclusions

In summary, we have described a detailed SAR study on a unique series of amino acid based inhibitors of LTA_4 hydrolase, resulting in the identification of a number of analogues that demonstrated exceptional potency in our enzyme, whole cell, and ex vivo assays. Clinical candidate **8d** was identified and demonstrated significant efficacy in a cotton-top tamarin model of spontaneous colitis, as well as in other animal models of inflammation. Unfortunately, prior to entering human phase I clinical trials, toxicity findings precluded this compound from further development. Efforts aimed at circumventing these toxicity issues have been carried out and will be reported in due course.

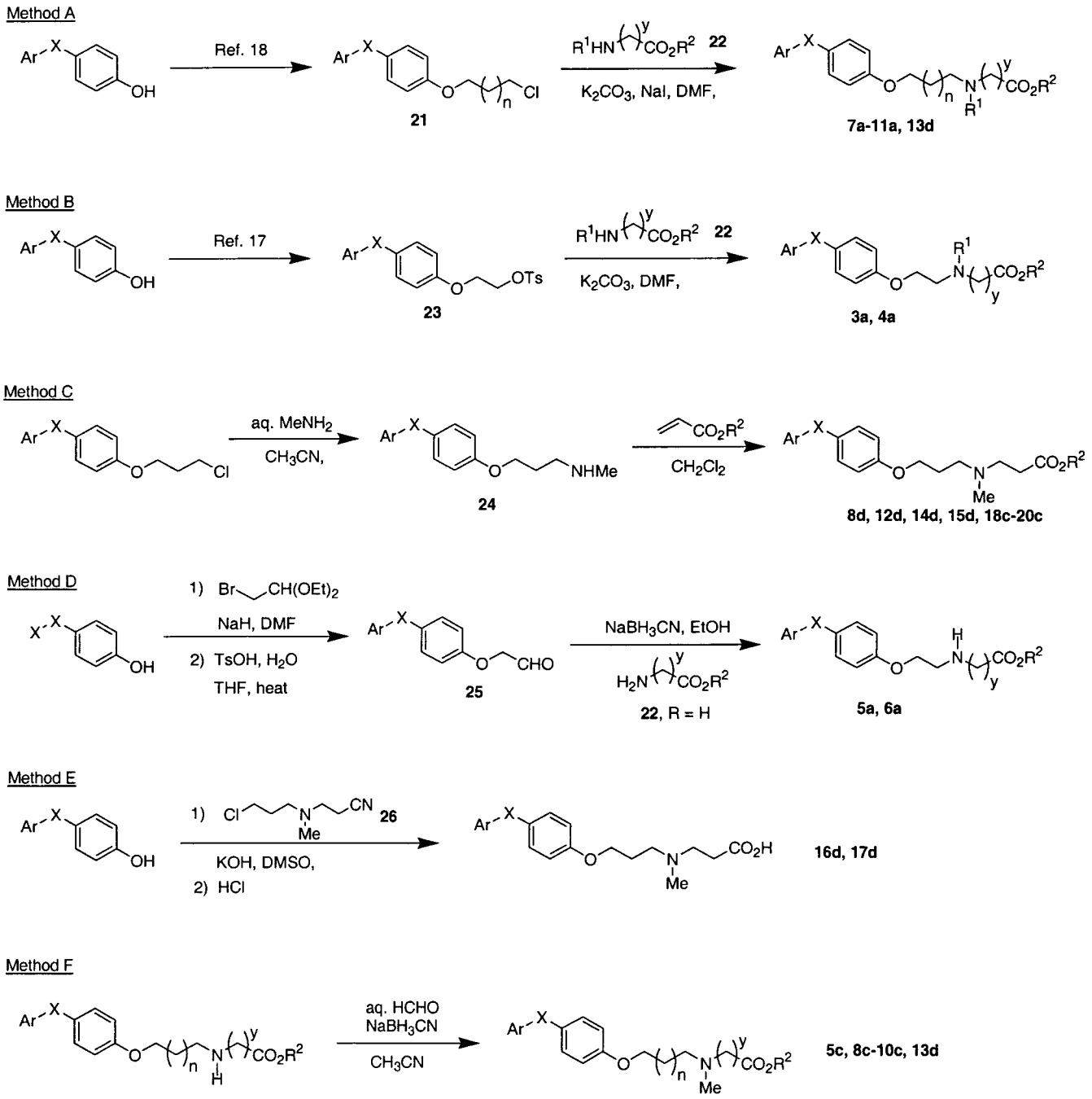
Experimental Section

Biological Methods. The human LTA_4 hydrolase, human whole blood LTB_4 production, and mouse ex vivo whole blood LTB_4 production assays have been described previously.[19,20]

Chemistry. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. High-field ^{1}H NMR spectra were recorded on GE QE-300 and Varian VXR-400 spectrometers at 300 and 400 MHz, respectively. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. High-resolution mass spectra were obtained on a Finnigan MAT-8430 instrument with electron impact (EI) or fast atom bombardment (FAB) ionization. Microanalyses were performed by the Searle Physical Methodology Department. Unless noted otherwise, elemental data for all new compounds are within ±0.4% of the theoretical values. All yields reported are unoptimized. All phenol starting materials were purchased from commercial sources or synthesized as described herein or previously.[17,18]

Procedure A. *N*-[4-[4-(Phenylmethyl)phenoxy]butyl]-glycine Ethyl Ester (9a). Step 1. Preparation of 1-Benzyl-4-(4-chlorobutoxy)benzene. To a solution of 4-hydroxy-

Scheme 1. Summary of Synthetic Routes



diphenylmethane (3.7 g, 20 mmol) in 10 mL of DMF was added NaH (0.8 g of a 60% dispersion in oil, 20 mmol), and the mixture was stirred at 25 °C for 30 min. A solution of 1-bromo-4-chlorobutane (3.4 g, 20 mmol) in 5 mL of DMF was added dropwise, and the mixture was stirred at 25 °C for 18 h. The mixture was poured into Et_2O and water, and the ether layer was separated, washed with water (2×), dried over Na_2SO_4, and concentrated to provide, after chromatography on silica using 95:5 heptane/EtOAc, the title compound: ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 4H), 3.61 (t, J = 6 Hz, 2H), 3.92 (s, 2H), 3.97 (t, J = 6 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H).

Step 2. Preparation of *N*-[4-[4-(Phenylmethyl)phenoxy]-butyl]glycine Ethyl Ester. The product of step 1 (1.4 g, 5 mmol), glycine ethyl ester hydrochloride (0.7 g, 5 mmol), K_2CO_3 (0.6 g, 4.3 mmol), and NaI (150 mg, 1 mmol) were stirred in 25 mL of DMF at 80 °C for 18 h. The mixture was cooled and poured into Et_2O and water. The ether layer was separated and the water layer washed with ether (2×). The combined ether extracts were washed with water (2×), dried over Na_2SO_4, and concentrated to give, after chromatography on silica using a gradient of 70:30:1 to 40:60:1 heptane/EtOAc/Et_3N, **9a** (1.7 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H), 1.60 (br, 1H), 1.66 (m, 2H), 1.82 (m, 2H), 2.68 (t, J = 7 Hz, 2H), 3.41 (s, 2H), 3.91 (s, 2H), 3.95 (t, J = 7 Hz, 2H), 4.19 (q, J = 7 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

Procedure B. *N*-[2-[4-(Phenylmethyl)phenoxy]ethyl]-glycine Ethyl Ester, Hydrochloride (3a). To a stirred solution of tosylate **22** (2-[4-(phenylmethyl)phenoxy]ethyl 4-methylbenzenesulfonate[18]) (10.0 g, 26.7 mmol) in 130 mL of dimethylformamide (DMF) was added glycine (7.45 g, 53.4 mmol) followed by K_2CO_3 (11.1 g, 80.1 mmol), and the reaction mixture was stirred at 65 °C for 18 h. The mixture was cooled and concentrated. Water was added, followed by extraction (3 × 100 mL) with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to provide the crude product, which was converted to the HCl salt, **3a**: ^{1}H NMR

(CD_3OD) δ 1.32 (t, $J = 8$ Hz, 3H), 3.53 (t, $J = 5$ Hz, 2H), 3.91 (s, 2H), 4.08 (s, 2H), 4.29 (m, 4H), 6.93 (d, $J = 9$ Hz, 2H), 7.16 (m, 5H), 7.24 (d, $J = 8$ Hz, 2H). Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.1H_2O$) C, H, N.

Procedure C. *N*-Methyl-*N*-[3-[4-(2-thienylmethyl)phenoxy]propyl]-*b*-alanine Methyl Ester (18c). Step 1. Preparation of 2-[4-(Chloropropoxy)benzyl]thiophene. To a solution of 4-(2-thienylmethyl)phenol[17] (1.23 g, 6.5 mmol) in 13 mL of methyl ethyl ketone was added K_2CO_3 (4.53 g, 32.5 mmol), and the mixture was stirred at 25 °C for 15 min. 1-Bromo-3-chloropropane (0.66 mL, 6.5 mmol) was added, and the mixture was heated at 85 °C for 19 h and at 95 °C for 8 h. The mixture was concentrated and the crude product partitioned between water and EtOAc. The organic layer was separated and the water layer extracted with EtOAc. The combined EtOAc extracts were washed with brine and concentrated to give a yellow oil. Flash chromatography on silica gel using 95:5 hexane/EtOAc provided the title compound (1.04 g, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.22 (p, $J = 6$ Hz, 2H), 3.74 (t, $J = 6$ Hz, 2H), 4.10 (s and t, $J = 6$ Hz, 4H), 6.78 (d, 1H), 6.85 (d, $J = 9$ Hz, 2H), 6.92 (dd, 1H), 7.16 (t, $J = 8$ Hz, 3H).

Step 2. Preparation of *N*-Methyl-*N*-[3-[2-thienylmethyl)phenoxy]propyl]amine. To a solution of the product of step 1 (0.57 g, 2.1 mmol) in 5 mL of acetonitrile was added 40% aqueous methylamine (17 mL, 215 mmol), and the mixture was heated at 60 °C for 7 h and at 25 °C for 17 h. The mixture was concentrated and the aqueous solution extracted with EtOAc (2 × 10 mL). The organic extracts were combined and acidified to pH 1 with 1 N HCl. The white precipitate that formed was filtered and washed with 1 N HCl and hexane to provide 0.47 g (75%) of the HCl salt of the title compound: ^{1}H NMR ($CDCl_3/CD_3OD$) δ 2.27 (p, $J = 6$ Hz, 2H), 2.72 (m, 2H), 2.93 (s, 3H), 3.18 (m, 2H), 4.07 (t, $J = 6$ Hz, 2H), 4.09 (s, 2H), 6.79 (d, 1H), 6.85 (d, $J = 9$ Hz, 2H), 6.92 (dd, 1H), 7.16 (t, $J = 8$ Hz, 3H). Conversion to the free base was carried out by dissolution in 20 mL of 10% NaOH and extraction with Et_2O (2 × 30 mL). The combined extracts were dried over Na_2SO_4 and concentrated to give the title compound as a pale-yellow oil.

Step 3. Preparation of *N*-Methyl-*N*-[3-[4-(2-thienylmethyl)phenoxy]propyl]-*β*-alanine Methyl Ester. To a solution of the product of step 2 (0.41 g, 1.6 mmol) in 8 mL of CH_2Cl_2 was added methyl acrylate (0.19 mL, 2.1 mmol), and the mixture was stirred at 25 °C for 18.5 h. An additional 0.2 mL (0.2 mmol) of methyl acrylate was added, and the mixture was stirred for an additional 2 h. The mixture was concentrated to give a colorless oil. Flash chromatography on silica gel using 10:1 CH_2Cl_2/MeOH gave **18c** (0.38 g, 68%) as a pale-yellow oil: ^{1}H NMR (CD_3OD) δ 1.93 (p, $J = 6$ Hz, 2H), 2.26 (s, 3H), 2.48 (t, $J = 6$ Hz, 2H), 2.53 (t, $J = 6$ Hz, 2H), 2.72 (t, $J = 6$ Hz, 2H), 3.65 (s, 3H), 3.99 (t, $J = 6$ Hz, 2H), 4.09 (s, 2H), 6.78 (d, $J = 3$ Hz, 1H), 6.83 (d, $J = 9$ Hz, 2H), 6.91 (dd, $J = 5$, 3 Hz, 1H), 7.13 (m, 3H). Anal. ($C_{19}H_{25}NO_3S \cdot 0.2H_2O$) C, H, N.

Procedure D. Ethyl 4-[[2-[4-(Phenylmethyl)phenoxy]-ethyl]amino]butanoate (5a). Step 1. Preparation of 1-Benzyl-4-(2,2-diethoxyethoxy)benzene. To a solution of 4-hydroxydiphenylmethane (18.4 g, 100 mmol) in 50 mL of DMF was added NaH (4 g of a 60% dispersion in oil, 100 mmol), and the mixture was stirred for 30 min. A solution of bromoacetaldehyde diethyl acetal (19.7 g, 100 mmol) in 20 mL of DMF was added dropwise, and the mixture was stirred at 25 °C for 20 h. The mixture was poured into ether and water, and the ether layer was separated, washed with water, dried over Na_2SO_4, and concentrated. Chromatography on silica gel using a gradient of 98:2 to 97:3 heptane/EtOAc furnished the title compound (20 g, 67%): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $J = 7$ Hz, 6H), 3.62 (m, 2H), 3.75 (m, 2H), 3.92 (s, 2H), 3.97 (d, $J = 6$ Hz, 2H), 4.82 (t, $J = 6$ Hz, 1H), 6.83 (d, $J = 9$ Hz, 2H), 7.08 (d, $J = 9$ Hz, 2H), 7.17 (m, 3H), 7.26 (m, 2H).

Step 2: Preparation of Ethyl 4-[[2-[4-(Phenylmethyl)-phenoxy]ethyl]amino]butanoate. To a solution of the compound from step 1 (6.0 g, 20 mmol) in 30 mL of THF and 1 mL of H_2O was added catalytic *p*-toluenesulfonic acid (150 mg), and the mixture was refluxed for 18 h. The mixture was cooled and concentrated, and the residue was dissolved in ether. The ether solution was washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated to provide the aldehyde: ^{1}H NMR ($CDCl_3$) δ 9.84 (s, 1H). A portion of the crude aldehyde (1.0 g, 4.4 mmol), ethyl 4-aminobutyrate hydrochloride (680 mg, 4.0 mmol), and KOH (56 mg, 1.0 mmol) were stirred in 10 mL of EtOH, and a solution of sodium cyanoborohydride ($NaBH_3CN$, 122 mg, 1.94 mmol) in 5 mL of EtOH was added. The mixture was stirred at 25 °C for 30 min, and the mixture was filtered and concentrated. The residue was dissolved in ether and washed with water, dried over Na_2SO_4, and concentrated. Chromatography on silica gel using a gradient of 40:60:1 to 20:60:1 heptane/EtOAc/Et_3N furnished **5a** (0.10 g, 7%): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, $J = 7$ Hz, 3H), 1.82 (p, $J = 7$ Hz, 2H), 2.37 (t, $J = 7$ Hz, 2H), 2.70 (t, $J = 7$ Hz, 2H), 2.98 (t, $J = 5$ Hz, 2H), 3.91 (s, 2H), 4.02 (t, $J = 5$ Hz, 2H), 4.12 (q, $J = 7$ Hz, 2H), 6.82 (d, $J = 9$ Hz, 2H), 7.09 (d, $J = 9$ Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{21}H_{27}NO_3 \cdot 0.4H_2O$) C, H, N.

Procedure E. *N*-Methyl-*N*-[3-[4-[4-(2-thiazolyl)phenoxy]phenoxy]propyl]-*β*-alanine (17d). Step 1. Preparation of 3-(Methyl-[3-[4-(4-thiazol-2-ylphenoxy)phenoxy]propyl]amino)propionitrile. To a suspension of powdered KOH (63 mg, 1.1 mmol) in 1 mL of DMSO was added a solution of 4-(4-thiazol-2-ylphenoxy)phenol (200 mg, 0.74 mmol) in 2 mL of DMSO. The mixture was stirred at room temperature for 5 min and **26** (methyl 3-(3-chloropropylamino)propionitrile) (118 mg, 0.74 mmol) in 1 mL of DMSO. The mixture was heated at 45 °C for 4 h, cooled, and partitioned between water and ether. The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was flash-chromatographed on silica using ethyl acetate to give the title compound (112 mg, 39%) as a crystalline solid: mp 63−64 °C. ^{1}H NMR (CDCl3) δ 7.90 (m, 2H), 7.81 (d, 1H, $J = 4$ Hz), 7.27 (d, 1H, $J = 4$ Hz), 7.00 (m, 4H), 6.91 (m, 2H), 4.03 (t, 2H, $J = 7$ Hz), 2.74 (t, 2H, $J = 7$ Hz), 2.60 (t, 2H, $J = 7$ Hz), 2.47 (t, 2H, $J = 7$ Hz), 2.30 (s, 3H), 1.95 (m, 2H).

Step 2. Preparation of *N*-Methyl-*N*-[3-[4-[4-(2-thiazolyl)-phenoxy]phenoxy]propyl]-*β*-alanine. A solution of the compound from step 1 (100 mg, 0.25 mmol) in 2 mL of 6 N HCl was heated at 90 °C for 17 h. The solution was cooled and brought to pH 8 with 10% NaOH. Extraction with CH_2Cl_2 (3 × 15 mL) and concentration provided the crude product, which was flash-chromatographed on silica using 85:14:1 CH_2Cl_2/MeOH/NH_4OH to give **17d** (40 mg, 39%) as a crystalline solid: mp 143−144 C; ^{1}H NMR (CD_3OD) δ 2.22 (m, 2H), 2.59 (m, 2H), 2.82 (s, 3H), 3.27 (m, 4H) 4.11 (t, 2H, $J = 6$ Hz), 6.96 (m, 2H), 7.01 (s, 4H), 7.55 (d, 1H, $J = 4.0$ Hz), 7.81 (d, 1H, $J = 4.0$ Hz), 7.87 (m, 2H). Anal. ($C_{22}H_{24}N_2O_4S \cdot 1.0H_2O$) C, N; H, calcd, 6.09; found, 5.57. HRMS *m/z* 413.1535 (calcd for $C_{22}H_{24}N_2O_4S$ (M + 1), 413.1551).

Procedure F. Ethyl 3-[Methyl-[3-[4-(phenylmethyl)-phenoxy]propyl]amino]propanoate (8c). To a solution of **8a** (170 mg, 0.5 mmol) and 37% aqueous formaldehyde (0.2 mL, 5 mmol) in 3 mL of CH_3CN was added $NaBH_3CN$ (50 mg, 0.8 mmol), and the mixture was stirred at 25 °C for 15 min. Three drops of AcOH were added over 45 min to maintain a neutral pH. The mixture was concentrated, and the residue was dissolved in ether and 2 N KOH. The ether layer was separated and washed with 0.5 N KOH followed by 1 N HCl (3×). The combined HCl extracts were neutralized with KOH and extracted with ether (3×). The combined extracts were dried over Na_2SO_4 and concentrated. Chromatography on silica gel using a gradient of 95:5:1 to 90:10:1 toluene/EtOAc/Et_3N furnished **8c** (100 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $J = 7$ Hz, 3H), 1.92 (p, $J = 7$ Hz, 2H), 2.24 (s, 3H), 2.45 (t, $J = 7$ Hz, 2H), 2.52 (t, $J = 7$ Hz, 2H), 2.71 (t, $J = 7$ Hz, 2H), 3.91 (s, 2H), 3.97 (t, $J = 7$ Hz, 2H), 4.10 (q, $J = 7$ Hz, 2H), 6.81 (d, $J = 9$ Hz, 2H), 7.08 (d, $J = 9$ Hz, 2H), 7.17 (m, 3H), 7.27 (m, 2H). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

Procedure G. *N*-Methyl-*N*-[3-[4-(2-thienylmethyl)phenoxy]propyl]-*β*-alanine, Hydrochloride (18d). To a solution

of **18c** (0.28 g, 0.81 mmol) in 5 mL of THF was added 1 mL of 6 N HCl, and the mixture was stirred at 75 °C for 14 h. The mixture was concentrated, and the white solid residue was recrystallized from MeOH/Et_2O to give **18d** (0.14 g, 47%) as a white solid: ^{1}H NMR (CD_3OD) δ 2.23 (p, J = 6 Hz, 2H), 2.87 (t, J = 6 Hz, 2H), 2.93 (s, 3H), 3.40 (m, 4H), 4.08 (s, 2H), 4.10 (t, J = 6 Hz, 2H), 6.78 (d, J = 3 Hz, 1H), 6.88 (m, 3H), 7.14 (m, 3H). Anal. ($C_{18}H_{23}NO_3S$·HCl) C, H, N.

Procedure H. *N*-Methyl-*N*-[4-[4-(phenylmethyl)phenoxy]butyl]glycine (9d). The benzyl ester of **9d** (prepared using general procedure F) (100 mg, 0.24 mmol) in 20 mL of EtOH with catalytic 4% Pd/C (25 mg) was hydrogenated in a Parr shaker under 5 psi of H_2 at 25 °C for 2 h. The mixture was filtered and concentrated to give, after recrystallization from EtOAc, **9d** (20 mg, 24%) as a white solid: ^{1}H NMR (CD3OD) δ 1.88 (m, 4H), 2.85 (s, 3H), 3.18 (t, J = 7 Hz, 2H), 3.53 (s, 2H), 3.92 (s, 2H), 3.99 (t, J = 7 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{20}H_{25}NO_3$·0.5H_2O) C, H, N.

***N*-[2-[4-(Phenylmethyl)phenoxy]ethyl]-β-alanine Methyl Ester (4a).** ^{1}H NMR ($CDCl_3$) δ 1.72 (br, 1H), 2.54 (t, J = 6 Hz, 2H), 2.95 (t, J = 6 Hz, 2H), 2.99 (t, J = 6 Hz, 2H), 3.68 (s, 3H), 3.91 (s, 2H), 4.03 (t, J = 6 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

Ethyl 5-[[2-[4-(Phenylmethyl)phenoxy]ethyl]amino]-pentanoate (6a). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.55 (m, 2H), 1.67 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.69 (t, J = 7 Hz, 2H), 2.99 (t, J = 5 Hz, 2H), 3.92 (s, 2H), 4.04 (t, J = 5 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.17 (m, 3H), 7.27 (m, 2H). Anal. ($C_{22}H_{29}NO_3$·0.3H_2O) C, N; H, calcd, 8.27; found, 7.80.

Ethyl *N*-[3-[4-(Phenylmethyl)phenoxy]propyl]glycinate (7a). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 8 Hz, 3H), 1.69 (br, 1H), 1.96 (p, J = 6 Hz, 2H), 2.69 (t, J = 6 Hz, 2H), 3.41 (s, 2H), 3.91 (s, 2H), 4.02 (t, J = 6 Hz, 2H), 4.18 (q, J = 8 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

Ethyl 3-[[3-[4-(Phenylmethyl)phenoxy]propyl]amino]-propanoate (8a). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.78 (br, 1H), 1.93 (p, J = 6 Hz, 2H), 2.50 (t, J = 6 Hz, 2H), 2.79 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.91 (s, 2H), 3.99 (t, J = 6 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.17 (m, 3H), 7.26 (m, 2H). Anal. ($C_{21}H_{27}NO_3$·0.2H_2O) C, H, N.

***N*-[3-[4-(Phenylmethyl)phenoxy]propyl]-β-alanine (8b).** Mp 148−149 °C; ^{1}H NMR (CD_3OD) δ 2.15 (p, J = 6 Hz, 2H), 2.49 (t, J = 6 Hz, 2H), 3.17 (t, J = 7 Hz, 2H), 3.22 (t, J = 7 Hz, 2H), 3.88 (s, 2H), 4.10 (t, J = 6 Hz, 2H), 6.89 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.16 (m, 3H), 7.24 (m, 2H). Anal. ($C_{19}H_{23}NO_3$·0.6H_2O) C, H, N.

***N*-[4-[4-(Phenylmethyl)phenoxy]butyl]glycine (9b).** Mp 167−170 °C; ^{1}H NMR (CD_3OD) δ 1.86 (m, 4H), 3.07 (t, J = 6 Hz, 2H), 3.48 (s, 2H), 3.88 (s, 2H), 3.99 (t, J = 6 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.15 (m, 3H), 7.23 (m, 2H). Anal. ($C_{19}H_{23}NO_3$·0.2H_2O) C, H, N.

Ethyl 3-[4-[4-(Phenylmethyl)phenoxy]butylamino]-propanoate (10a). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.37 (br, 1H), 1.63 (m, 2H), 1.79 (m, 2H), 2.49 (t, J = 7 Hz, 2H), 2.66 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.90 (s, 2H), 3.92 (t, J = 7 Hz, 2H), 4.13 (q, J = 7 Hz, 2H), 6.80 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.17 (m, 3H), 7.26 (m, 2H). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

3-[[4-[4-(Phenylmethyl)phenoxy]butyl]amino]-propanoic Acid (10b). ^{1}H NMR (CD_3OD) δ 1.87 (m, 4H), 2.48 (t, J = 6 Hz, 2H), 3.07 (t, J = 6 Hz, 2H), 3.14 (t, J = 6 Hz, 2H), 3.87 (s, 2H), 4.00 (t, J = 6 Hz, 2H), 6.82 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.14 (m, 3H), 7.22 (m, 2H). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

***N*-[5-[4-(Phenylmethyl)phenoxy]pentyl]glycine Ethyl Ester (11a).** ^{1}H NMR (CDCl3) δ 1.27 (t, J = 6 Hz, 3H), 1.52 (m, 4H), 1.61 (br, 1H), 1.78 (p, J = 6 Hz, 2H), 2.63 (t, J = 6 Hz, 2H), 3.39 (s, 2H), 3.91 (s, 2H), 3.92 (t, J = 6 Hz, 2H), 4.19 (q, J = 6 Hz, 2H), 6.79 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.16 (m, 3H), 7.27 (m, 2H). Anal. ($C_{22}H_{29}NO_3$·0.5H_2O) C, H, N.

Methyl 4-[Methyl[2-[4-(phenylmethyl)phenoxy]ethyl]-amino]butanoate (5c). ^{1}H NMR ($CDCl_3$) δ 1.81 (p, J = 7 Hz, 2H), 2.32 (s, 3H), 2.37 (t, J = 7 Hz, 2H), 2.48 (t, J = 7 Hz, 2H), 2.78 (t, J = 6 Hz, 2H), 3.64 (s, 3H), 3.92 (s, 2H), 4.02 (t, J = 6 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{21}H_{27}NO_3$·0.2H_2O) C, H, N.

3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-propanoic Acid, Hydrochloride (8d). ^{1}H NMR ($CDCl_3$/CD_3-OD) δ 2.33 (m, 2H), 2.85 (s, 3H), 2.95 (t, J = 7 Hz, 2H), 3.31 (m, 2H), 3.38 (m, 2H), 3.92 (s, 2H), 4.07 (t, J = 7 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.28 (m, 2H). Anal. ($C_{20}H_{25}NO_3$·HCl) C, H, N.

3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-propanoic Acid (8d). Mp 121−123 °C; ^{1}H NMR (CD_3OD) δ 2.21 (p, J = 6 Hz, 2H), 2.55 (t, J = 6 Hz, 2H), 2.85 (s, 3H), 3.28 (t, 2H), 3.30 (t, 2H), 3.88 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.15 (m, 3H), 7.23 (m, 2H). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

***N*-Methyl-*N*-[4-[4-(phenylmethyl)phenoxy]butyl]glycine Ethyl Ester (9c).** ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3H), 1.66 (m, 2H), 1.78 (m, 2H), 2.38 (s, 3H), 2.53 (t, J = 7 Hz, 2H), 3.25 (s, 2H), 3.92 (s, 2H), 3.95 (t, J = 7 Hz, 2H), 4.18 (q, J = 7 Hz, 2H), 6.80 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.17 (m, 3H), 7.27 (m, 2H). Anal. ($C_{22}H_{29}NO_3$·0.2H_2O) C, H, N.

Ethyl [Methyl[4-[4-(phenylmethyl)phenoxy]butyl]amino]propanoate (10c). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.62 (m, 2H), 1.77 (m, 2H), 2.23 (s, 3H), 2.40 (t, J = 7 Hz, 2H), 2.46 (t, J = 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 3.91 (s, 2H), 3.93 (t, J = 7 Hz, 2H), 4.13 (q, J = 7 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{23}H_{31}NO_3$) C, H, N.

3-[[3-[4-[(4-Fluorophenyl)methyl]phenoxy]propyl]-methylamino]propanoic Acid, Hydrochloride (12d). ^{1}H NMR (CD_3OD) δ 2.23 (p, J = 6 Hz, 2H), 2.87 (t, J = 6 Hz, 2H), 2.92 (s, 3H), 3.40 (m, 4H), 3.88 (s, 2H), 4.09 (t, J = 6 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 6.97 (dd, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.26 (dd, J = 9 Hz, 2H). Anal. ($C_{20}H_{24}FNO_3$·HCl·0.2H_2O) C, H, N.

3-[Methyl[3-(4-phenoxyphenoxy)propyl]amino]propanoic Acid (13d). ^{1}H NMR ($CDCl_3$) δ 2.22 (p, J = 6 Hz, 2H), 2.54 (s, 3H), 2.60 (t, J = 6 Hz, 2H), 2.92 (t, J = 6 Hz, 4H), 4.02 (t, J = 6 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 6.95 (m, 4H), 7.05 (m, 1H), 7.29 (m, 2H). Anal. ($C_{19}H_{23}NO_4$·0.2H_2O) C, H, N.

***N*-[3-[4-(4-Fluorophenoxy)phenoxy]propyl]-*N*-methyl-β-alanine (14d).** ^{1}H NMR (CD_3OD) δ 2.27 (p, J = 6 Hz, 2H), 2.88 (t, J = 6 Hz, 2H), 2.94 (s, 3H), 3.42 (m, 4H), 4.11 (t, J = 6 Hz, 2H), 6.93 (m, 6H), 7.04 (dd, J = 10 Hz, 2H). Anal. ($C_{19}H_{22}$-FNO_4·HCl·0.2H_2O) C, N, Cl; H, calcd, 6.09; found, 5.61. HRMS m/z 347.1540 (calcd for $C_{19}H_{22}FNO_4$, 347.1533).

***N*-[3-[4-([1,1′-Biphenyl]-4-yloxy)phenoxy]propyl]-*N*-methyl-β-alanine, Hydrochloride (15d).** ^{1}H NMR (CD_3OD) δ 2.28 (p, J = 6 Hz, 2H), 2.89 (t, J = 6 Hz, 2H), 2.96 (s, 3H), 3.43 (m, 4H), 4.12 (t, J = 6 Hz, 2H), 6.99 (m, 6H), 7.29 (dd, J = 8 Hz, 1H), 7.40 (dd, J = 8 Hz, 2H), 7.56 (d, J = 9 Hz, 4H). Anal. ($C_{25}H_{27}NO_4$·HCl·0.8H_2O) C, H, N, Cl.

***N*-Methyl-*N*-[3-[4-[4-(2-oxazolyl)phenoxy]phenoxy]propyl]-β-alanine, Hydrochloride (16d)**. Anal. ($C_{22}H_{24}N_2O_5$·1.5HCl·H_2O) C, H, Cl; N, calcd, 5.97; found, 5.32. HRMS m/z 397.1773 (calcd for $C_{22}H_{24}N_2O5$ (M + 1), 397.1763).

***N*-Methyl-*N*-[3-[4-(3-thienylmethyl)phenoxy]propyl]-β-alanine Methyl Ester (19c).** ^{1}H NMR (CD_3OD) δ 1.92 (p, J = 6 Hz, 2H), 2.25 (s, 3H), 2.47 (t, J = 6 Hz, 2H), 2.52 (t, J = 6 Hz, 2H), 2.71 (t, J = 6 Hz, 2H), 3.65 (s, 3H), 3.90 (s, 2H), 3.98 (t, J = 6 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 6.88 (d, J = 4 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.22 (dd, J = 5, Hz, 1H). Anal. ($C_{19}H_{25}NO_3S$) C, H, N.

***N*-Methyl-*N*-[3-[4-(3-thienyl)phenoxy]propyl]-β-alanine, Hydrochloride (19d).** ^{1}H NMR (CD_3OD) δ 2.23 (p, J = 6 Hz, 2H), 2.86 (t, J = 6 Hz, 2H), 2.94 (s, 3H), 3.40 (m, 4H), 3.90 (s, 2H), 4.10 (t, J = 6 Hz, 2H), 6.87 (m, 3H), 6.96 (d, J =

3 Hz, 1H), 7.12 (d, J = 9 Hz, 2H), 7.28 (dd, J = 5,3 Hz, 1H). Anal. ($C_{18}H_{23}NO_3S \cdot HCl \cdot 0.9H_2O$) C, N; H, calcd, 6.73; found, 6.22. HRMS m/z 333.1417 (calcd for $C_{18}H_{23}NO_3S$, 333.1399).

***N*-Methyl-*N*-[3-[4-(3-pyridinylmethyl)phenoxy]propyl]-*β*-alanine Methyl Ester (20c).** ^{1}H NMR (CD_3OD) δ 1.94 (p, J = 6 Hz, 2H), 2.28 (s, 3H), 2.50 (t, J = 6 Hz, 2H), 2.56 (t, J = 6 Hz, 2H), 2.74 (t, J = 6 Hz, 2H), 3.66 (s, 3H), 3.92 (s, 2H), 3.98 (t, J = 6 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.18 (dd, J = 8,5 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 8.43 (d, J = 5 Hz, 1H), 8.48 (s, 1H). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-propanamide (8e). A mixture of **8d** (200 mg, 0.55 mmol) and trifluoromethylsulfonamide (90 mg, 0.6 mmol) in 2 mL of $POCl_3$ was stirred at 90 °C. Toluene was added until the solution was homogeneous, and the mixture was heated at 90 °C for 4 h. The mixture was cooled and concentrated. Water was added, and the solution was made basic with NH_4OH. This was extracted with EtOAc (3×), and the combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica using 94:6:1 CH_2Cl_2/MeOH/NH_4OH provided **8e** (95 mg, 53%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.98 (p, J = 6 Hz, 2H), 2.30 (s, 3H), 2.41 (t, J = 6 Hz, 2H), 2.63 (t, J = 6 Hz, 2H), 2.67 (t, J = 6 Hz, 2H), 3.92 (s, 2H), 3.98 (t, J = 6 Hz, 2H), 6.79 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.28 (m, 2H). Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***N*-Methyl-*N*-[3-[4-(phenylmethyl)phenoxy]propyl]-1*H*-tetrazole-5-ethanamine (8f).** A solution of 3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]propionitrile (prepared using procedure E) (100 mg, 0.3 mmol), NaN_3 (65 mg, 1.0 mmol), Bu_3SnCl (150 mg, 0.45 mmol), and LiCl (42 mg, 1.0 mmol) in 5 mL of xylene was heated at 130 °C for 48 h. The mixture was cooled, filtered, and concentrated. The residue was partitioned between CH_2Cl_2 and water, and the water layer was brought to pH 4 with 3 N HCl. The organic layer was separated, dried over Na_2SO_4, and concentrated. Reverse-phase chromatography on a C18 column using a gradient of 50:50 MeOH/H_2O to 100% MeOH provided, after recrystallization from EtOAc, **8f** (16.5 mg, 16%): ^{1}H NMR ($CDCl_3$) δ 2.09 (p, J = 6 Hz, 2H), 2.53 (s, 3H), 2.94 (t, J = 6 Hz, 2H), 3.06 (t, J = 6 Hz, 2H), 3.23 (t, J = 6 Hz, 2H), 3.90 (s, 2H), 4.02 (t, J = 6 Hz, 2H), 6.79 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 7.17 (m, 3H), 7.28 (m, 2H), 7.35 (br, 1H). Anal. ($C_{20}H_{25}N_5O \cdot 0.3H_2O$) C, H, N.

3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-*N*−(methylsulfonyl)propanamide (8g). A mixture of **8d** (500 mg, 1.37 mmol) and methanesulfonamide (131 mg, 1.37 mmol) in 1 mL of $POCl_3$ was stirred at 90 °C. Toluene was added until the solution was homogeneous, and the mixture was heated at 90 °C for 4 h. The mixture was cooled and concentrated. The residue was triturated with toluene and dissolved in water. The solution was made basic with NH_4OH and extracted with EtOAc (3×). The combined extracts were dried over $MgSO_4$ and concentrated to provide, after flash chromatography on silica using 95:5:1 CH_2Cl_2/MeOH/NH_4OH, **8g** (150 mg, 26%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.08 (p, J = 7 Hz, 2H), 2.47 (s, 3H), 2.56 (t, J = 7 Hz, 2H), 2.83 (m, 4H), 2.97 (s, 3H), 3.90 (s, 2H), 4.02 (t, J = 6 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.16 (m, 3H), 7.27 (m, 2H). Anal. ($C_{21}H_{28}N_2O_4S(H_2O)$ C, H, N.

3-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-*N*-(phenylsulfonyl)propanamide (8h). To a suspension of **8d** (500 mg, 1.37 mmol) in 20 mL of CH_2Cl_2 was added benzenesulfonamide (219 mg, 1.37 mmol) and 4-(dimethylamino)pyridine (218 mg, 1.79 mmol), followed by 5 g of 4 Å molecular sieves and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (270 mg, 1.37 mmol). The mixture was stirred at 25 °C for 17 h and diluted with 50 mL of CH_2Cl_2. A 10% aqueous HCl solution (20 mL) was added, and the organic layer was separated. The water layer was extracted with CH_2Cl_2 (2×), and the combined extracts were dried over $MgSO_4$ and concentrated to provide, after flash chromatography on silica using 95:5:1 CH_2Cl_2/MeOH/NH_4OH, **8h** (130 mg, 20%) as a white solid. Anal. ($C_{26}H_{30}N_2O_4S$) C, H, N.

2-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-ethanesulfonic Acid (8i). To a solution of 1-benzyl-4-(3-chloropropoxy)benzene[18] (1.0 g, 3.8 mmol) in 5 mL of DMF was added *N*-methyltaurine sodium salt (617 mg, 3.8 mmol) and Et_3N (1.08 g, 10 mmol), and the mixture was stirred at 40 °C for 60 h. The mixture was cooled and poured into water, and the solid was filtered to provide **8i** (508 mg, 37%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.08 (p, J = 7 Hz, 2H), 2.83 (s, 3H), 2.91 (t, J = 7 Hz, 2H), 3.21 (m, 2H), 3.44 (m, 2H), 3.86 (s, 2H), 4.00 (t, J = 6 Hz, 2H), 6.87 (d, J = 8 Hz, 2H), 7.16 (m, 5H), 7.26 (d, J = 7 Hz, 2H), 9.06 (br, 1H). Anal. ($C_{19}H_{25}NO_4S$) C, H, N.

2-[Methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-ethanesulfonamide (8j). To a suspension of **8i** (200 mg, 0.55 mmol) in EtOAc was added oxalyl chloride (140 mg, 1.1 mmol) followed by a drop of DMF. The mixture was heated at 40 °C for 15 h and concentrated. Concentrated NH_4OH was added, and the mixture was stirred at 90 °C for 4 h. The mixture was cooled and extracted with EtOAc (3×). The combined extracts were dried over $MgSO_4$ and concentrated to provide, after flash chromatography on silica using 98:2:1 CH_2Cl_2/MeOH/NH_4OH, **8j** (20 mg, 10%) as a brown solid: HRMS m/z 362.1663 (calcd for $C_{19}H_{26}N_2O_3S$, 362.1664).

4-(4-Thiazol-2-yl)phenoxyphenol (Used in Preparation of 17d). Step 1. Preparation of 4-(4-Methoxyphenoxy)-thiobenzamide. To a suspension of 4-(4-methoxyphenoxy)-benzonitrile[17] (10.0 g, 44 mmol) in *tert*-butyl alcohol (80 mL) was added 30 mL of dimethyl sulfoxide (DMSO) and powdered KOH (9.1 g, 162 mmol). The mixture was heated at reflux for 2 h. The mixture was cooled and diluted with water (100 mL). The white solid precipitate was collected by filtration and washed with water (4 × 150 mL). The solid was concentrated to give the title compound (9.6 g, 89%): mp 195−196 °C.

Step 2. Preparation of 4-(4-Methoxyphenoxy)thiobenzamide. To a suspension of the compound from step 1 (4.2 g, 17.3 mmol) in toluene (80 mL) was added Lawesson's reagent (7.0 g, 17.3 mmol). The mixture was heated at reflux for 3 h, cooled, and concentrated. The residue was flash-chromatographed on silica gel (1:1 hexane/ethyl acetate) to give the title compound (2.2 g, 49%).

Step 3. Preparation of 2-[4-(4-Methoxyphenoxy)phenyl]thiazole. A mixture of oxalic acid (590 mg, 6.5 mmol) and chloroacetaldehyde dimethyl acetal (0.75 mL, 6.5 mmol) was heated at reflux for 1 h. The compound from step 2 (1.7 g, 6.5 mmol) was added, and the mixture was heated at reflux for 2 h. The mixture was cooled, 30% HCl (3.5 mL) was added, and the mixture was heated to reflux for 10 min. After cooling and dilution with water, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried over Na_2SO_4 and concentrated, and the residue was flash-chromatographed (3:1 hexane/ethyl acetate) to give the title compound (925 mg, 50%) as a crystalline solid: mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 6.88 (m, 2H), 6.97 (m, 4H), 7.20 (d, 1H, J = 4 Hz), 7.78 (d, 1H, J = 4 Hz), 7.98 (m, 2H). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94. Found: C, 67.66; H, 4.50; N, 4.86.

Step 4. Preparation of 4-(4-Thiazol-2-yl)phenoxyphenol. To a solution of the compound from step 3 (280 mg, 1.0 mmol) in 3 mL of CH_2Cl_2 at −78 °C was added boron tribromide (1.8 mL of a 1 M solution in CH_2Cl_2). The solution was stirred at −78 °C for 1 h and then warmed to room temperature over 2 h. The mixture was diluted with water and extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated to give the title compound (210 mg, 78%): ^{1}H NMR (CD_3OD) δ 6.88 (m, 4H), 6.97 (m, 4H), 7.02 (m, 2H), 7.90 (m, 3H), 8.10 (d, 1H, J = 4 Hz).

Methyl 3-(3-Chloropropylamino)propionitrile (26) (Used in General Procedure E). A solution of *N*-methyl-*β*-alaninenitrile (5.0 g, 59.4 mmol), 1-bromo-3-chloropropane (18.7 g, 118.9 mmol), and K_2CO_3 (16 g, 118.9 mmol) in 40 mL of DMF was stirred at 50 °C for 2 h. The mixture was cooled and diluted with 100 mL of H_2O. The solution was extracted with EtOAc (2 × 40 mL), and the combined extracts were

washed with brine and concentrated. Flash chromatography on silica gel using 60:40 heptane/EtOAc provided **26** (6.2 g, 65%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.92 (p, J = 6 Hz, 2H), 2.28 (s, 3H), 2.48 (t, J = 6 Hz, 2H), 2.56 (t, J = 6 Hz, 2H), 2.72 (t, J = 6 Hz, 2H), 3.63 (t, J = 6 Hz, 2H).

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