Structure−Activity Relationship Studies on 1-[2-(4-Phenylphenoxy)ethyl]pyrrolidine (SC-22716), a Potent Inhibitor of Leukotriene A_4 (LTA_4) Hydrolase

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Leukotriene B_4 (LTB_4) is a pro-inflammatory mediator that has been implicated in the pathogenesis of a number of diseases including inflammatory bowel disease (IBD) and psoriasis. Since the action of LTA_4 hydrolase is the rate-limiting step for LTB_4 production, this enzyme represents an attractive pharmacological target for the suppression of LTB_4 production. From an in-house screening program, SC-22716 (**1**, 1-[2-(4-phenylphenoxy)ethyl]pyrrolidine) was identified as a potent inhibitor of LTA_4 hydrolase. Structure−activity relationship (SAR) studies around this structural class resulted in the identification of a number of novel, potent inhibitors of LTA_4 hydrolase, several of which demonstrated good oral activity in a mouse ex vivo whole blood assay.

Introduction

Leukotriene B_4 (LTB_4) is a 5-lipoxygenase (5-LO)-derived metabolite of arachidonic acid which is synthesized by a number of cell types, including eosinophils, neutrophils (PMNs), and macrophages.[1] LTB_4 is a pro-inflammatory mediator that is a potent stimulant of human neutrophils, inducing chemotaxis, aggregation, degranulation, adherence, and priming of inflammatory cells. There is substantial evidence that LTB_4 may play 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 inflammatory lung diseases[7] such as asthma. A therapeutic agent which inhibits the biosynthesis of LTB_4 therefore may be useful for the treatment of these inflammatory conditions.

Leukotriene A_4 (LTA_4) hydrolase is a 69 kDa zinc-containing enzyme[8] which stereospecifically catalyzes the hydrolysis of the unstable epoxide LTA_4 to the diol LTB_4. This process is the rate-limiting step in the biosynthesis of LTB_4. In addition to its epoxide hydrolase activity, the enzyme also possesses intrinsic aminopeptidase activity toward a variety of substrates.[9] LTA_4 hydrolase is a cytosolic, monomeric enzyme which is ubiquitously distributed in mammalian tissues,[10] even in cell types that do not express 5-LO.[11] Compounds which selectively inhibit LTA_4 hydrolase would preferentially block the formation of LTB_4 and thus be an attractive pharmacological target.

Several inhibitors of LTA_4 hydrolase have been reported over the past few years. One approach involved inhibitors based on the structure of the natural substrate itself, LTA_4.[12,13] After the discovery of the zinc-containing nature of LTA_4 hydrolase, inhibitors of other Zn^{2+}-containing metalloproteinases, such as bestatin[14] and captopril,[15] were shown to inhibit LTA_4 hydrolase. A series of bestatin analogues and related α-keto-β-amino acid transition-state mimics[16] were reported as inhibitors of LTA_4 hydrolase, as well as a related series that incorporated a zinc-chelating thiol or hydroxamate moiety.[17] The hydroxamic acid kelatorphan and some related analogues were recently reported and were among the most potent inhibitors of LTA_4 hydrolase described to date.[18] However, these analogues were unable to penetrate cell membranes as evidenced from their lack of activity in a human whole blood assay. More recently, thiol SA6541[19] and a screening hit from a microorganism[20] have also been reported.

In the present study, we describe a unique series of nonpeptidic, presumably non-zinc-chelating inhibitors of LTA_4 hydrolase.

Chemistry

An initial chemical lead, SC-22716 (**1**), was identified through the Monsanto Structure−Activity Screening Program. SC-22716 was found to be a potent, competitive, reversible inhibitor of both the hydrolase and peptidase activity of human LTA_4 hydrolase[21] (IC_{50} = 0.20 and 0.23 μM, respectively). Since LTA_4 hydrolase is an intracellular enzyme, good cellular penetration is a prerequisite for a successful drug candidate. SC-22716 was able to penetrate cellular membranes, with an IC_{50} of 0.79 μM in a human whole blood LTB_4 production assay. However, the compound showed no activity when dosed orally in a mouse ex vivo whole blood LTB_4 production assay (9% inhibition at 10 mg/kg). On the basis of these findings, a number of analogues were synthesized to explore the SAR of this series. These

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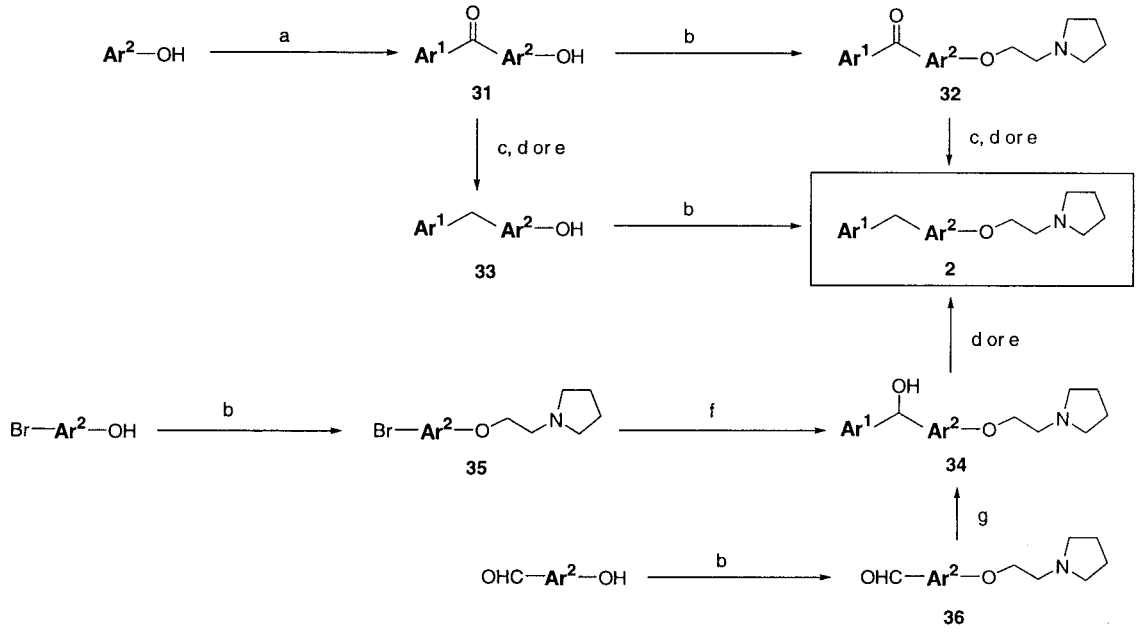
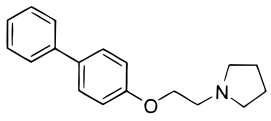
Scheme 1[a]

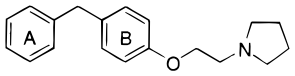


[a] (a) (1) $Ar^1C(O)Cl$, pyridine, CH_2Cl_2, (2) $AlCl_3$, Δ; (b) 1-(2-chloroethyl)pyrrolidine-HCl, K_2CO_3, DMF, Δ; (c) $NaBH_4$, EtOH, H_2O; (d) H_2, 4% Pd/C, MeOH, AcOH; (e) Et_3SiH, TFA, CH_2Cl_2; (f) (1) *t*-BuLi, THF, (2) Ar^1CHO; (g) Ar^1Li, THF.

efforts were directed at improving both the enzyme potency and ex vivo activity of this novel lead.



1 (SC-22716)



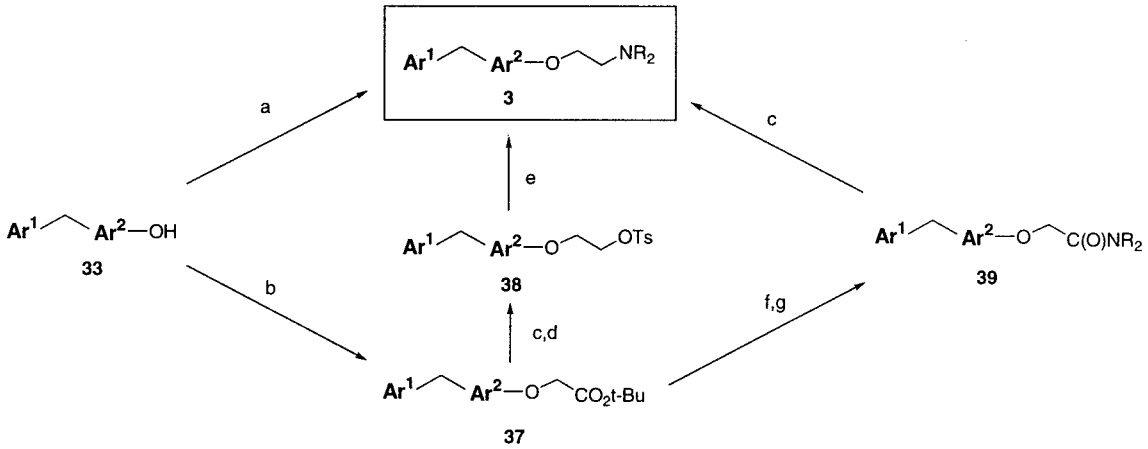
2a

Initially, the biphenyl moiety of **1** was replaced with a diphenylmethyl functional group. This compound (**2a**) was nearly an order of magnitude more potent at inhibiting the hydrolase activity of LTA_4 hydrolase and, in addition, was more potent in the human whole blood and mouse ex vivo assays. On the basis of these results, the **2a** structure was used as a template for further exploration. Examples in which the tertiary amine was pyrrolidine were synthesized simply by alkylation of a phenol with commercially available 1-(2-chloroethyl)-pyrrolidine as shown in Scheme 1. Phenols which were not commercially available were prepared using a variety of literature methods. Scheme 1 outlines the preparation of phenols via benzophenones and/or diarylcarbinols. Two distinct methods were utilized. The first involved Friedel−Crafts/Fries methodology to provide benzophenone **31**, followed by alkylation with 1-(2-chloroethyl)pyrrolidine to give **32**. A two-step reduction using $NaBH_4$ to generate the carbinol, followed by a deoxygenation using either catalytic hydrogenation or trifluoroacetic acid/triethylsilane, gave **2**. Alternatively, reversal of the final two steps (two-step deoxygenation to give **33**, followed by alkylation) also provided **2**. The second method involved addition of an aryllithium to an aryl carboxaldehyde, followed by reduction of the resultant carbinol **34**, to provide **2**. This was accomplished either by addition of the lithium anion generated from 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (**35**) to an aryl (Ar^1) carboxaldehyde or by addition of an aryl (Ar^1) lithium to 4-[2-(1-pyrrolidinyl)ethoxy]-benzaldehyde (**36**). Reduction of **34** then provided **2**. The synthesis of analogues in which the amine moiety was other than pyrrolidine is described in Scheme 2. Alkylation of phenol **33** with a commercially available chloroethylamine in the presence of K_2CO_3 or NaH provided **3**. Alternatively, the phenol could be alkylated with *tert*-butyl bromoacetate to give **37** followed by reduction with lithium aluminum hydride (LAH) to the corresponding alcohol and tosylation to afford **38**. Reaction of tosylate **38** with an amine in DMF/K_2CO_3 provided **3**. In addition, *tert*-butyl ester **37** could be hydrolyzed to the acid with trifluoroacetic acid and coupled with an amine using disuccinyl carbonate (DSC) in DMF to give the corresponding amide **39**. Reduction with LAH provided **3**. Diphenyl ether analogues **4** (Scheme 3) were synthesized using a standard Ullmann coupling to give phenol **40**, followed by alkylation with 1-(2-chloroethyl)pyrrolidine.

Results and Discussion

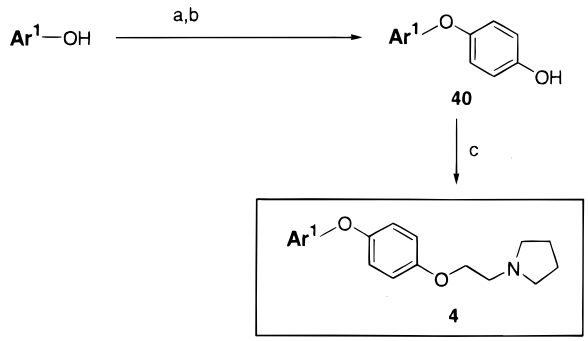
Table 1 highlights the results obtained from modification of the amine moiety of **2a**. In general, the steric environment about the amine had little effect on the potency of inhibition of LTA_4 hydrolase or LTB_4 production in human whole blood. Compounds ranging from the minimal structure **3a** to the sterically congested **3j** had very similar IC_{50}s in both assays. In general, the majority of these analogues had IC_{50}s of 200 nM or less in both enzyme and human whole blood assays. Dimethylamine **3b**, along with **3a**, were the most potent compounds against the enzyme, with IC_{50}s of 6 and 9 nM, respectively. Compound **3b** was the most potent in the whole blood assay with an IC_{50} = 73 nM. Compounds **3g** and **3i** were among the least potent, particularly in the whole blood assay. A comparator inhibitor, kelatorphan, demonstrated equivalent enzyme potency to some of our more potent analogues; however, it was unable to penetrate whole cells in the human whole

Scheme 2[a]



[a] (a) NaH or K_2CO_3, DMF, $ClCH_2CH_2NR_2$, Δ; (b) NaH, $BrCH_2CO_2t$-Bu, THF; (c) LAH, THF; (d) *p*-toluenesulfonyl chloride, pyridine, CH_2Cl_2; (e) HNR_2, K_2CO_3, DMF, Δ; (f) TFA, CH_2Cl_2, MeOH; (g) disuccinylcarbonate (DSC), DMF, pyridine, HNR_2.

Scheme 3[a]

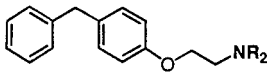


[a] (a) 4-Iodoanisole, KOH, cat. Cu, Δ; (b) BBr_3, CH_2Cl_2; (c) 1-(2-chloroethyl)pyrrolidine-HCl, K_2CO_3, DMF, Δ.

blood assay. The majority of these compounds showed very poor oral activity in the mouse ex vivo whole blood LTB_4 production assay. While **1** was essentially inactive (9% inhibition at 10 mg/kg) in the ex vivo assay, **2a** and **3a** showed moderate oral activity, with 35% and 53% inhibition of LTB_4 production at 10 mg/kg. All other analogues in Table 1 demonstrated diminished oral activity in this assay. Selected ex vivo assay results are summarized in Table 6. Since pyrrolidine **2a** was one of the more potent amines investigated, it was used as a template to probe the effects of further modification of this molecule.

Table 2 outlines modifications of the linker atom(s) between the A and B aryl rings. The initial chemical lead **1** was relatively potent in both the enzyme and whole blood assays with IC_{50}s of 0.20 and 0.79 μM, respectively. Insertion of a methylene or ether linkage into the biphenyl moiety (**2a** and **4a**) increased potency almost an order of magnitude in both assays. In addition, both had improved oral activity in the ex vivo model (35% and 25% inhibition, respectively, at 10 mg/kg). Increasing the oxidation level of the methylene group (**6** and **7**) dramatically decreased potency in both hydrolase and whole blood assays. However, difluoromethylene **5** was essentially equipotent to **2a**. Two atom linkers were also investigated, with $-CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, and $-CH_2NH_2-$ combinations giving reasonably potent compounds, particularly **9**, **13**, and **15**. In addition, **15** showed a 56% inhibition of LTB_4 production at 10 mg/kg in the ex vivo assay. Again, as with the methylene analogues, any increase in oxidation level, such as sulfide **10** to sulfoxide **11** or sulfone **12**, methylene **14** to amide **16**, or ethyl **8** to ethenyl **17**, resulted in a dramatic decrease in enzyme inhibitory potency. This study demonstrated that methylene and ether linkers were optimal for enzyme and whole blood

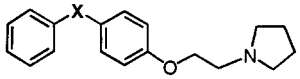
Table 1. Amine Modifications



compd	-NR_2	IC_{50} (μM)[a] hLTA$_4$ hydrolase	human whole blood
2a		0.026	0.12
3a	$-NH_2$	0.009	0.28
3b	$-NMe_2$	0.006	0.073
3c	$-NEt_2$	0.40 (2)	0.16
3d	-Ni-Pr_2	0.10 (2)	0.14
3e		0.055 (2)	0.17
3f		0.037	0.12
3g		0.23	1.32
3h		0.075	0.62 (2)
3i		0.19	1.65
3j		0.02 (2)	0.18
3k		0.10	0.19
3l		0.017	0.41
	kelatorphan	0.005	>50
	zileuton	>100	0.85
	A-78773	>3	0.078

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

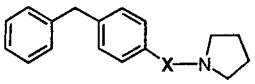
Table 2. Aryl-Linker Modifications



compd	-X-	IC_{50} (μM)[a,b] hLTA$_4$ hydrolase	human whole blood
1	"bond"	0.2 (2)	0.79
2a	-CH_2-	0.026	0.12
4a	-O-	0.03 (2)	0.079
5	-CF_2-	0.011	0.17
6	-C(O)-	1.8 (2)	–
7	-CH(OH)-	1.8 (2)	4.6 (2)
8	-CH_2CH_2-	0.22 (2)	0.22
9	-CH_2O-	0.03 (2)	0.31
10	-CH_2S-	0.15 (2)	0.31
11	-CH_2SO-	7.5 (2)	24.5 (2)
12	-CH_2SO_2-	4.0 (2)	7.7
13	-SCH_2-	0.067	0.19
14	-CH_2NH-	0.15 (2)	0.42
15	-$NHCH_2$-	0.027	0.15
16	-C(O)NH-	>25	–
17		1.35 (2)	1.5
18		>25	–

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

Table 3. Amine-Linker Modifications



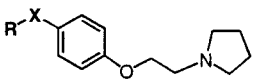
compd	-X-	IC_{50} (μM)[a,b] hLTA$_4$ hydrolase	human whole blood
2a	-OCH_2CH_2-	0.026	0.12
19	-$OCH(CH_3)CH_2$-	0.7 (2)	0.79
20	-$NHCH_2CH_2$-	>3	–
21	-SCH_2CH_2-	0.48	0.94
22	-$SOCH_2CH_2$-	9.7	14 (2)
23	-$CH_2CH_2CH_2$-	0.67	1.3
24	-CH=$CHCH_2$-	0.26	0.32
25	-$CH_2OCH_2CH_2$-	2.8	1.6 (2)
26		0.37	0.51

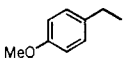
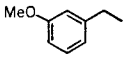
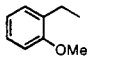
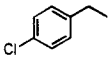
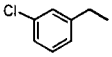
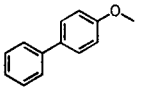
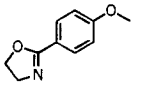
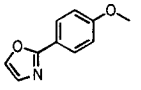
[a] Average of at least three determinations except where noted in parentheses. [b] - = not determined.

potency and, along with **15**, were the only analogues in Table 2 to show any significant oral activity. Since analogues containing these two linker groups were somewhat more synthetically accessible, additional analogues utilized only these two linkers.

While maintaining the diphenylmethane and pyrrolidine moieties, we explored a number of modifications to the linker atoms between the B-ring and amine moiety (Table 3). Essentially all specified modifications resulted in diminished potency relative to **2a**. Replacement of the oxygen atom of **2a** with sulfur or carbon (**21** or **23**) resulted in a 20- to 30-fold reduction in potency in the LTA$_4$ hydrolase assay, although **23** did show moderate oral activity (44% inhibition at 10 mg/kg) in the ex vivo assay. Introduction of unsaturation

Table 4. A-Ring Modifications



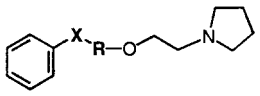
compd	R-X-	IC_{50} (μM)[a,b] hLTA$_4$ hydrolase	human whole blood
2a		0.026	0.12
27	$CH_3(CH_2)_6O$-	0.9 (2)	2.2
28		0.04	0.53 (2)
2b		0.07	0.89
2c		0.84	2.5
2d		>10	–
2e		0.06	1.0
2f		0.08	0.16
2g		0.63	1.56
2h		0.087	0.26
2i		0.069	0.37
2j		0.19	0.24
2k		0.077	0.22 (2)
2l		0.077	0.25 (2)
2m		0.047	0.075 (2)
2n		0.033	0.10
4b		0.0066	0.14
4c		0.59	0.55
4d		0.043	0.055

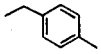
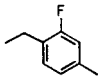
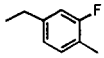
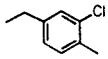
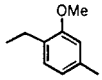
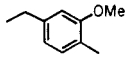
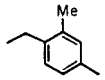
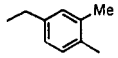
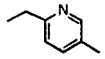
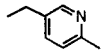
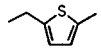
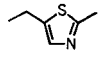
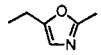
[a] Average of at least three determinations except where noted in parentheses. [b] - = not determined.

to **23** improved potency somewhat, but **24** was still 10-fold less potent than **2a**. Analogues in which the oxygen atom was replaced with either nitrogen or sulfoxide (**20** and **22**) were essentially inactive against the enzyme. Insertion of a methylene unit between the phenyl ring and oxygen atom (**25**) resulted in a 100-fold decrease in potency relative to **2a**. Alkyl substitution of this linker (**19**) also substantially decreased potency. The oxyethyl linker appeared to be optimal at this site, in terms of chain length, substitution, and heteroatom identity and location.

A number of A-ring modifications were also explored (Table 4). In general, an aromatic or heteroaromatic

Table 5. B-Ring Modifications



compd	-X-R-	IC_{50} (μM)[a,b] hLTA$_4$ hydrolase	human whole blood
1		0.2 (2)	0.79
29		0.7 (2)	8.2
30		>3	–
2a		0.026	0.12
2o		0.053	1.09
2p		0.06	0.19
2q		1.23	2.0
2r		>100	–
2s		24.7	9.0 (2)
2t		>3	–
2u		>3	>3
2v		1.8	6.7 (2)
2w		0.007 (2)	0.082
2x		0.036	0.53 (2)
2y		2.9 (2)	4.3 (2)
2z		>3	–

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

Table 6. Mouse ex Vivo Data for Selected Analogues

compd	mouse *ex vivo* %inhibition @ 10 mg/kg
1	9%
2a	35%
2b	74%
2k	57%
2n	63%
3a	53%
4a	25%
4c	83%
4d	93%
15	56%
23	44%
zileuton	≥95%
A-78773	≥94%

group was required at this site for optimal potency (i.e., see **27**), although cyclohexyl (**28**) had reasonably good potency against the enzyme. Ortho substitution (**2d**) eliminated any inhibitory activity, while meta- and para-substituted analogues (**2b,c,e,f**) maintained good, but diminished potency relative to **2a**. Many heterocyclic derivatives showed good potency with IC_{50}s of less than 100 nM in the hydrolase assay, including 3-pyridyl (**2h**), 2- and 5-thiazolyl (**2i,k**), furyl (**2l,m**), and thienyl (**2n**). One particularly potent analogue was biphenyl **4b**, with an IC_{50} of 6.6 nM in the hydrolase assay. Likewise, a related analogue, phenyloxazole **4d**, also had very good potency in both hydrolase and whole blood assays. In addition, it was in this class of analogues that we first demonstrated encouraging oral activity. *p*-Methoxy analogue **2b**, thiazole **2k**, and thiophene **2n** all showed a significant potency enhancement over **2a** in the ex vivo assay, with 74%, 57%, and 63% inhibition, respectively, at 10 mg/kg vs 35% for **2a**. Even more promising was the oral activity of phenyloxazolidine **4c** and phenyloxazole **4d**, which inhibited LTB_4 production in the ex vivo assay 83% and 93%, respectively, at 10 mg/kg. In general, unsubstituted phenyl and several heteroaryls and biaryls at this position were optimal for good in vitro potency. In addition, it was within the heterocyclic, and more specifically, the phenyloxazole class of analogues that significant progress was made toward obtaining satisfactory oral activity.

Table 5 summarizes modifications that were carried out on the B-ring of **2a**. *m*-Biphenyl analogue **29** had diminished hydrolase inhibitory activity relative to **1**, while *trans*-cyclohexyl analogue **30** was inactive. Likewise, the analogous *cis*-cyclohexyl analogue was also inactive (data not shown). Any substituents on the central phenyl ring of **2a**, other than fluoro (i.e., **2o**,**p**—which were about equipotent to **2a**), resulted in a dramatic decrease in potency in both hydrolase and whole blood assays (**2q,r,s,t,u**). A number, of other substituents on this phenyl ring, including $-CONH_2$, Ac–, $-NO_2$, $-NH_2$, and –NHAc, also demonstrated diminished potency (data not shown). Only two heterocyclic analogues, pyridine **2w** and thiophene **2x**, showed good potency in both assays. All other heterocycles were very poor inhibitors. It is interesting to note that pyridine analogue **2w**, unlike pyridine **2v**, was among the most potent of our inhibitors. Unsubstituted phenyl appeared to be optimal at this site, with pyridine **2w** and thiophene **2x** also showing good activity. However, these modifications failed to provide any enhancement in oral activity relative to **2a** in the mouse ex vivo assay.

One class of compounds that is potential competition for LTA_4 hydrolase inhibitors is 5-lipoxygenase (5-LO) inhibitors. We investigated two standard 5-LO inhibitors, zileuton and a second-generation analogue, A-78773, as comparators in our in vivo and ex vivo assays. The results are shown in Tables 1 and 6. As expected, neither zileuton nor A-78773 inhibited LTA_4 hydrolase. In the human whole blood assay, many of our inhibitors were significantly more potent than zileuton and a few were equipotent to A-78773. Both 5-LO inhibitors demonstrated excellent oral activity in the mouse ex vivo model, giving essentially maximal inhibition at 10 mg/kg. In this study, one of our LTA_4 hydrolase inhibitors, **4d**, demonstrated similar potency with 93% inhibition at 10 mg/kg.

Selected compounds from this series also inhibited the peptidase activity of the LTA_4 hydrolase enzyme with

very similar IC_{50}s (generally within an order of magnitude). However, unlike many of the zinc-chelating inhibitors such as kelatorphan,[18] these compounds did not block the protease activity of other zinc-containing aminopeptidases, such as neutral endopeptidase (NEP) or angiotensin converting enzyme (ACE), at concentrations of up to 100 μM. In addition, extended X-ray absorption fine structure (EXAFS) spectroscopy of the zinc-containing LTA_4 hydrolase enzyme carried out either in the presence or absence of a related inhibitor, SC-57461, was similar within the first coordination shell of the Zn atom (data not shown). This provides evidence for a lack of interaction of this class of inhibitors with the zinc atom of the enzyme. These data will be reported at a later date.

Conclusions

We have discovered a novel series of potent nonpeptidic, presumably non-zinc-chelating inhibitors of LTA_4 hydrolase. Many analogues showed excellent potency in a human whole blood LTB_4 production assay, and a few demonstrated good oral activity in a mouse ex vivo whole blood assay. Further SAR studies on this series of LTA_4 hydrolase inhibitors, with a primary emphasis on further modification of the amine moiety, will be reported shortly.

Experimental Section

Biological Methods. Human LTA_4 Hydrolase Assay. Recombinant human LTA_4 hydrolase was prepared as previously described[21] and stored at −20 °C as a stock solution in 50 mM Tris buffer pH 8.0 containing 150 mM NaCl, 2.5 mM β-mercaptoethanol, and 50% glycerol (specific activity = 650 nmol/min/mg). LTA_4 substrate was prepared from the methyl ester in THF (Biomol, Plymouth Meeting, PA) by room temperature incubation with 30 molar equivalents of LiOH for 18 h, and it was stored at −80 °C until used. Enzyme was diluted into assay buffer (0.1 M potassium phosphate pH 7.4, 5 mg/mL fatty acid free bovine serum albumin, and 10% DMSO), and 250 ng (18 nM final assay concentration) in 25 μL was incubated with test compound, also in assay buffer, for 10 min at room temperature. LTA_4 substrate was diluted in assay buffer without DMSO to a concentration of 350 ng/mL, and 25 μL (8 ng) was added. The reaction (total volume 200 μL) was allowed to proceed at room temperature for 10 min. A 25 μL sample was added to 500 μL of assay buffer without DMSO to stop the reaction. LTB_4 was quantified in the diluted sample by a commercially available enzyme-linked immunoassay (ELISA, Cayman Chemical Co., Ann Arbor, MI).

Human Whole Blood Assay. Human blood collected in heparin was diluted 1:4 with RPMI-1640 media (GIBCO BRL, Grand Island, NY), and 200 μL was added per well in 96-well microtiter plates. Compounds diluted in DMSO (1%) were added to the blood in duplicate and allowed to incubate for 15 min at 37 °C in a humidified incubator (5% CO_2). Calcium ionophore A23187 (20 μg/mL, 1% DMSO final concentration) was added and the incubation continued for 10 min. The incubation was terminated by centrifugation (833 g, 10 min, 4 °C), and the supernatants were analyzed for LTB_4 by ELISA.

Mouse ex Vivo Whole Blood Assay. Test compounds were administered in physiologic saline with 2% DMSO and 1% Tween-80 to adult male outbred mice (CD-1, 20−30 g, 5−8 animals/treatment group) by gavage. One hour after dosing, blood was collected on heparin from the retroorbital sinus and added to microtiter plates (100 μL) along with an equal volume of RMPI-1640 media. Calcium ionophore A23187 (20 μL/mL final concentration) was added, and the mixture incubated at 37 °C for 10 min in a humidified incubator. The incubation was terminated by centrifugation and the supernatants analyzed for LTB_4 by ELISA.

Chemistry. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. High field ^1H 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.

Procedure A: Alkylation of a Phenol with 1-(2-Chloroethyl)pyrrolidine. A solution of a phenol, 1−2 equivalents of 1-(2-chloroethyl)pyrrolidine·HCl, and 2−3 equivalents of powdered K_2CO_3 in DMF was stirred at 80−90 °C for 12−48 h. The solution was cooled, poured into water, and extracted with Et_2O or EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc or CH_2Cl_2/MeOH/NH_4OH mixtures to give the desired product.

Procedure B: Alkylation of a Phenol with a Chloroethylamine. To a solution of a phenol in DMF was added 1−2 equivalents of a 50% NaH dispersion in oil, and the mixture stirred for 10 min. The appropriate 1-(2-chloroethyl)amine was added, and the mixture stirred at 80 °C for 2 h. The reaction mixture was cooled, and water and EtOAc were added. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was converted to the HCl salt using ethanolic HCl to provide the desired product.

Procedure C: $NaBH_4$ Reduction of a Benzophenone. To a solution of a benzophenone in EtOH was added a solution of 0.5−0.75 equivalents of $NaBH_4$ in water. The mixture was stirred at 25 °C for 2 h and the reaction quenched with 3 N NaOH. The mixture was extracted with ether and the ether washed with brine, dried over Na_2SO_4, and concentrated to provide the corresponding alcohol.

Procedure D: Reduction of Diarylcarbinols Using Catalytic Hydrogenation. A diarylcarbinol in 60:40 MeOH/AcOH was hydrogenated in the presence of catalytic 4% Pd/C in a Parr shaker under 5 psi H_2 for 5 h. The solution was filtered and made basic with 10% NaOH. Extraction with EtOAc and concentration gave the desired product.

Procedure E: Reduction of Diarylcarbinols Using TFA/Triethylsilane. To a solution of a diarylcarbinol in CH_2Cl_2 was added a large excess of trifluoroacetic acid (TFA) and Et_3SiH. After being stirred at 25 °C for 1−30 h, the mixture was concentrated and poured into CH_2Cl_2 and 2 N NaOH, and the CH_2Cl_2 was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a CH_2Cl_2/MeOH/NH_4OH mixture gave the desired product.

Procedure F: Addition of 1-[2-(4-Lithiophenoxy)ethyl]-pyrrolidine to an Aldehyde. To a solution of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (**2f**, step 1) in THF at −78 °C was added 2 equivalents of 1.8 M *t*-BuLi in hexanes, and the mixture was stirred at −78 °C for 4 h. A solution of 1 equivalent of an appropriate aldehyde in THF was added, and the mixture was stirred at −78 °C for 30 min followed by warming to 0 °C. The reaction was quenched with H_2O, and the solution was extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel using a CH_2Cl_2/EtOH/NH_4OH mixture provided the corresponding alcohol.

Procedure G: Benzoylation of a Phenol. To a stirred solution of a phenol and 1 equivalent of pyridine in CH_2Cl_2 was added 1 equivalent of benzoyl chloride over 15 min. The solution was stirred at 25 °C for 4 h, poured onto crushed ice, warmed to 25 °C, and stirred for 18 h. The mixture was extracted with EtOAc, and the extracts were washed successively with 10% aqueous HCl, water, 10% aqueous NaOH, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide the crude benzoate. This was treated with 1.6 equivalents of $AlCl_3$ in portions and

heated to 160 °C for 2 h. After cooling and treatment with ice/concentrated HCl, the mixture was extracted with EtOAc and the extracts washed twice with 10% NaOH. The combined aqueous extracts were washed with EtOAc and acidified with concentrated HCl. The resulting precipitate was filtered, washed with water, and dried to provide the product.

1-[2-(4-Phenylphenoxy)ethyl]pyrrolidine (1). The title compound was prepared from 4-phenylphenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **1** as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4 H), 2.64 (m, 4 H), 2.93 (t, J = 5 Hz, 2H), 4.16 (t, J = 5 Hz, 2H), 6.99 (d, J = 9 Hz, 2H), 7.30 (m, 1H), 7.41 (t, J = 8 Hz, 2H), 7.53 (m, 4H). Anal. ($C_{18}H_{21}NO$) C, H, N.

1-[2-(4-Phenylmethyl)phenoxyethyl]pyrrolidine Hydrochloride (2a). The title compound was prepared from 4-benzylphenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide the free base (69%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.60 (m, 4H), 2.86 (t, J = 6 Hz, 2H), 3.91 (s, 2H), 4.07 (t, J = 6 Hz, 2H), 6.84 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.22 (m, 5H). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.10; H, 8.36; N, 4.95. A solution of the amine in Et_2O was treated with ethanolic HCl to provide the HCl salt **2a** as a tan solid: mp 163−165 °C. Anal. ($C_{19}H_{23}NO$·HCl·0.2H_2O) C, H, N.

1-[2-[4-[4-(Methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine (2b). The title compound was prepared from 4-anisaldehyde using procedure F, followed by procedure D, to provide **2b**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.62 (m, 4H), 2.89 (t, J = 6 Hz, 2H), 3.77 (s, 3H), 3.85 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.83 (m, 4H), 7.08 (m, 4H). Anal. ($C_{20}H_{25}NO_2$·0.2 H_2O) C, H, N.

1-[2-[4-[(3-Methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine (2c). The title compound was prepared from 3-anisaldehyde using procedure F, followed by procedure D, to provide **2c**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.61 (m, 4H), 2.88 (t, J = 6 Hz, 2H), 3.75 (s, 3H), 3.89 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.75 (m, 2H), 6.85 (d, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.21 (m, 2H). Anal. ($C_{20}H_{25}NO_2$·0.4H_2O) C, H, N.

1-[2-[4-[2-(Methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine (2d). The title compound was prepared from 2-anisaldehyde using procedure F, followed by procedure D, to provide **2d**: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.60 (m, 4H), 2.86 (t, J = 6 Hz, 2H), 3.80 (s, 3H), 3.90 (s, 2H), 4.06 (t, J = 6 Hz, 2H), 6.85 (m, 4H), 7.11 (m, 4H). Anal. ($C_{20}H_{25}NO_2$) C, N; H, calcd, 8.09; found, 7.61.

1-[2-[4-[(4-Chlorophenyl)methyl]phenoxy]ethyl]-pyrrolidine (2e). The title compound was prepared from 4-chloro-4′-hydroxybenzophenone and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A, followed by reduction using procedures C and E, to give **2e** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.62 (m, 4H), 2.89 (t, J = 6.0 Hz, 2H), 3.87 (s, 2H), 4.08 (t, J = 6.0 Hz, 4H), 6.84 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H). Anal. ($C_{19}H_{22}ClNO$) C, H, N.

1-[2-[4-[(3-Chlorophenyl)methyl]phenoxy]ethyl]-pyrrolidine (2f). Step 1: Preparation of 1-[2-(4-Bromophenoxy)ethyl]pyrrolidine. The title compound was prepared from 4-bromophenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide the title compound (48%) as a light yellow oil.

Steps 2 and 3: Preparation of 1-[2-[4-[(3-Chlorophenyl)methyl]phenoxy]ethyl]pyrrolidine. The title compound was prepared from the product of step 1 and 3-chlorobenzaldehyde using procedure F, followed by reduction using procedure E, to give **2f** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 4H), 2.65 (m, 4H), 2.91 (t, J = 6.0 Hz, 2H), 3.88 (s, 2H), 4.10 (t, J = 6.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 7.06 (m, 3H), 7.16 (m, 3H). Anal. ($C_{19}H_{22}ClNO$·0.3H_2O) C, H, N, Cl.

4-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl methyl]pyridine (2g). The title compound was prepared from 4-pyridinecarboxyaldehyde using procedure F, followed by procedure D, to provide **2g**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.60 (m, 4H), 2.89 (t, J = 6 Hz, 2H), 3.90 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 7.07 (m, 4H), 8.48 (d, J = 6 Hz, 2H). Anal. ($C_{18}H_{22}N_2O$·0.3H_2O) C, H, N.

3-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl methyl]pyridine (2h). The title compound was prepared from 3-pyridinecarboxyaldehyde using procedure F, followed by procedure D, to provide **2h**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.60 (m, 4H), 2.88 (t, J = 6 Hz, 2H), 3.90 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.55 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.17(dd, J = 9 Hz, 6 Hz, 1H), 7.44 (d, J = 9 Hz, 1H), 8.44 (dd, J = 6 Hz, 2 Hz, 1H), 8.49 (d, J = 2 Hz, 1H). Anal. ($C_{18}H_{22}N_2O$·0.2H_2O) C, H, N.

2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]thiazole (2i). Step 1: Preparation of 4-[2-(1-Pyrrolidinyl)ethoxy]benzaldehyde. The title compound was prepared from 4-hydroxybenzaldehyde and 1-(2-chloroethyl)-pyrrolidine·HCl using procedure A to provide the title compound (72%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 4H), 2.63 (m, 4H), 2.92 (t, J = 6 Hz, 2H), 4.19 (t, J = 6 Hz, 2H), 7.02 (d, J = 9 Hz, 2H), 7.82 (d, J = 9 Hz, 2H), 9.90 (s, 1H); HRMS m/z 219.1239 (calcd for $C_{13}H_{17}NO_2$, 219.1259).

Step 2: Preparation of α-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]-2-thiazolemethanol. To a solution of thiazole (0.5 g, 5.87 mmol) in THF (15 mL) at 0 °C was added 1.6 M *n*-BuLi in hexanes (3.75 mL, 6 mmol), and the mixture was stirred at 0 °C for 15 min. This solution was added to a solution of the product from step 1 (1.1 g, 5.0 mmol) in THF (20 mL) at −78 °C and the mixture stirred for 45 min. The reaction mixture was quenched with saturated NH_4Cl and poured into Et_2O and water. The ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 100:1:0.5 to 100:2:0.5 CH_2Cl_2/MeOH/NH_4OH gave the title compound (1.12 g, 74%) as a light brown solid: ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 4H), 2.59 (m, 4H), 2.83 (t, J = 6 Hz, 2H), 3.98 (t, J = 6 Hz, 2H), 5.72 (br, 1H), 5.96 (s, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 3.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 3.3 Hz, 1H). Anal. ($C_{16}H_{20}N_2O_2S$·0.3H_2O) C, H, N.

Step 3: Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]thiazole. The product of step 2 was reduced using procedure E to give the starting alcohol (21%), along with **2i** (37%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.62 (m, 4H), 2.90 (t, J = 6 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 4.28 (s, 2H), 6.89 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 3.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 3.3 Hz, 1H); HRMS m/z 288.1290 (calcd for $C_{16}H_{20}N_2OS$, 288.1297).

4-[[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]methyl]-thiazole (2j). Step 1: Preparation of 1-Bromo-3-(4-methoxyphenyl)-2-propanone. To a solution of 4-methoxyphenylacetic acid (3.32 g, 20 mmol) in benzene (30 mL) was added oxalyl chloride (2.0 mL, 23 mmol) followed by 1 drop of DMF. The mixture was stirred at 25 °C for 1.5 h and concentrated. To a solution of the crude acid chloride in Et_2O (50 mL) at 0 °C was added ethereal diazomethane until N_2 evolution ceased. HBr(g) was bubbled through the solution at 0 °C for 30 min. The solution was washed with water, dilute $NaHCO_3$, and brine and the ether layer dried over Na_2SO_4 and concentrated to provide a brown oil (4.79 g, 98%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.89 (s, 2H), 3.92 (s, 2H), 6.88 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H).

Step 2: Preparation of 4-[(4-Methoxyphenyl)methyl]-thiazole. A solution of thioformamide in dioxane was prepared by refluxing formamide (1.5 mL, 43 mmol) and P_2S_5 (3.3 g, 7.3 mmol) in 70 mL of dioxane for 2 h. The solution was added to a solution of the product from step 1 (1.0 g, 4.1 mmol) and 2 g of $MgCO_3$ in 10 mL of dioxane, and the mixture was refluxed for 1 h. The mixture was cooled and poured into Et_2O and 1 N NaOH. The ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography using a gradient of 10:1 to 5:1 hexane/EtOAc provided the title compound (0.52 g, 62%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 4.14 (s. 2H), 6.83 (s, 1H), 6.87 (d, J = 9 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 8.78 (s, 1H).

Step 3: Preparation of 4-(4-Thiazolylmethyl)phenol. To a solution of the product from step 2 (0.52 g, 2.53 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added 8 mL of 1 N BBr_3 in CH_2Cl_2, and the mixture was stirred at −78 °C for 20 min and at 25 °C for 16 h. The mixture was poured into H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to provide the product as a boronic acid complex: ^{1}H NMR ($CDCl_3$) δ 4.74 (s, 2H), 5.13 (br, 1H), 6.87 (d, J = 9 Hz, 2H), 7.04 (s, 1H), 7.13 (d, J = 9 Hz, 2H), 10.33 (s, 1H). The product was stirred in 10:1 MeOH/concentrated HCl at 25 °C for 25 h and the mixture concentrated to give the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 2H), 6.64 (d, J = 9 Hz, 2H), 6.93 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 9 Hz, 2H), 8.02 (br, 1H), 8.80 (d, J = 1.5 Hz, 1H).

Step 4: Preparation of 4-[[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]methyl]thiazole. The title compound was prepared from the product of step 3 and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **2j** (44%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.63 (m, 4H), 2.90 (t, J = 6 Hz, 2H), 4.08 (t, J = 6 Hz, 2H), 4.11 (s, 2H), 6.83 (s, 1H), 6.88 (d, J = 9 Hz, 2H), 7.19 (d, J = 9 Hz, 2H), 8.66 (s, 1H); HRMS m/z 288.1286 (calcd for $C_{16}H_{20}N_2OS$, 288.1296).

5-[[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]methyl]-thiazole (2k). Step 1: Preparation of α-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-5-thiazolemethanol. To a solution of 2-trimethylsilylthiazole (1.09 g, 6.9 mmol) in THF (25 mL) at −78 °C was added 1.6 M *n*-BuLi in hexanes (4.5 mL, 7.2 mmol), and the mixture was warmed to −50 °C for 1 min and cooled to −78 °C. A solution of 4-[2-(1-pyrrolidinyl)ethoxy]-benzaldehyde (**2i**, step 1) (1.4 g, 6.4 mmol) in THF (6 mL) was added, and the mixture was stirred at −78 °C for 45 min. The reaction mixture was quenched with saturated NH_4Cl and poured into Et_2O and water. The ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 100:2:0.5 to 100:3:0.5 CH_2Cl_2/MeOH/NH_4OH gave 0.42 g (20%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.59 (m, 4H), 2.86 (t, J = 6 Hz, 2H), 4.00 (t, J = 6 Hz, 2H), 5.17 (br, 1H), 5.99 (s, 1H), 6.83 (d, J = 9 Hz, 2H), 7.31 (m, 2H), 7.54 (s, 1H), 8.64 (s, 1H).

Step 2: Preparation of 5-[[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]methyl]thiazole. The title compound was prepared using procedure E from the product of step 1 to provide **2k** as a yellow oil (70%): ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.61 (m, 4H), 2.90 (t, J = 6 Hz, 2H), 4.09 (t, J = 6 Hz, 2H), 4.12 (s, 2H), 6.86 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.62 (s, 1H), 8.66 (s, 1H); HRMS m/z 288.1299 (calcd for $C_{16}H_{20}N_2OS$, 288.1296).

1-[2-[4-[(3-Furanyl)methyl]phenoxy]ethyl]pyrrolidine (2l). The title compound was prepared from 3-furaldehyde using procedure F, followed by procedure D, to provide **2l**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.64 (m, 4H), 2.90 (t, J = 6 Hz, 2H), 3.70 (s, 2H), 4.09 (t, J = 6 Hz, 2H), 6.23 (s, 1H), 6.35 (d, J = 9 Hz, 2H),7.11 (d, J = 9 Hz, 2H), 7.20 (s, 1H), 7.35 (m, 1H); MS m/z 271 (M^+).

1-[2-[4-[(2-Furanyl)methyl]phenoxy]ethyl]pyrrolidine (2m). The title compound was prepared from 2-furaldehyde using procedure F, followed by procedure D, to provide **2m**: ^{1}H NMR ($CDCl_3$) δ 1.86 (m, 4H), 2.77 (m, 4H), 3.01 (t, J = 6 Hz, 2H), 3.90 (s, 2H), 4.15 (t, J = 6 Hz, 2H), 5.97 (d, J = 4 Hz, 1H), 6.29 (m, 1H), 6.85 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.32 (m, 1H); MS m/z 271 (M^+).

1-[2-[4-[(3-Thienyl)methyl]phenoxy]ethyl]pyrrolidine (2n). The title compound was prepared from 3-thiophenecarboxaldehyde using procedure F, followed by procedure D, to provide **2n**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.61 (m, 4H), 2.89 (t, J = 6 Hz, 2H), 3.90 (s, 2H), 4.09 (t, J = 6 Hz, 2H), 6.88 (m, 4H), 7.10 (d, J = 9 Hz, 2H), 7.23 (m, 1H). Anal. ($C_{17}H_{21}NOS$) C, H, N.

1-[2-[3-Fluoro-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2o). 2-Fluoro-4-hydroxybenzophenone was prepared from 3-fluorophenol using procedure G. This was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using procedure A and reduced using procedures C and D to provide **2o**: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.60 (m, 4H), 2.88 (t, J = 7 Hz, 2H), 3.90 (s, 2H), 4.05 (t, J = 7 Hz, 2H), 6.63 (d, J = 10 Hz, 2H), 7.00 (t, J = 8 Hz, 1H), 7.15−7.40 (m, 5H); HRMS m/z 299.1681 (calcd for $C_{19}H_{22}FNO$, 299.1685).

1-[2-[2-Fluoro-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2p). 3-Fluoro-4-hydroxybenzophenone was prepared from 2-fluorophenol using procedure G. This was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using procedure A and reduced using procedures C and D to provide **2p**: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.63 (m, 4H), 2.92 (t, J = 7 Hz, 2H), 3.89 (s, 2H), 4.14 (t, J = 7 Hz, 2H), 6.80−6.95 (m, 3H), 7.15−7.35 (m, 5H); HRMS m/z 299.1678 (calcd for $C_{19}H_{22}FNO$, 299.1685).

1-[2-[2-Chloro-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2q). 3-Chloro-4-hydroxybenzophenone was prepared from 2-chlorophenol using procedure G. This was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using procedure A and reduced using procedures C and E to provide **2q**: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.65 (m, 4H), 2.93 (t, J = 7 Hz, 2H), 3.89 (s, 2H), 4.12 (t, J = 7 Hz, 2H), 6.85 (d, J = 8 Hz, 1H), 7.00 (dd, J = 8 Hz, 2 Hz, 1H), 7.12−7.35 (m, 6H); HRMS m/z 315.1385 (calcd for $C_{19}H_{22}{}^{35}ClNO$, 315.1390).

1-[2-[3-Methoxy-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2r). The title compound was prepared from 3-methoxyphenol in the same manner as described for the preparation of **2s** to provide **2r**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.60 (m, 4H), 2.88 (t, J = 7 Hz, 2H), 3.77 (s, 3H), 3.89 (s, 2H), 4.08 (t, J = 7 Hz, 2H), 6.41 (dd, J = 8 Hz, 3 Hz, 1H), 6.50 (d, J = 3 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 7.13−7.30 (m, 5H); HRMS m/z 311.1895 (calcd for $C_{20}H_{25}NO_2$, 311.1885).

1-[2-[2-Methoxy-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2s). 2-Methoxyphenol (2.0 g, 16.1 mmol), benzoic acid (2.0 g, 16.4 mmol), and 50 mL of polyphosphoric acid (PPA) were heated at 120 °C for 1 h. The mixture was cooled, treated with 50 g of ice, and poured into H_2O. The mixture was extracted with EtOAc, and the extracts were washed successively with water, 5% aqueous Na_2SO_3, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated to provide, after flash chromatography on silica gel using a gradient of 1:9 to 1:4 EtOAc/hexane, 3-methoxy-4-hydroxybenzophenone (0.47 g, 13%): HRMS m/z 228.0796 (calcd for $C_{14}H_{12}O_3$, 228.0786). This was alkylated with 1-(2-chloroethyl)-pyrrolidine·HCl using procedure A and reduced using procedures C and E to provide **2s**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.62 (m, 4H), 2.93 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.93 (s, 2H), 4.12 (t, J = 7 Hz, 2H), 6.70 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 7.15−7.32 (m, 5H); HRMS m/z 311.1875 (calcd for $C_{20}H_{25}NO_2$, 311.1885).

1-[2-[3-Methyl-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2t). 2-Methyl-4-hydroxybenzophenone was prepared from 3-methylphenol using procedure G. This was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using procedure A and reduced using procedures C and E to provide **2t**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.20 (s, 3H), 2.62 (m, 4H), 2.88 (t, J = 7 Hz, 2H), 3.91 (s, 2H), 4.08 (t, J = 7 Hz, 2H), 6.70 (dd, J = 8 Hz, 3 Hz, 1H), 6.76 (d, J = 3 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 7.07−7.29 (m, 5H); HRMS m/z 295.1914 (calcd for $C_{20}H_{25}NO$, 295.1936).

1-[2-[2-Methyl-4-(phenylmethyl)phenoxy]ethyl]pyrrolidine (2u). 3-Methyl-4-hydroxybenzophenone was prepared from 2-methylphenol using procedure G. This was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using procedure A and reduced using procedures C and E to provide **2u**: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.18 (s, 3H), 2.63 (m, 4H), 2.91 (t, J = 7 Hz, 2H), 3.88 (s, 2H), 4.08 (t, J = 7 Hz, 2H), 6.73 (d, J = 7 Hz, 1H), 6.95 (d and overlapping s, J = 7 Hz, 2H), 7.15−7.31 (m, 5H); HRMS m/z 295.1945 (calcd for $C_{20}H_{25}NO$, 295.1936).

2-(Phenylmethyl)-5-[2-(1-pyrrolidinyl)ethoxy]pyridine (2v). Step 1: Preparation of 2-(Phenylmethyl)-3-hydroxypyridine. A solution of 1,2-bis(chlorodimethylsilyl)-ethane (6.36 g, 29.5 mmol) in 11 mL of CH_2Cl_2 was added to 2-aminomethylfuran (2.6 mL, 29.5 mmol) and Et_3N in 19 mL of CH_2Cl_2 at 0 °C, and the mixture was stirred at 25 °C for 2 h. The mixture was filtered and concentrated. To a solution

of this crude product (4.5 g, 18.8 mmol) in 50 mL of THF at −78 °C was added 1.7 M *t*-BuLi in hexanes (12.2 mL, 20.7 mmol), and the mixture was stirred at −40 °C for 2 h. Benzaldehyde (3.0 g, 28.2 mmol) was added and the mixture stirred at 25 °C for 1 h. Next 10% aqueous HCl was added and the mixture refluxed for 18 h. The mixture was cooled, diluted with Et_2O, and extracted with 10% HCl. The acid extracts were neutralized with 10% NaOH and extracted with Et_2O. The extracts were dried over Na_2SO_4 and concentrated to provide the title compound: ^{1}H NMR ($CDCl_3$) δ 4.10 (s, 2H), 7.04 (d, J = 9 Hz, 1H), 7.17 (dd, J = 9, 4 Hz, 1H), 7.23 (m, 5H), 8.17 (d, J = 4 Hz, 1H).

Step 2: Preparation of 2-(Phenylmethyl)-5-[2-(1-pyrrolidinyl)ethoxy]pyridine. The product of step 1 was alkylated with 1-(2-chloroethyl)pyrrolidine·HCl using the procedure described in step 2 for the preparation of **30** to give **2v**: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.62 (m, 4H), 2.89 (t, J = 6 Hz, 2H), 4.09 (s, 2H), 4.11 (t, J = 6 Hz, 2H), 7.00 (d, J = 8 Hz, 1H), 7.12 (dd, J = 8, 3 Hz, 1H), 7.24 (m, 5H), 8.26 (d, J = 3 Hz, 1H). Anal. ($C_{18}H_{22}N_2O$·0.3H_2O) C, H, N.

5-Phenylmethyl-2-[2-(1-pyrrolidinyl)ethoxy]pyridine (2w). Step 1: Preparation of (6-Chloro-3-pyridinyl)-phenylmethanone. To a solution of 6-chloronicotinic acid (1.0 g, 6.35 mmol) in 10 mL of THF at 25 °C was added oxalyl chloride (0.56 mL, 6.35 mmol), followed by a drop of DMF. After gas evolution, the solution was concentrated and the crude acid chloride stirred in 20 mL benzene. $AlCl_3$ (2.1 g, 15.9 mmol) was added and the reaction mixture refluxed for 1.5 h. The mixture was cooled and poured into EtOAc and water, and the organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel provided the title compound (1.4 g, 100%) as a yellow solid: mp 55−56.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 3H), 7.66 (t, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 3H), 8.11 (dd, J = 9, 2 Hz, 1H), 8.78 (d, J = 2 Hz, 1H).

Step 2: Preparation of Phenyl [6-[2-(1-Pyrrolidinyl)-ethoxy]-3-pyridinyl]methanone. To pyrrolidinoethanol (0.304 g, 1.84 mmol) in 20 mL of benzene was added 75 mg of NaH (60% dispersion in oil, 1.84 mmol). After the mixture was stirred at 25 °C for 10 min, the product from step 1 (0.40 g, 1.84 mmol) was added, and the mixture was stirred at 25 °C for 4 h. The mixture was poured into EtOAc and water, and the organic layer was dried over Na_2SO_4 and concentrated. Radial band chromatography on silica gel using a gradient of 1:1 hexane/EtOAc to 100% EtOAc provided the title compound (0.48 g, 88%): ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 4H), 2.62 (m, 4H), 2.91 (t, J = 6 Hz, 2H), 4.54 (t, J = 6 Hz, 2H), 6.88 (d, J = 9 Hz, 1H), 7.49 (m, 2H), 7.58 (m, 1H), 7.77 (m, 2H), 8.09 (dd, J = 9, 2 Hz, 1H), 8.60 (d, J = 2 Hz, 1H). Anal. ($C_{18}H_{20}N_2O_2$·0.2H_2O) C, H, N.

Steps 3 and 4: Preparation of 5-Phenylmethyl-2-[2-(1-pyrrolidinyl)ethoxy]pyridine. The product of step 2 was reduced using procedures C and D to give **2w**: ^{1}H NMR ($CDCl_3$) δ 1.98 (m, 4H), 3.18 (m, 4H), 3.33 (t, J = 5 Hz, 2H), 3.89 (s, 2H), 4.60 (t, J = 5 Hz, 2H), 6.67 (d, J = 8 Hz, 1H), 7.22 (m, 5H), 7.38 (dd, J = 8, 2 Hz, 1H), 7.99 (d, J = 2 Hz, 1H). Anal. ($C_{18}H_{22}N_2O$·0.3H_2O) C, H; N: calcd, 9.73; found: N, 9.25.

1-[2-[[5-(Phenylmethyl)-2-thienyl]oxy]ethyl]pyrrolidine Hydrochloride (2x). Step 1: Preparation of 1-[2-(2-Thienyloxy)ethyl]pyrrolidine. To 1-(2-hydroxyethyl)pyrrolidine (20 mL, 171 mmol) were added sodium pellets (1.3 g, 56.5 mmol). After the initial reaction subsided, the mixture was heated to 80 °C until the sodium was dissolved, and the solution was cooled to 25 °C. To this solution was added copper(II) oxide (1.2 g, 15 mmol), sodium iodide (0.025 g, 0.17 mmol), and 2-bromothiophene (5 g, 30.7 mmol). This mixture was heated to 120 °C for 40 h. The mixture was cooled, poured into 100 mL to H_2O, and extracted with Et_2O. The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to provide the title compound (0.43 g, 7%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.60 (m, 4H), 2.89 (t, J = 7 Hz, 2H), 4.18 (t, J = 7 Hz, 2H), 6.23 (dd, J = 3 Hz, 2 Hz, 1H), 6.55 (dd, J = 7 Hz, 2 Hz, 1H), 6.70 (dd, J = 7 Hz, 3 Hz, 1H); HRMS m/z 197.0873 (calcd for $C_{10}H_{15}NOS$, 197.0874).

Step 2: Preparation of 1-[2-[[5-(Phenylmethyl)-2-thienyl]oxy]ethyl]pyrrolidine Hydrochloride. To a solution of the product of step 1 (0.42 g, 2.12 mmol) in 4 mL of THF at 0 °C was added 1.6 M *n*-BuLi in THF (1.5 mL, 2.4 mmol). The mixture was slowly warmed to 25 °C, stirred for 15 min, and cooled to 0 °C, and 0.26 mL (2.2 mmol) of benzyl bromide was added. After being stirred for 30 min, the mixture was poured into water and extracted with of EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by reverse phase HPLC eluting with a MeOH/1% aqueous NH_4OH gradient, followed by treatment with ethereal HCl, provided **2x** (0.06 g, 9%): ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.58 (m, 4H), 2.84 (t, J = 7 Hz, 2H), 3.98 (s, 2H), 4.10 (t, J = 7 Hz, 2H), 6.02 (d, J = 3 Hz, 1H), 6.39 (d, J = 3 Hz, 1H), 7.15−7.35 (m, 5H); HRMS m/z 287.1346 (calcd for $C_{17}H_{21}NOS$, 287.1344).

5-(Phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]thiazole (2y). Step 1: Preparation of 2-[2-(1-Pyrrolidinyl)-ethoxy]thiazole. 1-(2-Hydroxyethyl)pyrrolidine (10 mL, 85.5 mmol) was treated with 0.5 g of NaH (50% dispersion in oil, 10.4 mmol) in small portions over 15 min and stirred an additional 30 min. 2-Bromothiazole (1.6 g, 9.6 mmol) was added and the mixture stirred at 25 °C for 18 h. The reaction mixture was poured into water and extracted with EtOAc and the extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel using a gradient of 1:1 Et_2O/hexane to 100% ether (saturated with NH_4OH) provided 1.4 g (74%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.60 (m, 4H), 2.90 (t, J = 7 Hz, 2H), 4.53 (t, J = 7 Hz, 2H), 6.68 (d, J = 4 Hz, 1H), 7.11 (d, J = 4 Hz, 1H); HRMS m/z 199.0924 (calcd for $C_9H_{15}N_2OS$, 199.0905).

Step 2: Preparation of α-Phenyl-2-[2-(1-pyrrolidinyl)-ethoxy]-5-thiazolemethanol. To a solution of the product of step 1 (0.1 g, 0.5 mmol) in 5 mL of THF at −40 °C was added 1.6 M *n*-BuLi in THF (0.38 mL, 0.6 mmol) dropwise. The mixture was stirred at 0 °C for 1 h, and benzaldehyde (0.1 mL, 1.0 mmol) was added. After being stirred at 0 °C for 15 min, the mixture was poured into water and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.10 g (66%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.58 (m, 4H), 2.88 (t, J = 7 Hz, 2H), 4.47 (t, J = 7 Hz, 2H), 5.91 (s, 1H), 6.88 (s, 1H), 7.28−7.45 (m, 5H); HRMS m/z 305.1326 (calcd for $C_{18}H_{21}N_2O_2S$, 305.1324).

Step 3: Preparation of 5-(Phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]thiazole. The product of step 2 was reduced using procedure E to provide **2y** (74%): ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.59 (m, 4H), 2.88 (t, J = 7 Hz, 2H), 3.97 (s, 2H), 4.48 (t, J = 7 Hz, 2H), 6.83 (s, 1H), 7.19−7.35 (m, 5H); HRMS m/z 289.1373 (calcd for $C_{16}H_{21}N_2OS$, 289.1375).

5-(Phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]oxazole (2z). Step 1: Preparation of 5-(Phenylmethyl)-2-(3H)-oxazolone. To a solution of potassium cyanate (0.32 g, 4.0 mmol) and Et_3N (0.46 g, 4.5 mmol) in 2 mL of DMF at 100 °C was added a solution of benzyl chloromethyl ketone (0.5 g, 2.96 mmol) in 1 mL of DMF, and the mixtures was stirred at 100 °C for 3 h. The reaction mixture was cooled, poured into 10% aqueous HCl, and extracted with EtOAc. The extracts were washed successively with 10% aqueous HCl, water, and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel using a gradient of 1:4 to 1:1 EtOAc/hexane provided the title compound (0.55 g, 100%): ^{1}H NMR (CD_3OD) δ 3.72 (s, 2H), 6.40 (s, 1H), 7.18−7.35 (m, 5H); HRMS m/z 175.0632 (calcd for $C_{10}H_9NO_2$, 175.0633).

Step 2: Preparation of 5-(Phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]oxazole. The title compound was prepared from the product of step 1 and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **2z** (43%): ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.51 (m, 4H), 2.68 (t, J = 7 Hz, 2H), 3.60 (t, J = 7 Hz, 2H), 3.70 (s, 2H), 6.18 (t, J = 1 Hz, 1H), 7.20−7.46 (m, 5H); HRMS m/z 272.1512 (calcd for $C_{16}H_{20}N_2O_2$, 272.1525).

2-[4-(Phenylmethyl)phenoxy]ethanamine Hydrochloride (3a). Step 1: Preparation of *tert*-Butyl [4-(Phenylmethyl)phenoxy]acetate. To a stirred suspension of 3.2 g of NaH (50% dispersion in oil, 67 mmol) in 100 mL of DMF was added 4-hydroxydiphenylmethane (10 g, 54 mmol). The mixture was stirred at 25 °C for 30 min and cooled to 0 °C, and catalytic *n*-Bu_4NI and *tert*-butyl bromoacetate (9.6 mL, 65 mmol) were added. After 30 min, the mixture was poured into 2 N HCl and ice and the mixture extracted with Et_2O. The extracts were washed with saturated $KHSO_4$ and saturated K_2CO_3, dried over Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel using 1:9 Et_2O/hexane provided the title compound (15.0 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 3.92 (s, 2H), 4.48 (s, 2H), 6.82 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2H), 7.17 (m, 3H), 7.26 (m, 2H).

Step 2: Preparation of 2-[4-(Phenylmethyl)phenoxy]-ethyl 4-Methylbenzenesulfonate. To a stirred suspension of lithium aluminum hydride (LAH, 500 mg, 13.2 mmol) in THF was added the product of step 1 (2.8 g, 10 mmol), and the mixture was stirred at 25 °C for 4 h. The reaction was quenched with 2 mL of H_2O and stirred for 1 h. The mixture was filtered, the solid was washed with THF, and the filtrate was concentrated to provide 2.05 g (90%) of a white solid, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 2H), 3.93 (t, 2H), 4.04 (t, J = 5 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). To a solution of this alcohol (2.3 g, 10 mmol) in 20 mL of CH_2Cl_2 and 10 mL of pyridine at 0 °C was added *p*-toluenesulfonyl chloride (1.9 g, 10 mmol), and the mixture was stirred at 0 °C for 30 min and at 25 °C for 16 h. The mixture was concentrated, dissolved in 25 mL of EtOAc, washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Recrystallization from Et_2O, gave 3.5 g (92%) of a white solid: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.90 (s, 2H), 4.10 (t, J = 4 Hz, 2H), 4.33 (t, J = 4 Hz, 2H), 6.71 (d, J = 8 Hz, 2H), 7.05 (d, J = 8 Hz, 2 H), 7.25 (m, 7H), 7.79 (d, J = 8 Hz, 2H). Anal. ($C_{22}H_{22}O_4S$) C, H.

Step 3: Preparation of 2-[4-(Phenylmethyl)phenoxy]-ethanamine Hydrochloride. A mixture of the product of step 2 (12.0 g, 31.4 mmol) and NaN_3 (2.78 g, 42.8 mmol) in 100 mL of DMF was heated at 60 °C for 5 h. The mixture was cooled and partitioned between Et_2O and water. The aqueous layer was extracted with EtOAc, and the extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 8.5 g of a yellow oil, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 3.47 (t, 2H), 3.89 (s, 2H), 4.03 (t, 2H), 7.05 (m, 9H). To a stirred suspension of $SnCl_2$ (10.0 g, 52.7 mmol) in 40 mL of MeOH was added a solution of the crude azide in 20 mL of MeOH dropwise over 15 min, and the mixture was stirred at 25 °C for 1 h. The mixture was concentrated and the residue partitioned between 10% NaOH and Et_2O and filtered through Celite. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The HCl salt was formed by treatment with HCl/dioxane to provide, after recrystallization from MeOH, **3a** (5.7 g, 69%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.48 (br, 2H), 3.04 (t, 2H), 3.92 (t, 2H), 3.90 (s, 2H), 7.05 (m, 9H). Anal. ($C_{15}H_{17}NO$·HCl) C, H, N, Cl.

***N,N*-Dimethyl-2-[4-(phenylmethyl)phenoxy]ethanamine Hydrochloride (3b).** The title compound was prepared from 4-benzylphenol and *N,N*-dimethylaminoethyl chloride·HCl using procedure B to provide **3b** (37%) as a white solid: ^{1}H NMR (CD_3OD) δ 3.05 (s, 6H), 3.55 (t, J = 5 Hz, 2H), 3.90 (s, 2H), 4.30 (t, J = 5 Hz, 2H), 6.92 (d, J = 8 Hz, 2H), 7.15 (m, 5H), 7.25 (m, 2H). Anal. ($C_{17}H_{21}NO$·HCl·0.2H_2O) C, H, N.

***N,N*-Diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine Hydrochloride (3c).** The title compound was prepared from 4-benzylphenol and *N,N*-diethylaminoethyl chloride·HCl using procedure B to provide **3c** (37%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.35 (t, J = 5 Hz, 6H), 3.30 (q, J = 5 Hz, 4H), 3.57 (t, J = 3 Hz, 2H), 3.90 (s, 2H) 4.30 (t, J = 3 Hz, 2H), 6.90 (d, J = 8 Hz, 2H), 7.15 (m, 5H), 7.25 (m, 2H). Anal. ($C_{19}H_{25}NO$·HCl) C, H, N.

***N,N*-Bis(1-methylethyl)-2-[4-(phenylmethyl)phenoxy]-ethanamine Hydrochloride (3d).** The title compound was prepared from 4-benzylphenol and *N,N*-diisopropylaminoethyl chloride·HCl using procedure B to provide **3d** (49%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.43 (t, J = 4 Hz, 12H), 3.60 (t, J = 3 Hz, 2H), 3.80 (m, 2H), 3.90 (s, 2H), 4.28 (t, J = 3 Hz, 2H), 6.90 (d, J = 8 Hz, 2H), 7.15 (m, 5H), 7.25 (m, 2H). Anal. ($C_{21}H_{29}NO$·HCl·0.3H_2O) C, H, N.

1-[2-[4-(Phenylmethyl)phenoxy]ethyl]piperidine Hydrochloride (3e). The title compound was prepared from 4-benzylphenol and 1-(2-chloroethyl)piperidine·HCl using procedure B to provide **3e** (52%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 2H), 1.60 (m, 4H), 2.51 (m, 4H), 2.75 (t, J = 8 Hz, 2H), 3.90 (s, 2H), 4.07 (t, J = 8 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 2H), 7.15 (m, 3H), 7.26 (t, J = 9 Hz, 2H). Anal. ($C_{20}H_{25}NO$·HCl) C, H, N.

Hexahydro-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1*H*-azepine Hydrochloride (3f). Step 1: Preparation of 2-[4-(Phenylmethyl)phenoxy]propanoic Acid. To a solution of *tert*-butyl [4-(phenylmethyl)phenoxy]acetate (**3a**, step 1) (9.60 g, 34.5 mmol) in 50 mL of CH_2Cl_2 and 5 mL of MeOH at 0 °C was added 50 mL of trifluoroacetic acid, and the mixture was stirred at 0 °C for 20 min and 25 °C overnight. The reaction mixture was concentrated and recrystallized from Et_2O/hexane to give the title compound (6.12 g, 73%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 2H), 4.64 (s, 2H), 6.84 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). Anal. ($C_{15}H_{14}O_3$·0.1H_2O) C, H.

Step 2: Preparation of Hexahydro-1-[[4-(phenylmethyl)phenoxy]acetyl]-1*H*-azepine. To a solution of the product of step 1 (800 mg, 3.31 mmol) in 10 mL of DMF and 2 mL of pyridine were added *N,N′*-disuccinimidyl carbonate (DSC, 842 mg, 3.29 mmol) and catalytic 4-(dimethylamino)pyridine, and the mixture was stirred at 25 °C for 50 min. Hexamethyleneimine (330 mg, 3.33 mmol) was added and the mixture stirred at 25 °C overnight. The mixture was concentrated and partitioned between EtOAc and saturated $KHSO_4$. The organic extracts were dried over Na_2SO_4 and concentrated to provide, after purification by flash chromatography on silica gel using 7:3 Et_2O/hexane, the title compound (800 mg, 75%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 4H), 1.74 (m, 4H), 3.50 (dd, J = 11, 6 Hz, 2H), 3.54 (dd, J = 11, 6 Hz, 2H), 3.93 (s, 2H), 4.67 (s, 2H), 6.88 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.18 (m, 3H), 7.28 (m, 2H). Anal. ($C_{21}H_{25}NO_2$·0.1H_2O) C, H, N.

Step 3: Preparation of Hexahydro-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1*H*-azepine Hydrochloride. To a stirred suspension of LAH (400 mg, 10.5 mmol) in 10 mL of THF at 25 °C was added the product from step 2 (700 mg, 2.16 mmol). The mixture was stirred at 25 °C for 3 h, quenched with 1 mL of water, and diluted with EtOAc. The mixture was filtered and the filtrate concentrated to afford a colorless oil. Conversion to the HCl salt and recrystallization from EtOH/Et_2O provided **3f** (545 mg, 73%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.76 (m, 4H), 1.94 (m, 4H), 3.45 (m, 4H), 3.61 (t, J = 7 Hz, 2H), 3.92 (s, 2H), 4.34 (t, J = 7 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 7.15 (m, 5H), 7.23 (m, 2H). Anal. ($C_{21}H_{27}NO$·HCl·0.2H_2O) C, H, N.

4-[2-[4-(Phenylmethyl)phenoxy]ethyl]morpholine Hydrochloride (3g). The title compound was prepared from 2-[4-(phenylmethyl)phenoxy]ethyl 4-methylbenzenesulfonate (**3a**, step 2) and morpholine, using the procedure described in step 1 for the preparation of **3h**, to provide **3g** (23%): ^{1}H NMR (CD_3OD) δ 3.31 (br, 2H), 3.53 (br, 2H), 3.61 (t, J = 5 Hz, 2H), 3.84 (br, 2H), 3.90 (s, 2H), 4.03 (br, 2H), 4.36 (t, J = 5 Hz, 2H),

6.93 (d, J = 8 Hz, 2H), 7.15 (m, 5H), 7.23 (m, 2H). Anal. ($C_{19}H_{23}NO_2$·HCl·0.3H_2O) C, H, N.

1-[2-[4-(Phenylmethyl)phenoxy]ethyl]piperazine (3h). Step 1: Preparation of 1-Acetyl-4-[2-[4-(phenylmethyl)-phenoxy]ethyl]piperazine. A mixture of 2-[4-(phenylmethyl)phenoxy]ethyl 4-methylbenzenesulfonate (**3a**, step 2) (1.0 g, 2.6 mmol), *N*-acetypiperazine (0.4 g, 3.1 mmol), and K_2CO_3 (1.0 g, 7.2 mmol) in 5 mL of DMF was heated to 80 °C for 16 h. The mixture was concentrated and the residue dissolved in EtOAc. The solution was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel using 85:14:1 $CHCl_3$/EtOH/NH_4-OH to give the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.53 (t, J = 5 Hz, 2H), 2.58 (t, J = 5 Hz, 2H), 2.81 (t, J = 6 Hz, 2H), 3.47 (t, J = 5 Hz, 2H), 3.63 (t, J = 5 Hz, 2H), 3.92 (s, 2H), 4.08 (t, J = 6 Hz, 2H), 6.83 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.14−7.22 (m, 3H), 7.28, (t, J = 8 Hz, 2H). Anal. ($C_{21}H_{26}N_2O_2$·1.1HCl·0.1H_2O) C, H, N, Cl

Step 2: Preparation of 1-[2-[4-(Phenylmethyl)phenoxy]ethyl]piperazine. The product of step 1 and excess 3 N HCl were heated on a steam bath for 16 h, and the mixture was concentrated to provide **3h** as a white solid: ^{1}H NMR (DMSO-d_6) δ 3.50 (m, 10H), 3.88 (s, 2H), 4.36 (br, 2H), 6.92 (d, J = 8 Hz, 2H), 7.13−7.23 (m, 5H), 7.27 (t, J = 8 Hz, 2H), 9.70 (br, 2H), 12.05 (br, 1H). Anal. ($C_{19}H_{24}N_2O$·2HCl) C, H, N, Cl.

1-Methyl-4-[2-[4-(phenylmethyl)phenoxy]ethyl]piperazine Dihydrochloride (3i). The title compound was prepared from 1-methylpiperazine and 2-[4-(phenylmethyl)-phenoxy]ethyl 4-methylbenzenesulfonate (**3a**, step 2), as described in step 1 for the preparation of **3h**, to give, after conversion to the HCl salt with ethanolic HCl and recrystallization from EtOH/Et_2O, **3i** (26.5%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 4H), 2.80 (s, 3H), 3.19 (m, 2H), 3.40 (m, 4H), 3.92 (s, 2H), 4.30 (m, 2H), 6.81 (d, J = 8 Hz, 2H), 7.10 (m, 2H), 7.18 (m, 3H), 7.30 (m, 2H). Anal. ($C_{20}H_{26}N_2O$·2HCl) C, H, N.

2,6-Dimethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidine Hydrochloride (3j). Step 1: Preparation of 2,6-Dimethyl-1-[[4-(phenylmethyl)phenoxy]acetyl]piperidine. The title compound was prepared from 4-benzylphenol and 1-(2-chloroacetyl)-2,6-dimethylpiperidine using procedure B to provide a white solid (47%): Anal. ($C_{22}H_{27}NO_2$·0.1H_2O): C, H, N.

Step 2: Preparation of 2,6-Dimethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidine Hydrochloride. The title compound was prepared from the product from step 1 using the procedure described in step 3 for the preparation of **3f**, to yield the free base (0.33 g, 52%) as a colorless gum. Treatment with ethanolic HCl furnished the HCl salt **3j**: ^{1}H NMR (CD_3OD) δ 1.36 (d, J = 5 Hz, 3H), 1.46 (d, J = 5 Hz, 3H), 2.20 (m, 6H), 3.50 (m, 2H) 3.75 (m, 1H) 3.90 (s, 2H) 4.18 (m, 1H) 4.32 (m, 2H), 6.90 (d, J = 8 Hz, 2H), 6.87 (m, 5H), 7.25 (m, 2H). Anal. ($C_{22}H_{29}NO$·HCl) C, H, N.

2-[2-[4-(Phenylmethyl)phenoxy]ethyl]-2-azabicyclo-[2.2.2]oct-5-ene (3k). 1,3-Cyclohexadiene (801 mg, 10 mmol), 37% aqueous formaldehyde (819 mg, 10 mmol), **3a** (2.0 g, 8.8 mmol), and 8.8 mL of 1 N HCl were placed in a Parr bottle and heated at 55 °C for 48 h. The mixture was cooled and concentrated and the residue partitioned between EtOAc and 10% aqueous Na_2CO_3. The aqueous layer was extracted with EtOAc, and the extracts were washed with brine, dried over K_2CO_3, and concentrated. Purification on a silica gel prep plate, eluting with 97.5:2:0.5 CH_2Cl_2/CH_3OH/NH_4OH, afforded **3k** (375 mg, 13%) as a light brown oil: ^{1}H NMR ($CDC1_3$) δ 1.27 (m, 2H), 1.54 (m, 1H), 1.98 (m, 1H), 2.10 (m, 1H), 2.49 (m, 1H), 2.60 (p, J = 5 Hz, 1H), 2.92 (p, J = 5 Hz, 1H), 3.05 (m, 1H), 3.42 (m, 1H), 3.90 (s, 2H), 3.98 (m, 2H), 6.35 (m, 2H), 6.75−7.30 (m, 9H). Anal. ($C_{22}H_{25}NO$·0.2H_2O) C, H, N.

2-[2-[4-(Phenylmethyl)phenoxy]ethyl]-2,5-diazabicyclo-[2.2.1]heptane Dihydrochloride (3l). Step 1: Preparation of 2-(Phenylmethyl)-5-[2-[4-(phenylmethyl)phenoxy]ethyl]-2,5-diazabicyclo[2.2.1]heptane. The title compound was prepared from 2-[4-(phenylmethyl)phenoxy]ethyl 4-methylbenzenesulfonate (**3a**, step 2) and 2-benzyl-2,5-diazabicyclo-[2.2.1]heptane dihydroiodide[22] using the procedure described in step 1 for the preparation of **3h** to provide a viscous yellow oil (79%): ^{1}H NMR ($CDCl_3$) δ 1.71 (q, J = 8 Hz, 2H), 2.84 (m, 6H), 3.27 (s, 1H), 3.40 (s, 1H), 3.71 (q, J = 14 Hz, 2H), 3.90 (s, 2H), 4.02 (t, J = 5 Hz, 2H), 7.10 (m, 14H).

Step 2: Preparation of 2-[2-[4-(Phenylmethyl)phenoxy]ethyl]-2,5-diazabicyclo[2.2.1]heptane Dihydrochloride. The product from step 1 (1.0 g, 2.5 mmol) in 20 mL of EtOH was hydrogenated in the presence of 20% $Pd(OH)_2$/C under 60 psi H_2 at 25 °C for 24 h. The mixture was filtered and concentrated, followed by purification on a silica gel prep plate, eluting with 79:20:1 $CHCl_3$/EtOH/NH_4OH. Conversion to the dihydrochloride salt with dioxane/HCl and recrystallization from EtOH/Et_2O afforded **3l** (250 mg, 26%) as a white solid: ^{1}H NMR (DMSO-d_6): δ 1.45 (d, J = 9 Hz, 1H), 1.65 (d, J = 9 Hz, 1H), 1.75 (s, 1H), 2.45 (d, J = 10 Hz, 1H), 2.77 (m, 4H), 3.00 (d, J = 10 Hz, 1H), 3.75 (s, 1H), 3.85 (t, J = 5 Hz, 2H), 7.05 (m, 9H). Anal. ($C_{20}H_{26}Cl_2N_2O$·0.5H_2O) C, H, N.

1-[2-(4-Phenoxyphenoxy)ethyl]pyrrolidine (4a). The title compound was prepared from 4-phenoxyphenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to give **4a** (76.5%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 4H), 2.63 (m, 4H), 2.91 (t, J = 6 Hz, 2H), 4.10 (t, J = 6 Hz, 2H), 6.97 (m, 7H), 7.08 (d, 2H), 7.29 (dd, J = 9 Hz, 2H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

1-[2-[4-([1,1′-Biphenyl]-4-yloxy)phenoxy]ethyl]pyrrolidine (4b). Step 1: Preparation of 4-(4-Methoxyphenoxy)-1,1′-biphenyl. A mixture of 4-phenylphenol (1.78 g, 10.3 mmol) and KOH (0.98 g, 16.2 mmol) was heated to 190 °C for 1.5 h. 4-Iodoanisole (2.03 g, 8.5 mmol) was added followed by catalytic copper powder (53 mg). The mixture was heated to 205 °C under argon for 2 h. The reaction was cooled to 25 °C, 10% NaOH was added, and the mixture was extracted with Et_2O. The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid. The crude product was washed with MeOH to provide the title compound (0.59 g, 25%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.89 (m, 2H), 7.02 (m, 4H), 7.44 (m, 7H).

Step 2: Preparation of 4-([1,1′-Biphenyl]-4-yloxy)-phenol. The product of step 1 (0.39 g, 1.4 mmol) was stirred in CH_2Cl_2 (4 mL) at −78 °C, and 1 N BBr_3 in CH_2Cl_2 (1.6 mL) was added. After being stirred at 0 °C for 30 min and 25 °C for 2 h, the mixture was poured into H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the title compound as an off-white solid (0.36 g, 98%): ^{1}H NMR ($CDCl_3$) δ 6.84 (m, 2H), 7.00 (m, 4H), 7.45 (m, 7H). Anal. ($C_{18}H_{14}O_2$·0.2H_2O) C, H.

Step 3: Preparation of 1-[2-[4-([1,1′-Biphenyl]-4-yloxy)-phenoxy]ethyl]pyrrolidine. The title compound was prepared from the product of step 2 and 1-(2-chloroethyl)-pyrrolidine·HCl using procedure A to give **4b** (39%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.64 (m, 4H), 2.91 (t, J = 6 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 6.97 (m, 4H), 7.44 (m, 7H). Anal. ($C_{25}H_{27}NO_2$·0.2H_2O) C, H, N.

4,5-Dihydro-2-[4-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]phenyl]oxazole (4c). The title compound was prepared from 4-cyanophenol using the procedures described in steps 1, 2, and 3 for the preparation of **4b**, followed by step 1 for the preparation of **4d**, to give **4c**: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.65 (m, 4H), 2.92 (t, J = 6 Hz, 2H), 4.00−4.15 (m, 4H), 4.41 (t, J = 8 Hz, 2H), 6.91 (m, 4H), 7.00 (d, J = 10 Hz, 2H), 7.88 (d, J = 10 Hz, 2H).

2-[4-[4-[2-(1-Pyrrolidinyl)ethoxy]phenoxy]phenyl]-oxazole (4d). Step 1: Preparation of 4,5-Dihydro-2-[4-(4-methoxyphenoxy)phenyl]oxazole. $ZnCl_2$ (0.78 g, 5.3 mmol) was fused under argon, and a mixture of 4-(4-methoxyphenoxy)benzonitrile (**4c**, step 1) (0.54 g, 2.2 mmol) in 8 mL of ethanolamine was added. After being stirred at 130−140 °C for 4 h, the reaction mixture was cooled, diluted with CH_2Cl_2, and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by

flash chromatography on silica gel using 20:1 CH_2Cl_2/MeOH provided the title compound (0.29 g, 49%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 4.05 (t, J = 8 Hz, 2H), 4.41 (t, J = 8 Hz, 2H), 6.91 (m, 4H), 7.01 (d, J = 10 Hz, 2H), 7.89 (d, J = 10 Hz, 2H).

Step 2: Preparation of 2-[4-(4-Methoxyphenoxy)phenyl]oxazole. A mixture of product of step 1 (149 mg, 0.59 mmol) and NiO_2 (838 mg, 8.9 mmol) in benzene (10 mL) was heated to reflux overnight. The reaction mixture was cooled and filtered through Celite, and the filtrate was concentrated to give the title compound (100 mg, 63%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.97 (m, 6H), 7.20 (s, 1H), 7.69 (s, 1H), 7.97 (d, J = 10 Hz, 2H).

Steps 3 and 4: Preparation of 2-[4-[4-[2-(1-Pyrrolidinyl)ethoxy]phenoxy]phenyl]oxazole. The title compound was prepared using the procedures described in steps 2 and 3 for the preparation of **4b**, to provide **4d**: ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.65 (m, 4H), 2.92 (t, J = 6 Hz, 2H), 4.12 (t, J = 6 Hz, 2H), 6.98 (m, 6H), 7.20 (s, 1H), 7.68 (s, 1H), 7.98 (d, J = 10 Hz, 2H). Anal. ($C_{21}H_{22}N_2O_3 \cdot 0.2H_2O$) C, H, N.

1-[2-[4-[(Difluoro)phenylmethyl]phenoxy]ethyl]-pyrrolidine (5). Benzophenone **6** (0.5 g, 1.69 mmol), 1,2-ethanedithiol (0.28 mL, 3.38 mmol) and $BF_3 \cdot 2AcOH$ (0.47 mL, 3.38 mmol), were stirred at 25 °C for 21 h. The mixture was poured into EtOAc and aqueous $NaHCO_3$, and the organic layer was washed with 15% NaOH and brine, dried over Na_2SO_4, and concentrated to give the crude thioketal. A solution of 1,3-dibromo-5,5-dimethylhydantoin (0.48 g, 1.69 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C, and hydrogen fluoride-pyridine (0.8 mL, 3.5 mmol) was added, followed by a solution of the thioketal in 3 mL of CH_2Cl_2. After being stirred at −78 °C for 1 h, the mixture was poured into CH_2Cl_2 and aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product. Flash chromatography on silica gel using a gradient of 2:1 hexane/EtOAc to 100% EtOAc provided **5** (0.11 g, 20%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.82 (4H, m), 2.65 (4H, m), 2.82 (2H, t), 4.15 (2H, t), 6.94 (2H, d), 7.44 (7H, m); HRMS m/z 317.1583 (calcd for $C_{19}H_{21}F_2NO$, 317.1591).

[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]phenylmethanone (6). The title compound was prepared from 4-hydroxybenzophenone and 1-(2-chloroethyl)-pyrrolidine·HCl using procedure A to provide **6** (73%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.64 (m, 4H), 2.96 (t, J = 6 Hz, 2H), 4.19 (t, J = 6 Hz, 2H), 6.98 (d, J = 9 Hz, 2H), 7.46 (m, 2H), 7.57 (m, 1H), 7.79 (m, 4H). Anal. ($C_{19}H_{21}NO_2$) C, H, N.

α-Phenyl-4-[2-(1-pyrrolidinyl)ethoxy]benzenemethanol (7). Compound **6** was reduced using procedure C to provide **7** as a white solid: mp 103−104 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.53 (m, 4H), 2.79 (t, J = 6 Hz, 2H), 3.98 (t, J = 6 Hz, 2H), 4.21 (br, 1H), 5.70 (s, 1H), 6.79 (d, J = 9 Hz, 2H), 7.17−7.41 (m, 7H). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

1-[2-[4-(2-Phenylethyl)phenoxy]ethyl]pyrrolidine (8). Compound **17** (0.103 g, 0.35 mmol) was hydrogenated in MeOH (20 mL) with catalytic 4% Pd/C under 5 psi H_2 at 25 °C for 4 h. The solution was concentrated and filtered through silica gel using EtOAc to give **8** (0.093 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 4H), 2.62 (m, 4H), 2.87 (m, 6H), 4.09 (t, J = 6 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.19 (m, 3H), 7.28 (m, 2H); HRMS m/z 295.1928 (calcd for $C_{20}H_{25}NO$, 295.1936).

1-[2-[4-(Phenylmethoxy)phenoxy]ethyl]pyrrolidine (9). The title compound was prepared from 4-(benzyloxy)phenol and 1-(2-chloroethyl)-pyrrolidine·HCl using procedure A to provide **9** (64%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5H), 6.92 (m, 4H), 5.03 (s, 2H), 4.13 (t, J = 5 Hz, 2H), 2.93 (t, J = 5 Hz, 2H), 2.69 (br, 4H), 1.86 (br, 4H). Anal. ($C_{19}H_{23}NO_2 \cdot 0.1\ H_2O$) C, H, N.

1-[2-[4-[(Phenylmethyl)thio]phenoxy]ethyl]pyrrolidine Hydrochloride (10). Step 1: Preparation of 4-[(Phenylmethyl)thio]phenol. The title compound was prepared from 4-hydroxythiophenol and benzylbromide using procedure A to afford a pale orange solid (24%): Anal. ($C_{13}H_{13}OS$) C, H.

Step 2: Preparation of 1-[2-[4-[(Phenylmethyl)thio]-phenoxy]ethyl]pyrrolidine Hydrochloride. The title compound was prepared from the product of step 1 and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide the free base (50%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.80 (br, 4H), 2.63 (br, 4H), 2.98 (t, J = 5 Hz, 2H), 3.98 (s, 2H), 4.08 (t, J = 5 Hz, 2H), 6.80 (d, J = 10 Hz, 2H), 7.22 (m, 7H). Anal. ($C_{19}H_{23}NOS \cdot 0.2H_2O$) C, H, N. Treatment of a CH_2Cl_2 solution of the amine with HCl (g) provided the hydrochloride salt **10** as a white solid. Anal. ($C_{19}H_{23}NOS \cdot HCl \cdot 0.4H_2O$) C, H, N.

1-[2-[4-[(Phenylmethyl)sulfinyl]phenoxy]ethyl]-pyrrolidine (11). To a solution of **10** (57 mg, 0.16 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added 80−85% mCPBA (36 mg, 0.17 mmol), and the reaction mixture was stirred for 1 h. The mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated to afford **11** (19 mg, 36%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.85 (br, 4H), 2.68 (br, 4H), 2.95 (t, J = 5 Hz, 2H), 4.10 (m, 4H), 6.95 (m, 4H), 7.27 (m, 5H). Anal. ($C_{19}H_{23}NO_2S \cdot 0.3H_2O$) C, H, N.

1-[2-[4-[(Phenylmethyl)sulfonyl]phenoxy]ethyl]-pyrrolidine (12). To a solution of **10** (126 mg, 0.36 mmol) in 10 mL of CH_2Cl_2 was added 80−85% mCPBA (158 mg, 0.73 mmol), and the reaction was stirred at 25 °C overnight. The mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated to afford **12** (10 mg, 7%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.85 (br, 4H), 2.66 (br, 4H), 2.95 (t, J = 5 Hz, 2H), 4.14 (t, J = 5 Hz, 2H), 5.46 (s, 2H), 7.07 (m, 9H); HRMS m/z 345.1403 (calcd for $C_{19}H_{29}NO_3S$, 345.1399).

1-[2-[4-[(Phenylthio)methyl]phenoxy]ethyl]-pyrrolidine (13). Step 1: Preparation of 4-[2-(1-Pyrrolidinyl)ethoxy]benzenemethanol. To a solution of 4-[2-(1-pyrrolidinyl)ethoxy]benzaldehyde (**2i**, step 1) (669 mg, 3.05 mmol) in 10 mL of EtOH was added 133 mg (3.52 mmol) of $NaBH_4$ in 2 mL of H_2O. The mixture was stirred at 25 °C for 12 h and quenched with 10% NaOH. The mixture was extracted EtOAc, and the extracts were dried over $MgSO_4$, filtered, and concentrated to afford the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.83 (br, 4H), 2.64 (br, 4H),. 2.85 (t, J = 5 Hz, 2H), 3.08 (m, 1H), 4.03 (t, J = 5 Hz, 2H), 4.60 (s, 2H), 6.83 (d, J = 10 Hz, 2H), 7.25 (d, J = 10 Hz, 2H).

Step 2: Preparation of 1-[2-[4-[(Phenylthio)methyl]-phenoxy]ethyl]pyrrolidine. To a solution of the crude product from step 1 (330 mg, 3.0 mmol) and 488 mg (2.2 mmol) of thiophenol in 40 mL of ethylene dichloride was added ZnI_2 (1.4 g, 4.4 mmol), and the mixture was refluxed for 24 h. After cooling, the mixture was poured into 100 mL of H_2O and the aqueous layer extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. Purification by flash chromatography on silica gel using 98:1:1 CH_2Cl_2/MeOH/NH_4OH furnished **13** as a yellow waxy solid: ^{1}H NMR ($CDCl_3$) δ 1.76 (br, 4H), 2.58 (br, 4H), 2.86 (t, J = 5 Hz, 2H), 4.03 (m, 4H), 6.76 (d, J = 10 Hz, 2H), 7.17 (m, 7H). Anal. ($C_{19}H_{23}NOS \cdot 0.4H_2O$) C, H, N.

***N*-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzenemethanamine (14).** To a solution of **16** (208 mg, 0.67 mmol) in 25 mL of THF was added 436 mg (11.5 mmol) of LAH. The mixture was stirred at 25 °C for 5 h and quenched with H_2O. The mixture was extracted with EtOAc, and the extracts were washed with brine and dried over $MgSO_4$. The crude yellow oil was filtered through silica gel to afford **14** (76 mg, 38%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.83 (br, 4H), 2.64 (br, 4H), 2.88 (t, J = 5 Hz, 2H), 4.07 (t, J = 5 Hz, 2H), 4.29 (s, 2H), 6.60 (d, J = 10 Hz, 2H), 6.80 (d, J = 10 Hz, 2H), 7.30 (m, 5H). Anal. ($C_{19}H_{24}N_2O \cdot 0.3H_2O$) C, H, N.

***N*-Phenyl-4-[2-(1-pyrrolidinyl)ethoxy]benzenemethanamine (15).** To a solution of aniline (1.5 g, 16.1 mmol) in 10 mL of MeOH was added 4-[2-(1-pyrrolidinyl)ethoxy]-benzaldehyde (**2i**, step 1) (0.6 g, 2.7 mmol), followed by 2 mL of 5 N methanolic HCl and sodium cyanoborohydride (0.12 g, 1.9 mmol). The mixture was stirred at 25 °C for 48 h and quenched with 10% NaOH. The mixture was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered, and

concentrated to give an amber oil. Purification on silica gel using 97:2:1 CH_2Cl_2/MeOH/NH_4OH, conversion to the HCl salt, and recrystallization from MeOH/Et_2O gave **15** (0.434 g, 54%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.83 (br, 4H), 2.64 (br, 4H), 2.90 (t, J = 5 Hz, 2H), 3.92 (m, 1H), 4.10 (t, J = 5 Hz, 2H), 4.24 (s, 2H), 6.68 (m, 3H), 6.88 (d, J = 10 Hz, 2H), 7.22 (m, 4H); HRMS m/z 296.1902 (calcd for $C_{19}H_{24}N_2O$, 296.1889).

***N*-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzamide (16). Step 1: Preparation of *N*-(4-Hydroxyphenyl)benzamide.** A solution of 4-aminophenol (4.06 g, 37.2 mmol), benzoyl chloride (4.5 mL, 38.8 mmol), and triethylamine (7 mL, 50.2 mmol) in 40 mL of THF was stirred at 25 °C for 24 h. The mixture was poured into 100 mL of H_2O and extracted with EtOAc. The extracts were dried over $NaSO_4$, filtered, and concentrated to afford a yellow solid. Recrystallization from EtOAc/hexane gave the title compound (4.0 g, 50%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.84 (d, J = 10 Hz, 2H), 7.51 (m, 5H), 7.87 (d, J = 10 Hz, 2H). Anal. ($C_{13}H_{11}NO_2$) C, H, N.

Step 2: Preparation of *N*-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzamide. The title compound was prepared from the product of step 1 and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **16** (0.62 g, 39%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.82 (br, 5H), 2.64 (br, 4H), 2.93 (t, J = 5 Hz, 2H), 4.13 (t, J = 5 Hz, 2H), 6.94 (d, J = 10 Hz, 2H), 7.51 (m, 4H), 7.73 (br, 1H), 7.87 (d, J = 10 Hz, 2H); HRMS m/z 310.1696 (calcd for $C_{19}H_{22}N_2O_2$, 310.1682).

1-[2-[4-(2-Phenylethenyl)phenoxy]ethyl]pyrrolidine (17). The title compound was prepared from *trans*-4-hydroxystilbene and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **17** (69%) as a white solid: mp 104−104.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.63 (m, 4H), 2.92 (t, J = 6 Hz, 2H), 4.14 (t, J = 6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 13.4 Hz, 1H), 7.37 (m, 8H). Anal. ($C_{20}H_{23}NO$) C, H, N.

1-[2-[4-(*trans*-2-Phenylcyclopropyl)phenoxy]ethyl]pyrrolidine (18). To **17** (0.10 g, 0.34 mmol) in 10 mL of Et_2O at 0 °C was added catalytic $Pd(OAc)_2$ followed by excess ethereal diazomethane. The mixture was warmed to 25 °C, filtered, and concentrated. Flash chromatography using a gradient of 2:1 hexane/EtOAc to 100% EtOAc provided **18** (96 mg, 92%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz, 2H), 1.81 (m, 4H), 2.10 (m, 2H), 2.62 (m, 4H), 2.90 (t, J = 6 Hz, 2H), 4.09 (t, J = 6 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 2H), 7.15 (m, 3H), 7.28 (d, J = 9 Hz, 2H). Anal. ($C_{21}H_{25}NO·0.7H_2O$) C, H, N.

1-[2-[4-(Phenylmethyl)phenoxy]propyl]pyrrolidine Hydrochloride (19). Step 1: Preparation of *tert*-Butyl 2-[4-(Phenylmethyl)phenoxy]propanoate. To a solution of *tert*-butyl [4-(phenylmethyl)phenoxy]acetate (**3a**, step 1) (2.78 g, 9.3 mmol) in 100 mL of THF at −78 °C was added 2 M lithium diisopropylamide in heptane/THF/ethylbenzene (6 mL, 12 mmol), and the mixture was stirred at −78 °C for 40 min. Methyl iodide (1.0 mL, 16 mmol) was added, and the mixture warmed to 25 °C. The mixture was concentrated and partitioned between Et_2O and saturated $KHSO_4$. The ether extracts were dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel using 1:4 Et_2O/hexane provided the title compound (2.76 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.56 (t, J = 7 Hz, 3H), 3.91 (s, 2H), 4.58 (q, J = 7 Hz, 1H), 6.79 (d, J = 9 Hz, 2H), 7.06 (d, J = 9 Hz, 2H), 7.14 (m, 3H), 7.25 (m, 2H).

Step 2: Preparation of 1-[2-[4-(Phenylmethyl)phenoxy]propyl]pyrrolidine Hydrochloride. The title compound was prepared from the product of step 2 using the three-step procedure described for the preparation of **3f** to give **19**: ^{1}H NMR (CD_3OD) δ 1.30 (d, J = 6 Hz, 3H), 2.08 (br, 4H), 3.40 (br, 4H), 3.42 (dd, J = 11, 1 Hz, 1H), 3.51 (dd, J = 11, 9 Hz, 1H), 4.80 (m, 1H), 6.94 (d, J = 9 Hz, 2H), 7.15 (m, 5H), 7.23 (m, 2H). Anal. ($C_{20}H_{25}NO$·HCl) C, H, N.

***N*-[4-(Phenylmethyl)phenyl]-1-pyrrolidine Ethanamine Hydrochloride (20).** The title compound was prepared from 4-benzylaniline and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide the free base (48%) as a colorless oil. The HCl salt was generated with ethanolic HCl and the solid recrystallized from CH_2Cl_2/hexane to give **20** as a white crystalline CO_2 complex: mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 2H), 2.12 (m, 2H), 2.89 (m, 2H), 3.36 (m, 2H), 3.50 (s, 2H), 3.81 (m, 2H), 4.43 (m, 2H), 5.91 (s, 1H), 7.32 (m, 9H). Anal. ($C_{19}H_{24}N_2·CO_2·HCl·0.6H_2O$) C, H, N, Cl.

1-[2-[4-(Phenylmethyl)phenylthio]ethyl]pyrrolidine Hydrochloride (21). Step 1: Preparation of 4-Benzylthiophenol. 4-Benzylphenol (25 g, 0.136 mol) was dissolved in a solution of KOH (7.6 g, 0.136 mol) in 90 mL of water and the solution cooled to 0 °C. A solution of dimethylthiocarbamoyl chloride (22.3 g, 0.181 mol) in THF (40 mL) was added dropwise, and the mixture was warmed to 25 °C and made basic with 10% KOH. The mixture was extracted with Et_2O, and the extracts were washed with brine, dried over Na_2SO_4, and concentrated. The brown oil was flushed through a pad of silica gel with 1:1 Et_2O/hexane and recrystallized from MeOH/hexane to provide a yellow solid (17.5 g). This was heated neat at 290 °C for 45 min and cooled. KOH (5.6 g, 100 mmol), water (7 mL), and ethylene glycol (50 mL) were added, and the mixture was refluxed for 1 h. After cooling, the mixture was poured into cold water and extracted with CH_2Cl_2. The aqueous layer was acidified with concentrated HCl and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated to provide the title compound (7.3 g, 27%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 1H), 3.92 (s, 2H), 7.04 (d, J = 9 Hz, 2H), 7.18 (m, 5H), 7.27 (d, J = 9 Hz, 2H). Anal. ($C_{13}H_{12}S$) C, H, S.

Step 2: Preparation of 1-[2-[4-(Phenylmethyl)phenylthio]ethyl]pyrrolidine Hydrochloride. The title compound was prepared from the product of step 1 and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide, after treatment with ethanolic HCl, **21** (92%) as a white solid: mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2H), 2.18 (m, 2H), 2.77 (m, 2H), 3.18 (m, 2H), 3.41 (m, 2H), 3.78 (m, 2H), 3.96 (s, 2H), 7.10−7.41 (m, 9H). Anal. ($C_{19}H_{23}NS$·HCl) C, H, N, Cl.

1-[2-[4-(Phenylmethyl)phenylsulfinyl]ethyl]pyrrolidine Hydrochloride (22). A solution of **21** (0.5 g, 1.5 mmol) and 80−85% mCPBA (0.32 g, 1.5 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 2 h. The mixture was concentrated and purified by flash chromatography on silica gel using a gradient of 100:1:1 to 100:4:1 CH_2Cl_2/MeOH/NH_4OH. Treatment with ethanolic HCl provided **22** (0.37 g, 71%) as a white solid: mp 180−182 °C (d); ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.55 (m, 4H), 2.67 (dt, J = 12, 7 Hz, 1H), 2.99 (m, 3H), 4.03 (s, 2H), 7.19 (m, 2H), 7.31 (m, 5H), 7.58 (d, J = 9 Hz, 2H). Anal. ($C_{19}H_{23}NOS$·HCl) C, H, N, Cl.

1-[3-[4-(Phenylmethyl)phenyl]propyl]pyrrolidine Hydrochloride (23). Step 1: Preparation of Methyl (2*E*)-3-[4-(Phenylmethyl)phenyl]-2-propenoate. A solution of 4-benzylbenzoic acid (8.5 g, 40 mmol) in 10 mL of oxalyl chloride was stirred at 25 °C for 2 h. The solution was concentrated, and a solution of the crude acid chloride and catalytic 10% Pd/C in THF/2,6-lutidine was hydrogenated in a Parr shaker under 5 psi H_2 for 6 h. The mixture was filtered, washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated. A solution of the crude aldehyde (8.0 g, 40 mmol) and methyl (triphenylphosphoranylidene)acetate (13.6 g, 40 mmol) in 100 mL of THF was stirred at reflux for 10 h. The mixture was cooled and concentrated. Purification by flash chromatography on silica gel using hexane/EtOAc furnished the title compound (6.8 g, 67%): ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.99 (s, 2H), 6.38 (d, J = 14 Hz, 1H), 7.20 (m, 5H), 7.28 (m, 2H), 7.44 (d, J = 8 Hz, 2H), 7.67 (d, J = 14 Hz, 1H).

Step 2: Preparation of 1-[1-Oxo-3-[4-(phenylmethyl)phenyl]propyl]pyrrolidine. A solution of the product of step 1 (2.4 g, 9.5 mmol) and catalytic Raney nickel in MeOH was hydrogenated under 5 psi H_2 for 15 min. The mixture was filtered and concentrated to provide the saturated ester (100%): ^{1}H NMR ($CDCl_3$) δ 2.61 (t, J = 9 Hz, 2H), 2.91 (t, J = 9 Hz, 2H), 3.66 (s, 3H), 3.94 (s, 2H), 7.11 (s, 4H), 7.18 (m, 3H), 7.27 (m, 2H). A solution of pyrrolidine (0.76 mL, 9.0 mmol) in CH_2Cl_2 and 2 M $AlMe_3$ in toluene (4.5 mL, 9.0 mmol) was stirred at 25 °C for 30 min. A solution of the crude ester (2.3 g, 9.0 mmol) in CH_2Cl_2 was added, and the mixture was refluxed for 7 h. The mixture was diluted with cold 1 N HCl

and extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel using 1:1 hexane/EtOAc furnished the title compound (1.8 g, 68%): ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 4H), 2.53 (d, J = 8 Hz, 2H), 2.94 (d, J = 8 Hz, 2H), 3.25 (d, J = 8 Hz, 2H), 3.45 (d, J = 8 Hz, 2H), 3.96 (s, 2H), 7.14 (m, 7H), 7.27 (m, 2H); HRMS m/z 293.1783 (calcd for $C_{20}H_{23}NO$, 293.1779).

Step 3: Preparation of 1-[3-[4-(Phenylmethyl)phenyl]-propyl]pyrrolidine Hydrochloride. To the product of step 2 (0.25 g, 0.85 mmol) in 10 mL of Et_2O was added LAH (0.03 g, 0.8 mmol), and the mixture was heated to reflux for 7 h. The mixture was cooled and quenched with H_2O, followed by 1 N NaOH. The mixture was partitioned between EtOAc and H_2O, and the organic layer washed with brine, dried over Na_2SO_4, and concentrated. Treatment with ethanolic HCl provided **23** (0.20 g, 74%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 2H), 2.22 (m, 4H), 2.34 (t, J = 5 Hz, 4H), 2.97 (m, 2H), 3.78 (m, 2H), 3.95 (s, 2H), 7.20 (m, 9H). Anal. ($C_{20}H_{25}N\cdot HCl\cdot 0.4H_2O$) C, H, N.

1-[3-[4-(Phenylmethyl)phenyl]-2*E*-propenyl]pyrrolidine (24). Step 1: Preparation of 1-[(1*E*)-3-Chloro-1-propenyl]-4-(phenylmethyl)benzene. To a solution of methyl (2*E*)-3-[4-(phenylmethyl)phenyl]-2-propenoate (**23**, step 1) (2.5 g, 10.0 mmol) in 20 mL of toluene at −78 °C was added 24 mL of 1 M diisobutylaluminum hydride in hexanes, and the mixture was stirred at −20 °C for 2 h. The reaction was quenched with MeOH, warmed to 25 °C, filtered, and concentrated. The residue was triturated with 1:1 Et_2O/toluene and filtered, and the filtrate was concentrated to provide 2.0 g of crude alcohol. To a solution of the alcohol (806 mg, 3.6 mmol) and LiCl (162 mg, 3.8 mmol) in 5 mL of DMF at 0 °C was added methanesulfonyl chloride (412 mg, 3.6 mmol) dropwise. After the mixture was stirred at 0 °C for 1 h, ice water was added and the mixture extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil which was purified by flash chromatography on silica gel using 9:1 hexane/EtOAc to afford the title compound (368 mg, 42%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 2H), 4.24 (d, 2H), 6.27 (dt, J = 10 Hz, 1H), 6.64 (d, J = 15 Hz, 1H), 7.25 (m, 9H). Anal. ($C_{16}H_{15}Cl$) C, H.

Step 2: Preparation of 1-[3-[4-(Phenylmethyl)phenyl]-2*E*-propenyl]pyrrolidine. A solution of the product of step 1 (85 mg, 0.35 mmol), pyrrolidine (32 mg, 0.45 mmol), K_2CO_3 (245 mg, 1.8 mmol), and n-Bu_4NI (20 mg) in 10 mL of DMF was heated at 60 °C for 12 h and poured into H_2O. The mixture was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel using 98:1:1 CH_2Cl_2/MeOH/NH_4OH afforded **24** (44 mg, 45%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.80 (br, 4H), 2.54 (br, 4H), 3.95 (d, J = 8 Hz, 2H), 6.29 (dt, J = 5 Hz, 2H), 6.51 (d, J = 15 Hz, 1H), 7.24 (m, 9H). Anal. ($C_{20}H_{23}N\cdot 0.2H_2O$) C, H, N.

1-[2-[4-(Phenylmethyl)phenylmethoxy]ethyl]-pyrrolidine Hydrochloride (25). To a stirred solution of 4-benzylbenzoic acid (24.5 g, 115 mmol) in 600 mL of THF at −78 °C was added LAH (3.7 g, 98 mmol) in portions over 5 min. The mixture was warmed to 25 °C and stirred for 16 h. Additional LAH (0.9 g, 24 mmol) was added and the mixture refluxed for 1.5 h. The mixture was cooled to −10 °C, treated with water and 15% NaOH, diluted with Et_2O, filtered, and concentrated to give 22.7 g (99%) of a white solid. To a mixture of the crude benzyl alcohol (0.4 g, 2.0 mmol) and 1-(2-chloroethyl)pyrrolidine·HCl (0.2 g, 1.2 mmol) in DMF was added 0.2 g of NaH (60% dispersion in oil, 5 mmol) and the mixture stirred at 25 °C overnight. The mixture was carefully added to ice water and extracted with EtOAc. The extracts were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel using 3:2 hexane/EtOAc containing 2% Et_3N to give, after treatment with ethereal HCl, **25** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.87 (m, 2H), 1.93 (m, 2H), 3.00 (m, 2H), 3.34 (q, J = 5 Hz, 2H), 3.48 (m, 2H), 3.77 (t, J = 5 Hz, 2H), 3.93 (s, 2H), 4.48 (s, 2H), 7.25 (m, 9H), 11.06 (br, 1H). Anal. ($C_{20}H_{25}NO\cdot 1.1HCl\cdot 0.7H_2O$) C, H, N, Cl.

1-[*cis*-3-[4-(Phenylmethyl)phenyl]cyclobutanyl]-piperidine Hydrochloride (26). Step 1: Preparation of 4-Benzylstyrene. To a suspension of methyltriphenylphosphonium bromide (32 g, 90 mmol) in 300 mL of THF at 25 °C was added potassium *tert*-butoxide (9.9 g, 88 mmol) in portions over 15 min. After 45 min, 4-benzylbenzaldehyde (13.85 g, 71 mmol) in 20 mL of THF was added, and the mixture was stirred for 16 h. Aqueous NH_4Cl was added, and the organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel using 20:1 hexane/EtOAc gave the title compound (12.5 g, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 2H), 5.20 (d, J = 11 Hz, 1H), 5.70 (d, J = 18 Hz, 1H), 6.68 (dd, J = 18, 11 Hz, 1H), 7.17 (m, 5H), 7.28 (t, J = 7 Hz, 2H), 7.34 (d, J = 8 Hz, 2H).

Step 2: Preparation of 3-[4-(Phenylmethyl)phenyl]-cyclobutanone. To a stirred mixture of 4-benzylstyrene (9.1 g, 47 mmol) and zinc−copper couple (prepared from 15 g of zinc and 0.96 g of $CuSO_4$) in 400 mL of Et_2O at 40 °C was added a solution of $POCl_3$ (13.3 mL, 143 mmol) and trichloroacetyl chloride (15.5 mL, 139 mmol) in 140 mL of Et_2O over 1 h. After being stirred for 30 min at 25 °C, the mixture was decanted and the residue washed with Et_2O. The combined ether extracts were filtered through Celite, cooled to 0 °C, washed with cold water and aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give the crude dichloroketone (13.8 g). This was dissolved in 50 mL of AcOH and added dropwise to 30 g of Zn−Cu couple in 50 mL of AcOH, and the mixture was heated to 100 °C for 3 h. After cooling, the mixture was diluted with Et_2O and filtered through Celite. The filtrate was treated with 150 mL of 30% NaOH, and the organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography using 5:1 hexane/EtOAc gave the title compound (7.2 g, 65%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 3.10 (m, 2H), 3.33 (m, 2H), 3.50 (p, J = 8 Hz, 1H), 3.91 (s, 2H), 7.11 (m, 7H), 7.23 (t, J = 8 Hz, 2H).

Step 3: Preparation of 1-[*cis*-3-[4-(Phenylmethyl)-phenyl]cyclobutanyl]piperidine Hydrochloride. To a solution of the product from step 2 (0.508 g, 2.15 mmol) and pyrrolidine (0.19 mL, 2.28 mmol) in 5 mL of EtOH was added borane−pyridine complex (0.22 mL, 2.18 mmol), and the mixture was stirred at 25 °C for 16 h. The mixture was concentrated and the residue treated with 1 N HCl followed by 1 N NaOH. The mixture was extracted with EtOAc, and the extracts were concentrated. Purification by flash chromatography on silica gel using 85:14:1 $CHCl_3$/EtOH/NH_4OH, treatment with ethereal HCl, and recrystallization from EtOH/Et_2O afforded **26** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 2H), 2.00 (m, 2H), 2.34 (q, J = 10 Hz, 2H), 2.60 (q, J = 8 Hz, 2H), 2.90 (m, 2H), 3.14 (p, J = 9 Hz, 1H), 3.40 (m, 2H), 3.70 (q, J = 8 Hz, 1H), 3.91 (s, 2H), 7.22 (m, 9H), 10.95 (br, 1H). Anal. ($C_{21}H_{25}N\cdot HCl$) C, H, N, Cl.

1-[2-(4-Hexyloxyphenoxy)ethyl]pyrrolidine (27). The title compound was prepared from 4-n-hexyloxyphenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **27** (48%) as a light green solid: ^{1}H NMR ($CDCl_3$) δ 0.92 (br, 3H), 1.40 (m, 6H), 1.75 (t, J = 4 Hz, 2H), 1.86 (br, 4 H), 2.67 (br, 4H), 2.92 (t, J = 4 Hz), 3.89 (t, J = 7 Hz, 2H), 4.08 (t, J = 4 Hz, 2H), 6.80 (m, 4H). Anal. ($C_{18}H_{29}NO_2\cdot 0.2H_2O$) C, H, N.

1-[2-[4-(Cyclohexylmethyl)phenoxy]ethyl]-pyrrolidine (28). The title compound was prepared from cyclohexanecarboxaldehyde using procedure F, followed by procedure D, to provide **28**: ^{1}H NMR ($CDCl_3$) δ 0.83−1.70 (m, 11H), 1.80 (m, 4H), 2.40 (d, J = 7 Hz, 2H), 2.60 (m, 4H), 2.88 (t, J = 6 Hz, 2H), 4.08 (t, J = 6 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 7.02 (d, J = 9 Hz, 2H). Anal. ($C_{19}H_{29}NO_2\cdot 0.1H_2O$) C, H, N.

1-[2-(3-Phenylphenoxy)ethyl]pyrrolidine (29). The title compound was prepared from 2-phenylphenol and 1-(2-chloroethyl)pyrrolidine·HCl using procedure A to provide **29** (48%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4 H), 2.64 (m, 4 H), 2.93 (t, J = 5 Hz, 2H), 4.20 (t, J = 5 Hz, 2H), 7.40 (m, 9H). Anal. ($C_{18}H_{21}NO\cdot 0.1H_2O$) C, H, N.

1-[2-[(*trans*-4-Phenyl)cyclohexyloxy]ethyl]pyrrolidine (30). Step 1: Preparation of *cis*- and *trans*-4-

Phenylcyclohexanol. To a solution of 4-phenylcyclohexanone (1.7 g, 10 mmol) in EtOH (30 mL) was added a solution of $NaBH_4$ (0.3 g, 7.9 mmol) in water (3 mL), and the mixture was stirred at 25 °C for 1 h. The mixture was poured into 1 N HCl and EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 5:1 to 3:1 hexane/EtOAc gave the *cis*-product (0.184 g, 10.4%) as a white solid [^{1}H NMR ($CDCl_3$) δ 1.45 (s, 1H), 1.69 (m, 4H), 1.90 (m, 4H), 2.53 (tt, J = 11.7, 2.9 Hz, 1H), 4.14 (br, 1H), 7.26 (m, 5H)] and the *trans*-product (0.50 g, 28.4%) as a white solid [^{1}H NMR ($CDCl_3$) δ 1.49 (m, 4H), 1.86 (s, 1H), 1.96 (m, 2H), 2.12 (m, 2H), 2.51 (tt, J = 11.7, 3.3 Hz, 1H), 3.69 (tt, J = 10.4, 4.3 Hz, 1H), 7.26 (m, 5H)].

Step 2: Preparation of 1-[2-[(*trans*-4-Phenyl)cyclohexyloxy]ethyl]pyrrolidine. To a solution of the *trans*-product from step 1 (0.48 g, 2.7 mmol) in DMF (25 mL) was added 0.22 g of NaH (60% dispersion in oil, 5.5 mmol), and the mixture stirred at 25 °C for 45 min. 1-(2-Chloroethyl)-pyrrolidine·HCl (0.48 g, 2.8 mmol) and *n*-Bu_4NI (1.04 g, 2.8 mmol) were added, and the mixture was stirred at 25 °C for 24 h and at 80 °C for 15 h. The mixture was poured into Et_2O and water, and the ether layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 2:1 hexane/EtOAc to 100% EtOAc gave **30** (0.283 g, 38%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 4H), 1.77 (m, 4H), 1.91 (m, 2H), 2.16 (m, 2H), 2.48 (m, 1H), 2.55 (m, 4H), 2.69 (t, J = 6 Hz, 2H), 3.29 (m, 1H), 3.64 (t, J = 6 Hz, 2H), 7.22 (m, 5H). Anal. ($C_{18}H_{27}NO\cdot0.2H_2O$) C, H, N.

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