Benzoxazolamines and Benzothiazolamines: Potent, Enantioselective Inhibitors of Leukotriene Biosynthesis with a Novel Mechanism of Action

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Received December 10, 1993®

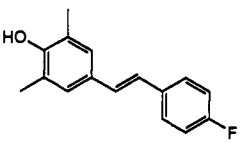
A series of benzoxazolamine and benzothiazolamine analogs that inhibit leukotriene (LT) biosynthesis are described. The initial lead, (*S*)-*N*-(benzothiazol-2-yl)phenylalanine ethyl ester (**5a**), was discovered in a screening program for inhibition of Ca-ionophore-A23187-induced LTB_4 release in human polymorphonuclear leukocytes (IC_{50} 0.23 μM). Through structural modification, it was determined that hydrophobic substituents in the 5-position and replacement of the phenyl ring of phenylalanine with a cyclohexyl group greatly enhance potency. Several ester bioisosteres that retain potency and enantiomeric selectivity are described. Lead optimization culminated in (*S*)-*N*-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-5-methyl-2-benzoxazolamine (**43b**), IC_{50} 0.001 μM. The compounds described are not inhibitors of 5-lipoxygenase but, rather, act at the level of arachidonic acid release.

Since the late 1970's, extensive research has been devoted to the discovery of compounds that block the biosynthesis or activity of leukotrienes (LTs). LTs are produced by the metabolism of arachidonic acid by 5-lipoxygenase (5-LO). Arachidonic acid is derived from membrane phospholipids upon hydrolysis by phospholipase A_2 (PLA_2). The now well-known biochemical pathway from arachidonic acid to LTs has been reviewed in the literature.[1,2] Reviews describing the status of research on inhibitors of leukotriene biosynthesis[3,4] and peptide leukotriene antagonists[5] have also appeared recently.

Leukotriene B_4 (LTB_4) is a potent chemotactic agent for leukocytes and stimulates a number of proinflammatory responses.[6] The peptide leukotrienes LTC_4, LTD_4, and LTE_4 are potent bronchoconstrictors of human lung in vitro[7] and in vivo.[8] The peptide LTs also promote mucus secretion[9] and airway hyperresponsiveness in normal[10] and asthmatic[11] subjects. These properties and the fact that LTs have been found in diseased tissues implicate LTs as major contributors in a number of diseases including asthma, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.[12,13] Several inhibitors of LT biosynthesis[3] as well as LTD_4 receptor antagonists[5] have been in clinical trials, and recent results are encouraging, especially in asthma.[14-16]

Inhibitors of LT biosynthesis can be generally divided into four classes. The majority are 5-LO inhibitors that inactivate 5-LO via their antioxidant properties, possibly by keeping the iron associated with the active site in the inactive reduced state. BI-L-239 (**1**)[17] is a representative of this class. *N*-Hydroxyurea derivatives are exemplified by zileuton (A-64077) (**2**). The design of this class was originally based on the ability of the hydroxamate functionality to bind to the active-site ferric ion.[4] Recent studies, however, indicate that representatives of this group, including **2**, can reduce 5-LO as measured by the ability to enhance a pseudoperoxidase reaction,[18] raising the possibility that antioxidant activity may also contribute to the mechanism of this class.

A series of enantioselective 5-LO inhibitors that possess neither redox nor iron-chelating properties have been described[19] and have led to development candidate ICI D2138 (**3**). Finally, MK-886 (**4**)[20] was the first compound reported to block the activation of 5-LO by an 18-kDa membrane protein termed 5-lipoxygenase-activating protein (FLAP).



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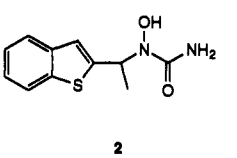

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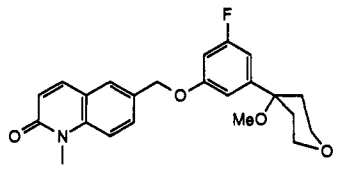

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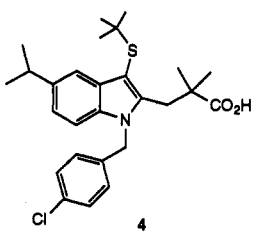

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In this paper, we describe a series of benzoxazoles and benzothiazoles that do not act by any of the mechanisms described above but, rather, inhibit LT biosynthesis by affecting the availability of arachidonic acid.

In Vitro Optimization

This series evolved from a hit in a screening program to detect inhibitors of Ca-ionophore-induced LTB_4 biosynthesis in human neutrophils. Compound **5a** was found to have an IC_{50} of 0.23 μM in this assay. For comparison, the antioxidant 5-LO inhibitor **1** has an IC_{50} of 0.34 μM in this assay. Compound **5a** did not inhibit other calcium-mediated events (oxidative burst or enzyme release) and was not structurally related to known 5-LO inhibitors.

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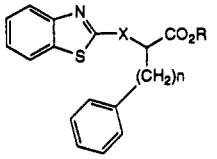
® Abstract published in *Advance ACS Abstracts*, February 15, 1994.

0022-2623/94/1837-0913$04.50/0

Table 1. Initial Modifications of Lead Compound



compd no.	R/S	X	R	n	syn meth	mp (°C)	formula[a]	IC_{50}[b] (μM) or % inh of LTB_4/conc
5a	*S*	NH	Et	1	A	oil	$C_{18}H_{18}N_2O_2S$	0.23 (0.18–0.27)
5b	*RS*	NH	Et	1	B	137–139	$C_{18}H_{18}N_2O_2S$	0.36 (0.32–0.41)
6	*RS*	NH	Et	2	B	69.5–72	$C_{19}H_{20}N_2O_2S$	0.52 (0.38–0.67)
7	*RS*	NH	Et	0	B	123–125	$C_{17}H_{18}N_2O_2S$	61%/3 μM
8	*RS*	NCH_3	Et	1	B	oil	$C_{19}H_{20}N_2O_2S$	1.0 (0.62–1.4)
9	*RS*	CH_2NH	Et	1	c	150–153	$C_{19}H_{19}ClN_2O_2S$·HCl	55%/3 μM
10	*RS*	CH_2	Et	1	c	46–48	$C_{19}H_{19}NO_2S$	56%/1 μM
11	*RS*	NH	H	1	B	250–251	$C_{16}H_{14}N_2O_2S$·HCl[d]	−19%/3 μM

[a] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N, unless otherwise noted. [b] IC_{50}s (the concentration required to inhibit the maximum response by 50%) were determined from $n \geq 3$ experiments by nonlinear regression analysis with 95% confidence bounds given in parentheses (SAS Software System, SAS Institute, Inc., Cary, NC). A Hill-type equation (the sigmoid E_{max} model) served as the model for analysis.[27,28] Percent inhibition is the average of duplicates from $n = 1$ experiment. [c] See Experimental Section. [d] C: calcd, 57.39; found 57.97.

We therefore embarked on a program to optimize for LTB_4 biosynthesis inhibition by structure modification. The racemate **5b** was prepared and found to be less potent (IC_{50} 0.36 μM), giving us our first indication of enantiomeric selectivity (Table 1). The homophenylalanine analog **6** is slightly less active (IC_{50} 0.52 μM), while the phenylglycine derivative **7** is much less potent. Substitution on or replacement of the 2-amino group led to a reduction in activity (**8–10**). Compound **11** is representative of several carboxylic acid analogs of active esters that we prepared. All of the carboxylic acid derivatives were totally inactive, indicating that the ester is the active species and a metabolically stable bioisosteric replacement was needed.

Halogen substitution on the aromatic ring of the phenylalanine ester gave modest improvements in potency (**12–14**, Table 2). An alkyl or methoxy substituent in the 6-position of the benzothiazole had a minor effect on potency (**15–17**). We found that replacement of the benzothiazole with a benzoxazole generally improved activity (for example, compare **18a** and **5a**). We therefore switched to the benzoxazole nucleus for the majority of subsequent analogs.

The two most significant breakthroughs in in vitro potency are illustrated by compounds **19–23a**. A comparison of **20** and **22** with **19** and **21** illustrates the striking enhancement in potency of an alkyl substituent in the 5-position, while in the 6-position there is relatively little effect in both a benzoxazole and a benzothiazole. Comparison of **23a** with **18a** shows that replacement of the R_2 phenyl with a cyclohexyl group also results in a dramatic increase in potency.

As mentioned above, we recognized the need to replace the ester with a metabolically stable group. Compounds **24–28** illustrate that the ester at R_3 could be replaced by a phenyl group and that potency can still be enhanced with a cyclohexyl group at R_2 and a substituent (in this case, Cl or OMe) in the 5-position at R_1. Comparison of **26a–c** shows that enantiomeric selectivity is retained. Compounds **29–33** show that various substituents in the 2-, 3-, or 4-position of the phenyl group at R_3 all reduce potency compared to the unsubstituted **26a**, probably indicating steric limitations at that position.

Several other functional groups or rings could be used to replace the ester and maintain activity, especially if in combination with a 5-substituent at R_1 or a cyclohexyl ring at R_2. This is illustrated with amides (**34** and **35**), ethers (**36–38**), a thioether (**39**), and a ketone (**40**). Compounds **36–38** clearly show that increasing the size of the ether group reduces potency, again consistent with steric limitations. The 3-methyl-5-oxadiazole group, which has been reported as an ester bioisostere for antimuscarinic compounds,[21] retained potent activity with a cyclohexyl at R_2 (**41**) and moderate activity with a 4-fluorophenyl at R_2 (**42**).

Compounds **43–45** illustrate the difference in potency of the pyridine isomers at R_3. The racemic 2-pyridyl isomer **43a** was 5 times more potent than the 3-isomer (**44**) which was more potent that the 4-isomer (**45**). We found similar potency ratios regardless of the substituents at R_1 and R_2.

The effect on potency of modifications at R_1 is illustrated by compounds **46–63**. Adding an isopropyl on the 5-position to compound **26a** results in **46** and only a slight increase in potency. We believe this reflects a limit in hydrophobicity in the molecule beyond which no substantial increase in potency can be demonstrated. Among other racemic compounds with a cyclohexyl at R_2 and a phenyl at R_3, **51** (R_1 = 5-cyano) and **47** (R_1 = ethoxycarbonyl) were the most potent followed by **53** (R_1 = 5-acetamido). The 5-sulfonamide **54**, 5-dimethylamide **49**, and 5-carboxylic acid **48** had similar potencies with IC_{50}s in the 150–170 nM range. The 5-hydroxymethyl **52** and 5-carboxamide **50** were least potent.

The potencies of additional R_1 substituents are illustrated by a second set of compounds having a 4-fluorophenyl group at R_2 and a 2-pyridyl ring at R_3 (**55–63**). A number of substituents in the 5-position (CF_3, OMe, iPr, NO_2, and Cl) resulted in compounds with IC_{50}s of 20 nM or less.

Additional modifications at R_2 are illustrated by compounds **64–73**. The 3-chlorophenyl substituent in **65** provides a more potent compound than the 4-chlorophenyl (**64**) or 4-fluorophenyl (**57**) groups. Compounds **66** and **67** show that a 4-methoxy substituent on the phenyl ring retains good activity but the 4-hydroxy substituent

drastically reduces potency. The effects of various heterocyclic substituents are illustrated with compounds **68–76**. A piperidine (**68a**), morpholine (**69**), and thiomorpholine (**70**) each provide reasonable activity, whereas the thiomorpholine sulfone **71** and *N*-methylpiperazine **72** are inactive. A 2-methyl-4-thiazolyl group is active with either a 2-pyridiyl (**73**) or an ester (**74**) at R_3. Histidine derivatives **75** and **76** are relatively inactive. Overall, these results suggest that an ionizable or hydrophilic group in the distal region of a group at R_2 has a deleterious effect on potency.

Stereoselectivity for LTB_4 biosynthesis inhibition is illustrated by several pairs of enantiomers in Table 2. Examples are given for compounds with a variety of substituents at R_2 and R_3. Esters (**18a,b** and **23a,b**) and phenyl (**26b,c**) and pyridyl bioisosteres at R_3 (**43b,c** and **59b,c**) show selectivities of between 10- and 57-fold. When absolute configuration was determined or known, the more active enantiomer corresponded to the L-amino acid or the *S*-configuration in most cases. In compounds **68–72**, this corresponds to the *R*-configuration. These results suggest that there is an enantioselective interaction of these compounds with a molecular target.

Compound **43b** (BIRM 270) has been selected from this group for more extensive evaluation and is presently under development as a topically administered treatment for asthma. In a sheep model of allergen-induced bronchoconstriction and hyperresponsiveness,[22] **43b** blocked the late-phase response and the airway hyperresponsiveness when given by aerosol administration at doses of 1, 3, or 10 mg. These results will be published separately.

Chemistry

The preparation of benzothiazoles is illustrated in Scheme 1. Reaction of a phenyl isothiocyanate and the appropriately substituted amine or amino acid ester gave a thiourea, which was cyclized using SO_2Cl_2 (method A). Alternatively, amino acids could be alkylated with 2-chlorobenzothiazole using NaOH in DMSO and then esterified (method B). The 5-substituted compound **22** was prepared from 3-ethylphenyl isothiocyanate and required separation from the 7-isomer.

Benzoxazoles were prepared either by alkylation of the appropriately substituted 2-chlorobenzoxazole with an amine or an amino acid as described in method B above or by using diisopropylethylamine with an amine or an amino acid ester (method C, Scheme 2). The substituted 2-chlorobenzoxazoles were prepared by chlorination of the corresponding 2-mercaptobenzoxazole. These were prepared by reaction of the appropriate aminophenol with CS_2.[23] If not available commercially, the aminophenols were prepared by nitration of the substituted phenol followed by reduction of the nitro group.[23]

1,2-Diarylethylamines and 1-aryl-2-cyclohexylethylamines were prepared as described in Scheme 3. The Grignard reagent was prepared from the benzyl- or cyclohexylmethyl bromide and allowed to react with the appropriate arylnitrile. In situ reduction of the intermediate imine with $NaBH_4$ gave the amine (method D). Alternatively, reaction of the Grignard reagent with an aldehyde gave an alcohol, which was oxidized to a ketone followed by reductive amination (method E). The ketone could also be prepared by Friedel–Crafts acylation, where applicable.

Scheme 4 outlines the synthesis of a number of compounds containing R_3 modifications that were derived from carboxylic acids or esters. Amides **34** and **35** were prepared by coupling of an amine with the carboxylic acid using CDI in DMF. Ketone **40** was prepared by reaction of the carboxylic acid with methyllithium. Methyl oxadiazole derivatives **41** and **42** were prepared from the corresponding esters with acetamide oxime and NaH as described in the literature.[21] Ethers **36–38** were synthesized by alkylation of the corresponding alcohol. Thioether **39** was prepared by reaction of the corresponding mesylate with sodium thiomethoxide. In each case, the ether or thioether was introduced onto the protected amine prior to the coupling step. Reduction of the ester followed by reaction with MsCl gave the mesylate.

Several compounds were prepared by further transformation after the coupling step as illustrated in Scheme 5. Hydrolysis of ester **47** gave **48**, which was converted to amides **49** and **50**. Treatment of amide **50** with trifluoroacetic anhydride gave nitrile **51**. Reduction of ester **47** gave alcohol **52**. Acetamide **53** and sulfonamide **54** were prepared from the amine, which was obtained by reduction of the 5-nitro compound.

The synthesis of **68a–72** is illustrated in Scheme 6. Method F outlines the preparation of single enantiomers, starting with (*R*)-phenylglycinol. Protection of the amine as the tBOC derivative is followed by formation of the mesylate. Displacement with the appropriate heterocycle followed by deprotection gave the desired amine which upon reaction with 2-chloro-5-isopropylbenzoxazole gave **68–70** and **72**. Racemic **71** was prepared (method G) by oxidation of morpholine followed by reaction with 2-chloroacetophenone. Reductive amination of the resulting ketone gave the desired amine, which was converted to **71**.

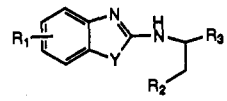
Chiral compounds were prepared by either of three methods. Amino acid derivatives **5a**, and **18a,b** were prepared from the commercially available chiral phenylalanine ester. Catalytic reduction of the phenylalanine ester with Rh/Al_2O_3 gave the cyclohexylalanine esters used for **23a,b**. Enantiomers of **26a** and **59a** were prepared by separation of the racemates using chiral HPLC. Enantiomers of **43a** were prepared by chromatographic separation of diastereomeric amides obtained from the precursor racemic amine and L-valine as described in a separate publication.[24]

Mechanism

Compound **43b** and others from this series had little to no activity in a calcium-ionophore-A23187-stimulated assay for 5-LO inhibition in which exogenous [^{14}C]-arachidonic acid is provided to the neutrophils and radiolabeled 5-LO metabolites are measured. This procedure,[25] unlike the assay used to characterize the compounds presented here, bypasses PLA_2 and is therefore a measurement of 5-LO activity. The relative lack of activity in this system initially indicated that our compounds were not acting directly on 5-LO. This was later confirmed by a similar lack of activity against 5-LO from RBL-1 and neutrophil cytosolic preparations.

We found that the inhibition of LTB_4 biosynthesis by **43b** could be overcome by addition of exogenous arachidonic acid. This suggested to us that the mechanism of action could involve limiting arachidonic acid availability. In fact, direct measurement of arachidonic acid and platelet-activating factor (PAF) released from calcium-ionophore-stimulated neutrophils showed that **43b** in-

Table 2. Inhibition of Leukotriene Biosynthesis by Benzoxazole and Benzothiazole Derivatives



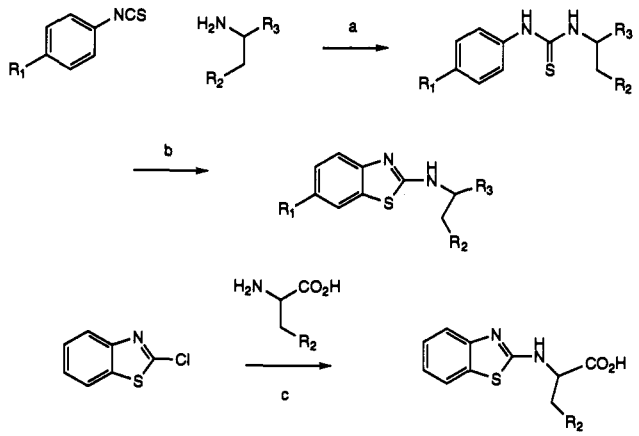
compd no.	R/S	Y	R_1	R_2	R_3	syn meth	mp (°C)	formula[a]	IC_{50}[b] (μM) or % inh of LTB_4/conc
12	RS	S	H	4-ClC_6H_4	CO_2Et	B	oil	$C_{16}H_{17}ClN_2O_2S$	0.20 (0.14–0.27)
13	RS	S	H	4-BrC_6H_4	CO_2Et	B	104–106	$C_{18}H_{17}BrN_2O_2S$	0.15 (0.12–0.19)
14	RS	S	H	4-FC_6H_4	CO_2Et	B	129–131	$C_{16}H_{17}FN_2O_2S$	0.33 (0.22–0.44)
15	RS	S	6-iPr	4-ClC_6H_4	CO_2Et	A	105–107	$C_{21}H_{23}ClN_2O_2S$	0.33 (0.29–0.37)
16	RS	S	6-nBu	4-ClC_6H_4	CO_2Et	A	113–114	$C_{22}H_{25}ClN_2O_2S$	0.18 (0.14–0.21)
17	RS	S	6-OMe	4-ClC_6H_4	CO_2Et	A	129–131	$C_{19}H_{19}ClN_2O_3S$	0.23 (0.16–0.30)
18a	S	O	H	C_6H_5	CO_2Et	B	oil	$C_{16}H_{18}N_2O_3 \cdot {}^1/_2H_2O$	0.15 (0.13–0.17)
18b	R	O	H	C_6H_5	CO_2Et	B	oil	$C_{16}H_{18}N_2O_3$	1.5 (0.63–2.3)
19	S	O	6-iPr	C_6H_5	CO_2Et	B	oil	$C_{21}H_{24}N_2O_3$	0.22 (0.15–0.28)
20	S	O	5-iPr	C_6H_5	CO_2Et	C	oil	$C_{21}H_{24}N_2O_3$	0.0005 (0.0004–0.0007)
21	S	S	6-Et	C_6H_5	CO_2Et	A	102–104	$C_{20}H_{22}N_2O_2S$	0.24 (0.19–0.29)
22	S	S	5-Et	C_6H_5	CO_2Et	A	oil	$C_{20}H_{22}N_2O_2S$[c]	0.012 (0.0091–0.016)
23a	S	O	H	C_6H_{11}	CO_2Me	C	oil	$C_{17}H_{22}N_2O_3$	0.005 (0.005–0.006)
23b	R	O	H	C_6H_{11}	CO_2Me	C	oil	$C_{17}H_{22}N_2O_3$[d]	0.10 (0.078–0.13)
24	RS	S	H	C_6H_5	C_6H_5	B	54–56	$C_{21}H_{18}N_2S$	0.17 (0.15–0.19)
25	RS	O	H	C_6H_5	C_6H_5	B	154–156	$C_{21}H_{18}N_2O$	0.051 (0.029–0.073)
26a	RS	O	H	C_6H_{11}	C_6H_5	C	131–132	$C_{21}H_{24}N_2O$	0.008 (0.007–0.010)
26b	–	O	H	C_6H_{11}	C_6H_5	e	oil	$C_{21}H_{24}N_2O$	0.006 (0.004–0.007)
26c	+	O	H	C_6H_{11}	C_6H_5	e	oil	$C_{21}H_{24}N_2O$	0.34 (0.13–0.55)
27	RS	O	5-Cl	C_6H_5	C_6H_5	C	149–151	$C_{21}H_{17}ClN_2O$	0.023 (0.012–0.034)
28	RS	O	5-OMe	C_6H_5	C_6H_5	C	148–150	$C_{22}H_{20}N_2O_2$	0.009 (0.004–0.02)
29	RS	O	H	C_6H_{11}	4-ClC_6H_4	C	142–144	$C_{21}H_{23}ClN_2O$	0.3[f]
30	RS	O	H	C_6H_{11}	4-FC_6H_4	C	144–145	$C_{21}H_{23}FN_2O$	0.17 (0.12–0.23)
31	RS	O	H	C_6H_{11}	4-$MeOC_6H_4$	C	63–67	$C_{22}H_{26}N_2O_2$	0.55 (0.38–0.71)
32	RS	O	H	C_6H_{11}	3-MeC_6H_4	C	136–138	$C_{22}H_{26}N_2O$	0.30 (0.28–0.33)
33	RS	O	H	C_6H_{11}	2-ClC_6H_4	C	146–148	$C_{21}H_{23}ClN_2O$	0.080 (0.062–0.097)
34	S	O	5-Me	C_6H_{11}	C(O)NHMe	g	202–204	$C_{16}H_{25}N_3O_2$	0.072 (0.059–0.085)
35	RS	O	5-iPr	4-FC_6H_4	$C(O)NC_5H_{10}$	g	109–110	$C_{24}H_{28}FN_3O_2$	0.3[f]
36	RS	O	5-iPr	4-FC_6H_4	CH_2OMe	g	oil	$C_{20}H_{23}FN_2O_2$	0.017 (0.010–0.023)
37	RS	O	5-iPr	4-FC_6H_4	CH_2OEt	g	oil	$C_{21}H_{25}FN_2O_2$	0.041 (0.027–0.055)
38	RS	O	5-iPr	4-FC_6H_4	CH_2OnPr	g	oil	$C_{22}H_{27}FN_2O_2$	0.17 (0.12–0.23)
39	S	O	5-iPr	C_6H_5	CH_2SMe	g	oil	$C_{20}H_{24}N_2OS \cdot {}^1/_4H_2O$	0.013 (0.0089–0.017)
40	S	O	6-iPr	C_6H_5	C(O)Me	g	107–110	$C_{20}H_{22}N_2OS$	0.35 (0.27–0.44)
41	S	O	5-Me	C_6H_{11}	5-(3-MeC_2N_2O)	g	118–119.5	$C_{19}H_{24}N_4O_2$	0.026 (0.019–0.032)
42	RS	O	5-iPr	4-FC_6H_4	5-(3-MeC_2N_2O)	g	86–88	$C_{21}H_{21}FN_4O_2$	0.44 (0.17–0.71)
43a	RS	O	5-Me	C_6H_{11}	2-C_5H_4N	B	104–105	$C_{21}H_{25}N_3O$	0.004 (0.003–0.004)
43b	S	O	5-Me	C_6H_{11}	2-C_5H_4N	C	80–85	$C_{21}H_{25}N_3O \cdot H_2O$	0.001 (0.0007–0.001)
43c	R	O	5-Me	C_6H_{11}	2-C_5H_4N	C	75–78	$C_{21}H_{25}N_3O$	0.040 (0.033–0.047)
44	RS	O	5-Me	C_6H_{11}	3-C_5H_4N	B	150–151	$C_{21}H_{25}N_3O$	0.020 (0.017–0.022)
45	RS	O	5-Me	C_6H_{11}	4-C_5H_4N	B	188–189	$C_{21}H_{25}N_3O \cdot {}^1/_2H_2O$	0.19 (*[h]–0.42)
46	RS	O	5-iPr	C_6H_{11}	C_6H_5	C	119–122	$C_{24}H_{30}N_2O \cdot {}^1/_2H_2O$	0.006 (0.005–0.008)
47	RS	O	5-CO_2Et	C_6H_{11}	C_6H_5	i	129–132	$C_{24}H_{28}N_2O_3$	0.045 (0.040–0.049)
48	RS	O	5-CO_2H	C_6H_{11}	C_6H_5	i	232–234	$C_{22}H_{24}N_2O_3$	0.15 (0.084–0.22)
49	RS	O	5-$C(O)NMe_2$	C_6H_{11}	C_6H_5	i	194–196	$C_{24}H_{29}N_3O_2$	0.17 (0.13–0.20)
50	RS	O	5-$C(O)NH_2$	C_6H_{11}	C_6H_5	i	181–183	$C_{22}H_{25}N_3O_2$	35%/0.3 μM
51	RS	O	5-CN	C_6H_{11}	C_6H_5	i	166–168	$C_{22}H_{23}N_3O$	0.015 (0.013–0.018)
52	RS	O	5-CH_2OH	C_6H_{11}	C_6H_5	i	187–189	$C_{22}H_{26}N_2O_2$	41%/0.3 μM
53	RS	O	5-NHC(O)Me	C_6H_{11}	C_6H_5	i	145–147	$C_{23}H_{27}N_3O_2$	0.078 (0.055–0.10)
54	RS	O	5-$NHSO_2Me$	C_6H_{11}	C_6H_5	i	188–190	$C_{22}H_{27}N_3O_3S$	0.16 (0.12–0.20)
55	RS	O	5-CF_3	4-FC_6H_4	2-C_5H_4N	B	105–107	$C_{21}H_{15}F_4N_3O$	0.008 (0.005–0.01)
56	RS	O	5-OMe	4-FC_6H_4	2-C_5H_4N	C	111–113	$C_{21}H_{18}FN_3O_2$	0.011 (0.0056–0.016)
57	RS	O	5-iPr	4-FC_6H_4	2-C_5H_4N	C	56–58	$C_{23}H_{22}FN_3O$	0.012 (0.0077–0.017)
58	RS	O	5-NO_2	4-FC_6H_4	2-C_5H_4N	C	174–175	$C_{20}H_{15}FN_4O_3$	0.016 (0.010–0.021)
59a	RS	O	5-Cl	4-FC_6H_4	2-C_5H_4N	C	113–115	$C_{20}H_{15}ClFN_3O$	0.020 (0.015–0.025)
59b	–	O	5-Cl	4-FC_6H_4	2-C_5H_4N	e	oil	$C_{20}H_{15}ClFN_3O$	0.020 (0.014–0.027)
59c	+	O	5-Cl	4-FC_6H_4	2-C_5H_4N	e	oil	$C_{20}H_{15}ClFN_3O$	0.32 (0.094–0.55)
60	RS	O	5-F	4-FC_6H_4	2-C_5H_4N	B	117–119	$C_{20}H_{15}F_2N_3O$	0.021 (0.015–0.027)
61	RS	O	5,6-diF	4-FC_6H_4	2-C_5H_4N	B	143–144	$C_{20}H_{14}F_3N_3O$	0.030 (0.018–0.042)
62	RS	O	5-CO_2Et	4-FC_6H_4	2-C_5H_4N	C	151–152	$C_{23}H_{20}FN_3O_3$	0.027 (0.0080–0.047)
63	RS	O	5-SO_2NMe_2	4-FC_6H_4	2-C_5H_4N	C	175–175	$C_{22}H_{21}FN_4O_3S$	0.050 (0.024–0.075)
64	RS	O	5-iPr	4-ClC_6H_4	2-C_5H_4N	C	65–67	$C_{23}H_{22}ClN_3O \cdot {}^1/_4H_2O$	0.029 (0.0042–0.053)
65	RS	O	5-iPr	3-ClC_6H_4	2-C_5H_4N	C	51–52	$C_{23}H_{22}ClN_3O$	0.005 (0.002–0.007)
66	RS	O	5-NO_2	4-$OMeC_6H_4$	2-C_5H_4N	C	162–163	$C_{21}H_{18}N_4O_4$	0.014 (0.011–0.017)
67	RS	O	5-NO_2	4-OHC_6H_4	2-C_5H_4N	C	153–154	$C_{20}H_{16}N_4O_4$[j]	27%/0.3 μM
68a	R	O	5-iPr	k	C_6H_5	F	180 dec	$C_{23}H_{29}N_3O \cdot 2HCl \cdot H_2O$	0.10 (0.084–0.12)
68b	S	O	5-iPr	k	C_6H_5	F	185 dec	$C_{23}H_{29}N_3O \cdot 2HCl \cdot H_2O$	1.2 (0.79–1.6)
69	R	O	5-iPr	l	C_6H_5	F	135–137	$C_{22}H_{27}N_3O_2$	0.052 (0.044–0.061)
70	R	O	5-Cl	m	C_6H_5	F	69–71	$C_{19}H_{20}ClN_3OS$	0.048 (0.035–0.061)
71	RS	O	5-Cl	n	C_6H_5	G	189–191	$C_{19}H_{20}ClN_3O_3S$	46%/1 μM
72	R	O	5-Cl	o	C_6H_5	F	58–60	$C_{20}H_{23}ClN_4O$	21%/1 μM
73	RS	O	5-iPr	p	2-C_5H_4N	C	116–117	$C_{21}H_{22}N_4OS$[q]	0.029 (0.029–0.030)

Table 2. (Continued)

compd no.	*R/S*	Y	R_1	R_2	R_3	syn meth	mp (°C)	formula[a]	IC_{50}[b] (μM) or % inh of LTB_4/conc
74	*RS*	O	5-iPr	*p*	CO_2Et	F	oil	$C_{19}H_{23}N_3O_3S$	0.016 (0.0057–0.026)
75	*S*	O	5-iPr	*r*	CO_2Et	C[e]	166–168	$C_{17}H_{20}N_4O_3 \cdot 2HCl$	26%/1 μM
76	*S*	O	5-iPr	*t*	CO_2Et	C[e]	143–146	$C_{19}H_{24}N_4O_3 \cdot 2HCl$[u]	59%/1 μM

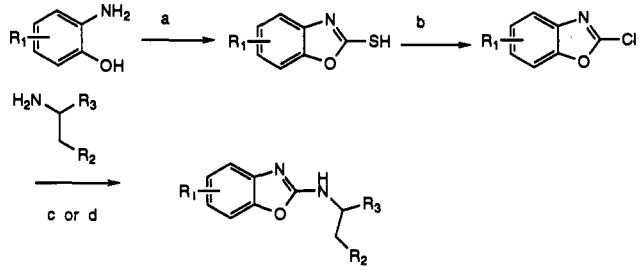
[a] See footnote *a*, Table 1. [b] See footnote *b*, Table 1. [c] FAB HRMS *m/z* 355.1474 $(M + H)^+$; calcd 355.1492. [d] C: calcd, 67.53; found, 67.07. [e] Prepared by chiral HPLC of the racemate. See Experimental Section. [f] Estimate. No nonlinear regression analysis due to curve shape. [g] Scheme 4. [h] Lower bound was negative or equal to zero. [i] Scheme 5. [j] FAB HRMS *m/z* 376.1177 $(M + H)^+$; calcd 376.1173. [k] *N*-Piperidinyl. [l] *N*-Morpholinyl. [m] *N*-Thiomorpholinyl. [n] *N*-*S*,*S*-Dioxothiomorpholinyl. [o] *N*-*N'*-Methylpiperizinyl. [p] 2-Methyl-4-thiazolyl. [q] FAB HRMS *m/z* 378.1493 $(M + H)^+$; calcd 378.1517. [r] 4-Imidazolyl. [s] Due to insolubility in CH_2Cl_2, toluene with enough MeOH to dissolve was used as solvent. [t] 3-Ethyl-4-imidazolyl. [u] C: calcd, 53.15; found, 54.64.

Scheme 1[a]



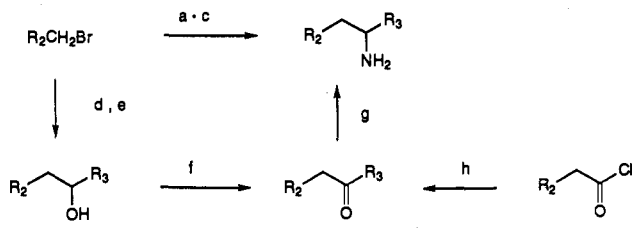
[a] (a) Ether, 0 °C; (b) chlorobenzene, SO_2Cl_2, 0 °C (method A); (c) NaOH, DMSO (method B).

Scheme 2[a]



[a] (a) CS_2, KOH, MeOH, H_2O; (b) PCl_5, $POCl_3$; (c) NaOH, DMSO (method B); (d) iPr_2NEt, CH_2Cl_2 (method C).

Scheme 3[a]



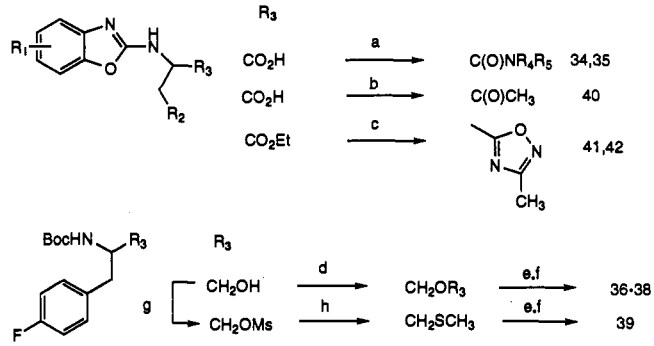
[a] (a) Mg, ether; (b) R_3CN; (c) $NaBH_4$, MeOH (method D); (d) Mg, ether; (e) R_3CHO; (f) MnO_2; (g) (1) $HC(O)NH_2$, HC(O)OH, (2) 2 N HCl (method E); (h) R_3H, $AlCl_3$, CH_2Cl_2.

hibited both, and the dose–response curves were coincidental with LTB_4. This is consistent with a site of action at the level of arachidonic acid release from phospholipids. However, no direct effect on cytosolic PLA_2 was observed for this compound, suggesting an indirect effect on PLA_2 activity. These results are being published separately.[26]

Experimental Section

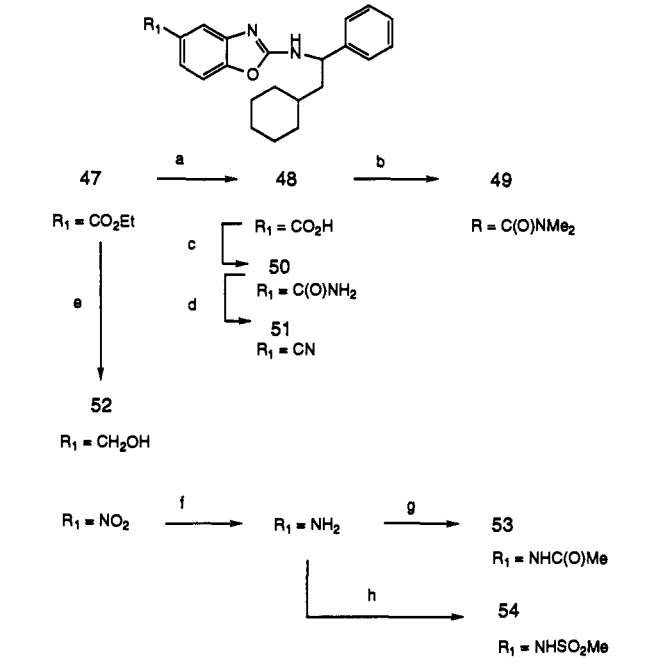
Melting points were taken on a Buchi 510 melting point apparatus and are uncorrected. ^1H NMR were all consistent with molecular structures and were recorded on a Bruker 250 WM spectrometer. Elemental analyses were performed at Midwest Microlab, Indianapolis, IN, and were within 0.4% of the calculated values unless otherwise indicated.

Scheme 4[a]



[a] (a) CDI, DMF, NHR_4R_5; (b) MeLi, THF; (c) NaH, $CH_3C(NOH)NH_2$; (d) $(Bu_4N)^+HSO_4^-$, R_3I, NaOH, H_2O; (e) TFA, CH_2Cl_2; (f) method C, R_1 = iPr; (g) MsCl, Et_3N, CH_2Cl_2; (h) $NaSCH_3$.

Scheme 5[a]

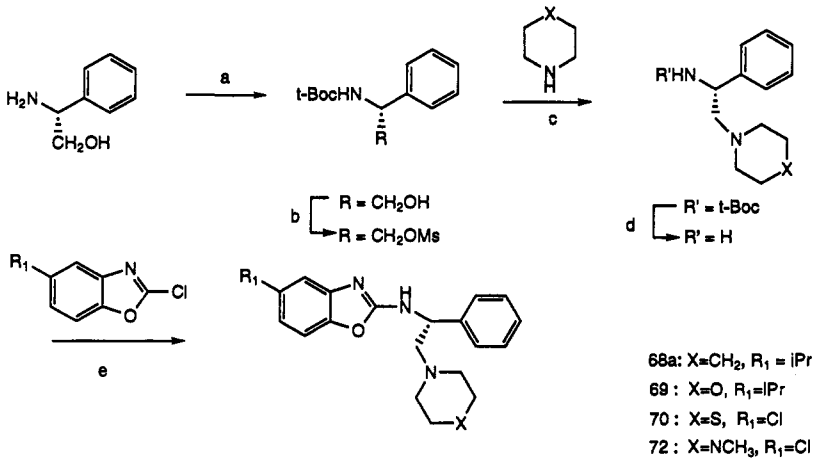


[a] (a) 2 N NaOH, EtOH; (b) CDI, DMF, Me_2NH; (c) CDI, DMF, NH_3; (d) Et_3N, THF, $[CF_3C(O)]_2O$; (e) LAH, THF; (f) H_2, Pd/C, EtOH; (g) AcCl, Et_3N, DMF; (h) MsCl, Et_3N, DMF.

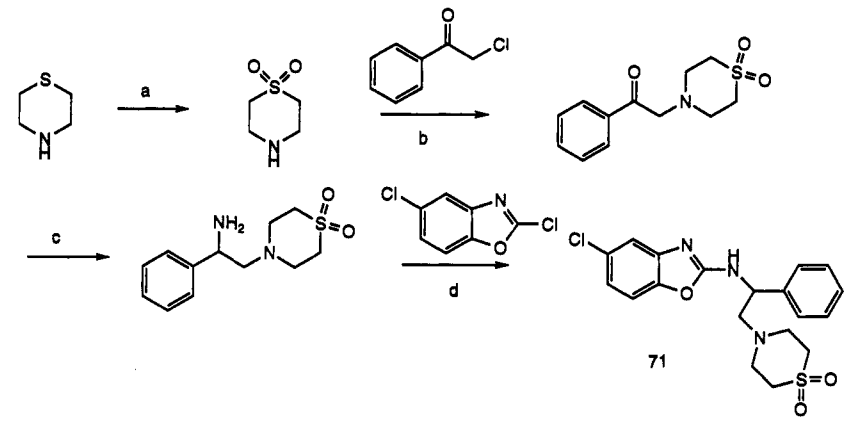
Ethyl (*R,S*)-*N*-(Benzothiazol-2-ylmethyl)-4-chlorophenylalanine HCl (9). (*R,S*)-4-Chlorophenylalanine ethyl ester HCl (1.85 g, 7 mmol) and several 4A molecular sieves were added to a solution of 2-benzothiazolecarboxaldehyde[29] (1 g, 6.1 mmol) in 30 mL of EtOH. $NaBH_3CN$ (0.8 g, 12.7 mmol) was added, and the reaction mixture was stirred at room temperature for 23 h. The reaction mixture was poured into 150 mL of H_2O, made basic with 2 N NaOH, and extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and

Scheme 6

Method F[a]



Method G[b]



[a] (a) $O(CO_2tBu)_2$; (b) MsCl, Et_3N; (c) THF, reflux; (d) TFA, CH_2Cl_2; (e) method B or C. [b] (a) H_2O_2, HOAc; (b) iPr_2NEt; (c) NH_4OAc, $NaBH_3CN$, (d) iPr_2NEt, CH_2Cl_2.

concentrated. The resulting oil was chromatographed on silica gel, eluting with 98 CH_2Cl_2:2MeOH, and the fractions containing the product were collected, concentrated, and treated with ethereal HCl. The HCl salt was recrystallized from EtOH giving **9** (0.4 g, 16%), mp 150–153 °C. ^1H NMR ($CDCl_3$): δ 8.0 (d, 1H, aromatic), 7.5 (d, 1H, aromatic), 7.3 (m, 7H, aromatic), 4.1 (q, 2H, CH_2), 3.3 (m, 5H, 2 CH_2S, 1 CH), 1.1 (t, 3H, CH_3). Anal. ($C_{19}H_{19}ClN_2O_2S$ HCl) C, H, N.

Ethyl (*R,S*)-3-(Benzothiazol-2-yl)-2-benzylpropionate (10). A solution of ethyl hydrocinnamic acid (3.56 g, 20 mmol) in 20 mL of THF was added under N_2 to a solution of lithium diisopropylamide prepared by addition of 15 mL of 1.6 N n BuLi (24 mmol) to 2.42 g (24 mmol) of diisopropylamine in 100 mL of THF at −78 °C. The temperature was maintained between −40 and −15 °C for 30 min after addition. A solution of 3.26 g of 2-benzothiazolecarboxaldehyde[29] in 30 mL of THF was added over 15 min (−40 to −20 °C). The reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was poured into a mixture of ice and water, made acidic with 2 N HCl, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated giving an oil which was chromatographed on silica gel, eluting with 99 CH_2Cl_2:1 MeOH. The fractions containing the product (a diastereomeric pair) were combined and concentrated giving 4.2 g (61%) of ethyl 3-(benzothiazol-2-yl)-3-hydroxy-2-benzylpropionate as an oil. A sample of the first eluting diastereomer was recrystallized (ligroine) and characterized, mp 94–96 °C. ^1H NMR ($CDCl_3$): δ 8.05 (d, 1H, aromatic), 7.95 (d, 1H, aromatic), 7.45 (m, 7H, aromatic), 5.1 (d, 1H, CH), 4.7 (d, 1H, OH), 4.1 (q, 2H, CH_2), 3.75 (m, 1H, CH), 3.3 (m, 2H, CH_2), 1.1 (t, 3H, CH_3).

The above hydroxy ester (4.2 g, 12.3 mmol) was dissolved in 20 mL of pyridine and cooled on an ice bath. $POCl_3$ (2.73 g, 17.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then heated to 90–100 °C for 2 h, cooled, and added to ice and water. The product was extracted with EtOAc, washed with 2 N HCl and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel, eluting with CH_2Cl_2, giving 1.47 g (37%) of ethyl 3-(benzothiazol-2-yl)-2-benzylpropenoate as an oil. ^1H NMR ($CDCl_3$): δ 8.1 (d, 1H, aromatic), 7.95 (s, 1H, olefin), 7.95 (d, 1H, aromatic), 4.5 (s, 2H, CH_2), 4.25 (q, 2H, CH_2), 1.25 (t, 3H, CH_3).

A solution of 1.43 g (4.43 mmol) of the above olefin in 75 mL of EtOH was combined with 650 mg of 10% Pt/C and hydrogenated under 40 psi until TLC (CH_2Cl_2) showed no starting material remained (24 h). The reaction mixture was filtered through Celite and concentrated. The residue was recrystallized from ligroine giving 0.57 g (39.5%) of **10**, mp 46–48 °C. ^1H NMR ($CDCl_3$): δ 8.0 (d, 1H, aromatic), 7.85 (d, 1H, aromatic), 7.3 (m, 7H, aromatic), 4.1 (q, 2H, CH_2), 3.45 (m, 1H, CH), 3.3 (m, 2H, CH_2), 3.05, (m, 2H, CH_2), 1.1, (t, 3H, CH_3). Anal. ($C_{19}H_{19}NO_2S$) C, H, N.

Method A. (*R,S*)-*N*-(6-Isopropylbenzothiazol-2-yl)-4-chlorophenylalanine Ethyl Ester (15). (*R,S*)-4-Chlorophenylalanine ethyl ester HCl (5 g, 18.9 mmol) was converted to the free base with Et_3N and dissolved in 75 mL of ether. This solution was added to a solution of 4-isopropylphenylisothiocyanate (3.36 g, 19 mmol) in 150 mL of ether. The temperature was maintained at 0 °C or less during the addition by cooling in an ice–salt bath. The reaction mixture was stirred for 4.5 h on the ice bath and then concentrated. The foamy residue was triturated with petroleum ether resulting in 6.1 g (15.1 mmol, 80%) of the intermediate thiourea, mp 73–75 °C.

The thiourea (6.0 g, 14.8 mmol) was dissolved in 25 mL of chlorobenzene and cooled on an ice bath to 0 °C. Sulfuryl chloride (2.76 g, 20.4 mmol) in 5 mL of chlorobenzene was added dropwise. After 5.5 h, the reaction mixture was concentrated and the residue

dissolved in EtOAc, washed with saturated Na_2CO_3 solution and brine, dried (Na_2SO_4), and concentrated. The product was recrystallized from EtOH giving 4.07 g (68%) of **15**, mp 105–107 °C. ^1H NMR ($CDCl_3$): δ 7.5–7.0 (m, 7H, aromatic), 5.6 (d, 1H, NH), 4.95 (m, 1H, CH), 4.2 (q, 2H, CH_2), 3.3 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 1.25 (d, 6H, $2CH_3$). Anal. ($C_{21}H_{23}ClN_2O_2S$) C, H, N.

General Procedure for Preparation of 2-Chlorobenzoxazoles. 2-Chloro-5-methylbenzoxazole. To a suspension of 1.0 g (6.05 mmol) of 5-methyl-2-mercaptobenzoxazole in 8.22 g (53.6 mmol) of $POCl_3$ at room temperature was added 1.26 g (7.2 mmol) of PCl_5 along with 5 mL of CH_2Cl_2. The reaction mixture turned into a solution after the addition. After 1 h of stirring at room temperature, the reaction mixture was concentrated to remove excess $POCl_3$, and the residue was treated with Na_2CO_3 solution until pH 8 was reached. The aqueous phase was extracted with CH_2Cl_2, and the combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 1.1 g of crude material after azeotroping with toluene. Short-column chromatography on silica gel starting with petroleum ether followed by 10% CH_2Cl_2/petroleum ether provided 820 mg (81% yield) of 2-chloro-5-methylbenzoxazole as an oil. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 7.1–7.4 (m, 3H, Ar).

Method B. (*R,S*)-*N*-(Benzothiazol-2-yl)phenylalanine Hydrochloride (11). A 11.8-g (71.4 mmol) sample of (*R,S*)-phenylalanine was added in portions to a suspension of 5.7 g of powdered NaOH (143 mmol) in 50 mL of DMSO and stirred under N_2 for 30 min. 2-Chlorobenzothiazole (11 g, 65 mmol) was added over 15 min at room temperature. The reaction mixture was heated on an oil bath set at 95 °C for 4 h. The cooled reaction mixture was poured into 200 mL of ice and water and the pH of the resulting solution adjusted to 1–2 by the addition of 10 N HCl. More ice was added, and the mixture was filtered. The white solid was dissolved in alkaline solution, stirred with Celite, filtered, and acidified with 2 N HCl, and the resulting white precipitate was filtered, rinsed with water and EtOH, and dried. This resulted in 6.47 g of 11 (30%), mp 250–251 °C. ^1H NMR (DMSO-d_6): δ 13.5 (br s, 2H, NH^{2+}), 10.1 (br s, 1H, CO_2H), 7.9–7.1 (m, 9H, aromatic), 5.1 (m, 1H, CH), 3.25 (m, 2H, CH_2). Anal. ($C_{16}H_{14}N_2O_2S$·HCl) H, N; C: calcd, 57.39; found, 57.97.

(*S*)-*N*-(Benzoxazol-2-yl)cyclohexylalanine Methyl Ester (23a). To a solution of 10.0 g (46.36 mmol) of (*S*)-(−)-phenylalanine methyl ester hydrochloride in 75 mL of MeOH was added 1.4 g of Rh/Al_2O_3. The resulting mixture was hydrogenated on a Parr shaker overnight at room temperature under 50 psi of hydrogen. The catalyst was filtered off with the aid of Celite. The filtrate was concentrated to give a white solid which was recrystallized from CH_2Cl_2/ether to give 9.2 g (95% yield) of (*S*)-(−)-cyclohexylalanine methyl ester hydrochloride, mp 154–155 °C. ^1H NMR ($CDCl_3$): δ 0.8–1.7 (m, 13H, aliph), 3.74 (s, 3H, OCH_3), 4.0 (t, 1H, CH), 8.6 (br, 3H, NH_3^+).

To a mixture of 2.21 g (10 mmol) of (*S*)-(−)-cyclohexylalanine methyl ester hydrochloride and 1.68 g (11 mmol) of 2-chlorobenzoxazole in 75 mL of CH_2Cl_2 was added 2.58 g (20 mmol) of diisopropylethylamine. The resulting mixture was refluxed overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The CH_2Cl_2 phase was dried and concentrated to give an oil material weighing 3.05 g. Flash column chromatography on silica gel starting with 1:1 petroleum ether:CH_2Cl_2 followed by 100% CH_2Cl_2 and 1% MeOH in CH_2Cl_2 gave a total of 1.78 g (59% yield) of **23a** as an oil. ^1H NMR ($CDCl_3$): δ 1.0–1.8 (m, 13H, aliph), 3.72 (s, 3H, CH_3), 4.65 (m, 1H, CH), 5.48 (br, 1H, NH), 7.02–7.38 (m, 4H, Ar). Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

Methods C and E. (*R,S*)-*N*-(2-Cyclohexyl-1-phenylethyl)-2-benzoxazolamine (26a). Cyclohexylacetyl chloride[30] (10 g, 62.2 mmol) in 75 mL of CH_2Cl_2 was added over 30 min to 8.29 g (62.2 mmol) of $AlCl_3$ in 75 mL of CH_2Cl_2 and stirred under N_2 on an ice bath. After 40 min, 5.08 g (65 mmol) of benzene in 30 mL of CH_2Cl_2 was added over 25 min. The reaction mixture was stirred on ice for 30 min and then stirred for 2 h at room temperature, refluxed for 3 h, and stirred overnight at room temperature. The reaction mixture was poured into cold 2 N HCl, the organic phase was separated, and the aqueous phase was washed with more CH_2Cl_2. The combined organic phases were washed with 2 N HCl and brine, dried (Na_2SO_4), and concentrated. The residual oil (12 g) was chromatographed on silica gel, eluting with CH_2Cl_2, giving 1-phenyl-2-cyclohexylethanone (10.4 g, 51.4%). ^1H NMR ($CDCl_3$): δ 7.9 (m, 2H, phenyl), 7.5 (m, 3H, phenyl), 2.85 (d, 2H, CH_2), 2.0 (m, 1H, CH), 1.7 (m, 5H, cyclohexyl), 1.1 (m, 5H, cyclohexyl).

A mixture of the above ketone (10.37 g, 51.4 mmol) and formamide (11.57 g, 250 mmol) was stirred on an oil bath. The oil-bath temperature was raised to 170 °C as 5.9 g (128 mmol) of formic acid was added in portions. Additional formamide and formic acid were added at various intervals over the next 30 h, until TLC (98 CH_2Cl_2:2 MeOH) showed the reaction was over. The cooled reaction mixture was then dissolved in EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting formamide (10.88 g, 91%) was suspended in 250 mL of 2 N HCl and heated to reflux. After 4 h, the reaction mixture was cooled and the precipitated amine hydrochloride filtered, rinsed with water, and dried giving 9.35 g (76% from ketone) of 1-phenyl-2-cyclohexylethylamine HCl, mp 288 °C. ^1H NMR ($CDCl_3$): δ 8.5 (br s, 3H, NH_3^+), 7.4 (m, 5H, phenyl), 4.25 (br t, 1H, CH), 1.7 (m, 7H, CH, CH_2), 1.0 (m, 6H, CH_2).

A mixture of 1.48 g (7.3 mmol) of the free base of the above amine, 1.12 g of 2-chlorobenzoxazole (Aldrich), and 1.14 g (8.8 mmol) of diisopropylethylamine in 30 mL of CH_2Cl_2 was heated at reflux for 24 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with H_2O, 1 N HCl, saturated Na_2CO_3 solution, and brine, dried (Na_2SO_4), and concentrated. The resulting solid was recrystallized from EtOH giving 1.4 g (60%) of **26a**, mp 131–132 °C. ^1H NMR ($CDCl_3$): δ 7.3 (m, 9H, aromatic), 6.3 (br s, 1H, NH), 5.0 (m, 1H, CH), 1.75 (m, 7H, CH, CH_2), 1.5–0.8 (m, 6H, aliphatic). Anal. ($C_{21}H_{24}N_2O$) C, H, N.

Method D. 1-(2-Pyridyl)-2-cyclohexylethylamine Dihydrochloride. Cyclohexylmethyl bromide (22.1 g, 0.125 mol) in 200 mL of anhydrous ether was added dropwise to 3.04 g of Mg turnings (0.125 mol) at a rate to maintain reflux. After the reaction subsided, the mixture was heated to reflux for 1 h and then cooled to 0 °C. 2-Cyanopyridine (10 g, 0.096 mol) in 100 mL of ether was then added, keeping the temperature under 10 °C. After addition, the reaction mixture was stirred for an additional 1 h on the ice bath and then 300 mL of MeOH was added slowly at first and then more quickly. A dark green gum settled which was stirred with a glass rod until it dissolved. After 30 min, 7.26 g of $NaBH_4$ was added in portions, keeping the temperature at about 10 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The solvent was then removed on a rotary evaporator, and the residue was treated with H_2O and then 2 N HCl. The mixture was extracted with CH_2Cl_2 and then made basic with 2 N NaOH and the product extracted into CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was dissolved in ether and filtered, and the dihydrochloride salt was precipitated with ethereal HCl giving 14.26 g (61%), mp 133–136 °C. NMR was identical to that of the sample prepared by method E.

(*S*)-3-Cyclohexyl-2-[(5-methylbenzoxazol-2-yl)amino]-*N*-methylpropionamide (34). A solution of 1.08 g (3.57 mmol) of (*S*)-*N*-(5-methylbenzoxazolyl)cyclohexylalanine in 15 mL of CH_2Cl_2 was cooled on an ice bath. Carbonyldiimidazole (0.88 g, 15.4 mmol) was added in portions. After the solution was stirred for 1 h, methylamine was bubbled in for 45 min. The reaction mixture was then diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel, eluting with 99 CH_2Cl_2:1 MeOH. After recrystallization from iPrOH, 0.2 g (18%) of **34** was obtained, mp 202–204 °C. ^1H NMR ($CDCl_3$): δ 7.15 (m, 2H, aromatic), 6.85 (d, 1H, aromatic), 6.55 (br d, 1H, NH), 5.9 (d, 1H, NH), 4.4 (m, 1H, CH), 2.8 (d, 3H, CH_3), 2.4 (s, 3H, CH_3), 1.9–0.85 (m, 13H, aliphatic). Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

(*R,S*)-5-Isopropyl-*N*-[3-(4-fluorophenyl)-1-(methoxymethyl)prop-2-yl]benzoxazolamine (36). To a solution of 6.5 g (33 mmol) of D,L-4-fluorophenylalanine methyl ester in 30 mL of dry THF was added 4.19 g (98.9 mmol) of LiCl followed by 3.74 g (98.9 mmol) of $NaBH_4$ and 60 mL of absolute EtOH under argon at room temperature. The reaction mixture was kept at 50–55 °C for 2 h and left overnight at room temperature. The reaction was quenched with saturated NH_4Cl and the mixture extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated to give 5.1 g of oil. Trituration of the partially crystallized material with ether provided a first crop of

D,L-4-fluorophenylalaninol (1.87 g) as a white crystalline solid, mp 160 °C. A second crop of 920 mg was obtained after flash column chromatography of the filtrate on silica gel with 2.5% MeOH in CH_2Cl_2. A total of 2.79 g (50% yield) was obtained. ^1H NMR ($CDCl_3$/DMSO-d_6): δ 2.83 (dd, 1H, CHPh), 3.0 (dd, 1H, CHPh), 3.3 (m, 1H, CH), 3.48 (dd, 1H, CHOH), 3.64 (dd, 1H, CHOH), 6.94 (t, 2H, Ar), 7.18 (dd, 2H, ArF).

D,L-*N*-(*tert*-Butoxycarbonyl)-*p*-fluorophenylalaninol was prepared by the same procedure described below in method F for (*R*)-(−)-*N*-(*tert*-butoxycarbonyl)-2-phenylglycinol. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 1.84 (br, 1H, OH), 3.5 (d, 2H, CH_2-Ph), 3.55 (dd, 1H, CHO), 3.67 (dd, 1H, CHO), 3.8 (m, 1H, CHN), 4.7 (br, 1H, NH), 7.0 (t, 2H, Ar), 7.15 (dd, 2H, ArF).

A solution of 350 mg (13 mmol) of the above alcohol, 440 mg (1.3 mmol) of tetrabutylammonium hydrogen sulfate, and 920 mg (6.5 mmol) of iodomethane in 4 mL of THF and 3 mL of 50% NaOH/H_2O was stirred vigorously overnight at room temperature. The reaction was quenched with H_2O. The aqueous phase was extracted with ether, dried ($MgSO_4$), and concentrated to give 380 mg of oil which crystallized on standing. Flash column chromatography starting with petroleum ether followed by 5% and then 20% EtOAc in petroleum ether afforded 360 mg (98% yield) of the methyl ether, mp 66–67.5 °C. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 2.8 (m, 2H, CH_2Ar), 3.3 (dd, 2H, CH_2O), 3.5 (s, 3H, CH_3O), 3.85 (m, 1H, CH), 4.84 (br, 1H, NH), 6.95 (t, 2H, Ar), 7.15 (dd, 2H, ArF).

A solution of 350 mg (1.24 mmol) of the above methyl ether in 1 mL of CF_3CO_2H and 1 mL of CH_2Cl_2 was stirred under anhydrous conditions. The reaction was quenched with 2 N NaOH to pH 9, and the aqueous phase was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to give 200 mg (88% yield) of D,L-4-fluorophenylalaninyl methyl ether as an oil which was used directly in the next step. ^1H NMR ($CDCl_3$): δ 1.5 (s, 2H, NH_2), 2.5 (dd, 1H, CHAr), 2.7 (dd, 1H, CHAr), 3.2 (m, 2H, CH_2O), 3.35 (dm, 4H, CH, OCH_3), 6.97 (t, 2H, Ar), 7.15 (dd, 2H, ArF).

The coupling of the 2-chloro-5-isopropylbenzoxazole and the above amine was done by using Method C to afford an 86% yield of **36** as an oil. ^1H NMR ($CDCl_3$): δ 1.28 (d, 6H, 2 Me), 3.0 (m, 3H, isoprCH, CH_2Ar), 3.37 (s, 3H, CH_3O), 3.37–3.4 (m, 2H, CH_2O), 4.2 (m, 1H, CH), 5.2 (br, 1H, NH), 6.9–7.28 (m, 7H, Ar). Anal. ($C_{20}H_{23}FN_2O_2$) C, H, N.

(*S*)-5-Isopropyl-*N*-[1-(methylthio)-3-phenylprop-2-yl]-2-benzoxazolamine (39). The mesylate derivative of (*S*)-*N*-tBoc-phenylalaninol was prepared by the same procedure as described in method F for the mesylate of (*R*)-*N*-tBoc-phenylglycinol. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 2.9 (dd, 2H, CH_2Ph), 3.0 (s, 3H, CH_3SO_3), 4.1 (dd, 2H, CH_2OSO_2), 4.25 (m, 1H, CH), 4.7 (br, 1H, NH), 7.15–7.3 (m, 5H, Ar).

Sodium thiomethoxide (210 mg, 3.06 mmol) was added to a solution of 1.0 g (2.78 mmol) of the above methane sulfonate in 5 mL of DMF at 0 °C under Argon. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature overnight. After being diluted with ether, the organic phase was washed with saturated NH_4Cl and H_2O. The combined aqueous phase was back-extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated to give 820 mg of residue. Flash column chromatography with petroleum ether followed by 5% EtOAc to 15% EtOAc in petroleum ether provided 560 mg (72% yield) of (*S*)-(−)-*N*-(*tert*-butoxycarbonyl)-1-(methylthio)-3-phenyl-2-propylamine, mp 82–90 °C. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 2.14 (s, 3H, CH_3S), 2.58 (d, 2H, CH_2S), 2.9 (d, 2H, CH_2Ph), 4.0 (m, 1H, CH), 4.65 (br, 1H, NH), 7.15–7.3 (m, 5H, Ar).

A solution of 200 mg (0.71 mmol) of the above N-protected thioether in 0.5 mL of CF_3CO_2H and 0.5 mL of CH_2Cl_2 was stirred at room temperature for 5 h under anhydrous conditions. The reaction was quenched with saturated Na_2CO_3 and the mixture extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to give (*S*)-(−)-2-amino-3-phenylpropyl methyl thioether (100 mg, 78%) as an oil. ^1H NMR ($CDCl_3$): δ 1.75 (br, 2H, NH_2), 2.1 (s, 3H, CH_3S), 2.48 (dd, 1H, CHS), 2.64 (dd, 1H, CHS), 2.7 (dd, 1H, CHPh), 2.85 (dd, 1H, CHPh), 3.2 (m, 1H, CH), 7.2–7.35 (m, 5H, Ar).

Via method C with 2-chloro-5-isopropylbenzoxazole and the above amine, **39** was obtained in 59% yield as an oil. ^1H NMR ($CDCl_3$): δ 1.28 (d, 6H, 2 Me), 2.14 (s, 3H, CH_3S), 2.76 (d, 2H, CH_2S), 2.97 (m, 1H, $CHMe_2$), 3.1 (dd, 2H, CH_2Ph), 4.3 (m, 1H, CH), 5.0 (d, 1H, NH), 6.9 (d, 1H, Ar), 7.1 (d, 1H, Ar), 7.3 (m, 6H, Ar). Anal. ($C_{20}H_{24}N_2OS \cdot {}^1/_4H_2O$) C, H, N.

(*S*)-3-[(6-Isopropylbenzothiazol-2-yl)amino]-4-phenyl-2-butanone (40). According to a general procedure for methyl ketones,[31] a solution of (*S*)-*N*-(6-isopropylbenzothiazol-2-yl)-phenylalanine (2 g, 5.9 mmol) in 60 mL of THF was stirred at −5 °C under N_2 on an ice–salt bath. A solution of 26 mL of 1.4 N MeLi in ether (36.4 mmol) was added via syringe, keeping the temperature below 10 °C. After the solution was stirred for 2 h at 0 °C, 8.56 g of chlorotrimethylsilane (78 mmol) was added, the reaction mixture was warmed to room temperature, and 45 mL of 1 N HCl was added. After stirring 30 min, the aqueous phase was extracted with ether, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. After chromatography on silica gel with CH_2Cl_2, the product was recrystallized from EtOH giving 0.71 g of **40** (36%), mp 107–110 °C. ^1H NMR ($CDCl_3$): δ 7.5 (m, 2H, aromatic), 7.2 (m, 6H, aromatic), 5.75 (d, 1H, NH), 5.0 (m, 1H, CH), 3.3 (m, 2H, CH_2), 2.95 (m, 1H, CH), 2.25 (s, 3H, CH_3), 1.25 (d, 6H, CH_3). Anal. ($C_{20}H_{22}N_2OS$) C, H, N.

Methods B and E. (*R,S*)-*N*-[2-Cyclohexyl-1-(2-pyridinyl)-ethyl]-5-methyl-2-benzoxazolamine (43a). A solution of 17.7 g (0.1 mol) of cyclohexylmethyl bromide in 50 mL of ether was added dropwise to a mixture of 2.43 g (0.1 mol) of Mg turnings in 25 mL of ether. The reaction mixture started to reflux immediately. At the end of the addition when the refluxing subsided, the reaction mixture was heated to reflux for an additional 0.5 h. After the mixture had cooled to room temperature, 5.36 g (0.05 mol) of 2-pyridinecarboxyaldehyde was added slowly to the freshly generated Grignard reagent. The reaction was exothermic during the addition. The resulting mixture was stirred at room temperature for 3 h before it was poured into ice–H_2O. The aqueous phase was treated with dilute HCl until pH 7 was reached. The aqueous phase was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 9.1 g of an oily residue. Crystallization from CH_2Cl_2/petroleum ether provided a total of 6.05 g (59% yield) of 2-cyclohexyl-1-(2-pyridyl)-ethanol, mp 72–74 °C. ^1H NMR ($CDCl_3$): δ 0.95–1.8 (m, 12H, 6 CH_2), 1.99 (m, 1H, CH), 4.05 (d, 1H, OH), 4.8 (m, 1H, CH), 7.2 (m, 2H, pyr), 7.7 (t, 1H, pyr), 8.5 (d, 1H, pyr).

To a solution of 4.63 g (22.5 mmol) of the above alcohol in 50 mL of CH_2Cl_2 was added a total of 8.88 g (0.1 mol) of MnO_2 in portions over a period of 5 h under anhydrous conditions. The resulting mixture was stirred at room temperature overnight. The catalyst was filtered off with the aid of Celite. The filtrate was concentrated to give an oil. Chromatography on a short column of silica gel, eluting with petroleum ether followed by 20% CH_2Cl_2 in petroleum ether, provided 4.1 g (89% yield) of (cyclohexylmethyl)-2-pyridyl ketone as an oil. ^1H NMR ($CDCl_3$): δ 1.07–1.3 (m, 5H, cyclohexyl), 1.74 (m, 5H, cyclohexyl), 2.0 (m, 1H, CH of cyclohexyl), 3.1 (d, 2H, CH_2), 7.45 (m, 1H, pyr), 7.85 (t, 1H, pyr), 8.05 (d, 1H, pyr), 8.7 (d, 1H, pyr).

A mixture of 1.8 g (8.85 mmol) of the above ketone and 2.22 g (49.2 mmol) of formamide was heated on an oil bath at 160 °C. To this was added 1.2 g (26.5 mmol) of formic acid in portions while keeping the temperature between 160 and 165 °C. The reaction was completed in 3 h. After cooling, 17 mL of 2 N HCl solution was added, and the resulting mixture was refluxed for 5 h. The reaction mixture was diluted with ether and treated with 10 N NaOH followed by saturated Na_2CO_3 until pH 9 was reached. The aqueous phase was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a dark oil. Upon treatment of the oil with ethereal HCl, a solid was obtained. The solid was recrystallized from MeOH/CH_2Cl_2/petroleum ether to give 1.3 g (54% yield) of 1-(2-pyridyl)-2-cyclohexylethylamine dihydrochloride. ^1H NMR (DMSO-d_6): δ 0.8–1.1 (m, 6H, aliph), 1.55–1.8 (m, 7H, aliph), 4.5 (m, 1H, CH), 7.5 (m, 1H, pyr), 7.67 (d, 1H, pyr), 7.95 (m, 1H, pyr), 8.6 (br, 2H, NH_2), 8.68 (d, 1H, pyr), 9.05 (br, 2H, $2NH^+$).

A mixture of 531 mg (13 mmol) of powdered NaOH in DMSO was stirred at room temperature for 10 min before 1.2 g (4.34 mmol) of the above amine dihydrochloride was added. After the mixture was stirred for 0.5 h at room temperature, 661 mg (3.95 mmol) of 2-chloro-5-methylbenzoxazole was added. The resulting

mixture was kept at 60 °C with stirring for 2 h. The reaction was quenched with H_2O. The aqueous phase (pH 9) was extracted with ether, dried, and concentrated to give an 1.3-g oily product. This residue was treated with ethereal HCl to give a gummy solid which was recrystallized from CH_2Cl_2/petroleum ether giving 1.1 g of product as the dihydrochloride salt (69% yield), mp > 140 °C. A portion (680 mg) of the salt was converted to the free base by dissolving in H_2O and adjusting the pH to 9. The aqueous phase was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to give 570 mg of oil. Upon trituration with petroleum ether, 458 mg of **43a** (82% recovery) was obtained, mp 104–105 °C. ^1H NMR ($CDCl_3$): δ 1.0–1.8 (m, 13H, aliph), 2.35 (s, 3H, CH_3), 5.1 (dd, 1H, CHN), 5.95 (d, 1H, NH), 6.8 (m, 1H, Ar), 7.1 (d, 1H, Ar), 7.18 (m, 2H, Ar, pyr), 7.3 (d, 1H, pyr), 7.64 (m, 1H, pyr), 8.55 (d, 1H, pyr). Anal. ($C_{21}H_{25}N_3O$) C, H, N.

2-[(2-Cyclohexyl-1-phenylethyl)amino]-5-benzoxazolecarboxylic Acid Ethyl Ester (47). This compound was prepared by method C in 66% yield, mp 129–132 °C. NMR ($CDCl_3$): δ 8.0 (s, 1H, Ar), 7.8 (d, 1H, Ar), 7.3 (m, 6H, Ar), 6.75 (d br, 1H, NH), 5.0 (m, 1H, CH) 2.0–0.85 (m, 13H, CH_2, cyclohexyl). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

2-[(2-Cyclohexyl-1-phenylethyl)amino]-5-benzoxazolecarboxylic Acid (48). A mixture of 1.8 g of **47** (4.6 mmol), 20 mL of 2 N NaOH, and 30 mL of EtOH was refluxed for 2.5 h. The solvent was then removed in vacuo and the residue treated with water and 2 N HCl giving a white suspension. After stirring for 2h, the product was filtered, rinsed with water, and recrystallized from MeOH giving 1.15 g of **48** (69%), mp 232–234 °C. ^1H NMR (DMSO): δ 12.75 (s, 1H, CO_2H), 8.7 (d, 1H, NH), 7.7 (m, 2H, Ar), 7.4 (m, 6H, Ar), 4.9 (m, 1H, CH), 1.9–0.8 (m, 13H, CH_2, cyclohexyl). Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

2-[(2-Cyclohexyl-1-phenylethyl)amino]-*N,N*-dimethyl-5-benzoxazolecarboxamide (48). A solution of 1.6 g (4.4 mmol) of **48** in 10 mL of DMF was cooled on an ice bath. CDI (1.22 g, 7.5 mmol) was added in portions, and the reaction mixture was stirred an additional 20 min. Dimethylamine was bubbled through the reaction for 15 min. After stirring an additional 30 min, the reaction mixture was poured into 50 mL of ice water. The precipitated product was filtered, washed with H_2O, dried, and boiled with EtOAc and a trace of EtOH. The product was filtered and dried giving 1.13 g of **49** (66%), mp 194–196 °C. ^1H NMR ($CDCl_3$): δ 7.3 (m, 7H, Ar), 7.05 (d, 1H, Ar), 6.65 (d br, 1H, NH), 4.95 (m, 1H, CH), 3.0 (d, 6H, N, CH_3), 1.9–0.8 (m, 13H, CH_2, cyclohexyl). Anal. ($C_{24}H_{29}N_3O_2$) C, H, N.

2-[(2-Cyclohexyl-1-phenylethyl)amino]-5-benzoxazolecarboxamide (50). This was prepared by the same method as **49**, using ammonia instead of dimethylamine (49%), mp 181–183 °C. ^1H NMR ($CDCl_3$): δ 8.6 (d, 1H, NH), 7.9–7.0 (m, 10H, Ar, NH_2), 4.85 (m, 1H, CH), 1.9–0.8 (m, 13H, CH_2, cyclohexyl). Anal. ($C_{22}H_{25}N_3O_2$) C, H, N.

2-[(2-Cyclohexyl-1-phenylethyl)amino]-5-benzoxazolenitrile (51). A solution of 1.27 g of **50** (3.5 mmol) and 1.1 mL of Et_3N (7.7 mmol) was cooled to 5 °C, and 0.54 mL (3.85 mmol) of trifluoroacetic anhydride was added over 5 min. The reaction mixture was stirred at room temperature for 2 h, the reaction quenched with H_2O, the mixture concentrated, and the product taken up in EtOAc. After being washed with 1 N HCl, saturated Na_2CO_3 solution, and brine, the solution was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2. After titration with hexane, 820 mg (68%) of **51** was obtained as a white solid, mp 166–168 °C. ^1H NMR ($CDCl_3$): δ 7.35 (m, 8H, Ar), 6.7 (d br, 1H, NH), 5.0 (m, 1H, CH), 2.0–0.8 (m, 13H, CH_2, cyclohexyl). Anal. ($C_{22}H_{23}N_3O$) C, H, N.

***N*-(2-Cyclohexyl-1-phenylethyl)-5-(hydroxymethyl)benzoxazolamine (52).** A solution of 785 mg **47** (2 mmol) in 10 mL of THF was added dropwise to a suspension of 0.17 g (4.5 mmol) of $LiAlH_4$ in 10 mL of THF. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 3 h. The reaction mixture was cooled, and excess $LiAlH_4$ and Li salts were decomposed with a few drops of EtOH followed by THF–H_2O. The reaction mixture was filtered and the filtrate diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The product was stirred with petroleum ether and then filtered and dried giving 250 mg of **52** (34%), mp 187–189 °C. ^1H NMR (DMSO): δ 8.45 (d, 1H, Ar), 7.3 (m, 6H, Ar), 6.9 (d, 1H, Ar), 5.1 (t, 1H, OH), 4.85 (m, 1H, CH), 4.45 (d, 2H, CH_2), 1.9–0.85 (m, 13H, CH_2 cyclohexyl). Anal. ($C_{22}H_{26}N_2O_2$) C, H, N.

5-Acetamido-*N*-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-2-benzoxazolamine (53). A solution of 1.75 g (4.79 mmol) of 5-nitro-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-2-benzoxazolamine in 17.5 mL of absolute EtOH with 200 mg of 10% Pd/C was hydrogenated on a Parr shaker overnight. The catalyst was filtered off with the aid of Celite. The filtrate was concentrated, and the residue was dissolved in ether and extracted with 2 N HCl. The acidic aqueous phase was washed with ether after which the pH was adjusted to 8 by the addition of saturated $NaHCO_3$. This aqueous phase was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated to give a residue which was crystallized from EtOH/petroleum ether to afford 928 mg (58%) of 5-amino-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-2-benzoxazolamine, mp 181–184 °C dec. ^1H NMR ($CDCl_3$): δ 0.97–1.8 (m, 13H, aliph), 3.6 (br, 2H, NH_2), 4.95 (m, 1H, CH), 6.35 (dd, 1H, Ar), 6.65 (d, 1H, Ar), 6.97 (d, 1H, Ar), 7.25–7.32 (m, 5H, Ph).

To a solution of 200 mg (0.6 mmol) of 5-amino-*N*-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-2-benzoxazolamine and 66 mg (0.66 mmol) of Et_3N in 2 mL of DMF at 0 °C was added 52 mg (0.66 mmol) of acetyl chloride. After stirring at 0 °C for 1 h followed by 2 h at room temperature, the reaction mixture was diluted with EtOAc, washed with 2 N HCl, saturated $NaHCO_3$, and brine. The EtOAc phase was dried (Na_2SO_4) and concentrated to give 240 mg of a brown oil. Preparative TLC on silica gel in 5% MeOH/CH_2Cl_2 (2×) gave 190 mg of solid. Upon recrystallization from EtOH/petroleum, 135 mg (60%) of **53** was obtained, mp 145–147 °C. ^1H NMR (DMSO-d_6): δ 0.9–1.8 (m, 13H, aliph), 2.0 (s, 3H, CH_3), 4.82 (m, 1H, CH), 7.1–7.5 (m, 7H, Ar), 8.45 (d, 1H, NH), 9.85 (s, 1H, NHCO). Anal. ($C_{23}H_{27}N_3O_2$) C, H, N.

***N*-[2-Cyclohexyl-1-(2-pyridinyl)ethyl]-5-methanesulfonamidobenzoxazolamine (54).** To a solution of 200 mg (0.6 mmol) of 5-amino-*N*-[2-cyclohexyl-1-(2-pyridinyl)ethyl]-2-benzoxazolamine in 2 mL of DMF and 66 mg (0.66 mmol) of Et_3N at 0 °C was added 75 mg (0.66 mmol) of methane sulfonyl chloride. After stirring at 0 °C for 1 h followed by 2 h at room temperature, the reaction mixture was diluted with EtOAc. The EtOAc solution was washed with 2 N HCl, saturated $NaHCO_3$, and brine. The EtOAc phase was dried and concentrated to give 270 mg of brown solid. Preparative TLC on silica gel with 5% MeOH/CH_2Cl_2 gave 180 mg of solid. Recrystallization from EtOH/petroleum ether provided 166 mg (68% yield) of white crystalline product, mp 188–190 °C. ^1H NMR (DMSO-d_6): δ 0.9–1.8 (m, 13H, aliph), 2.87 (s, 3H, CH_3), 4.85 (m, 1H, CH), 6.8 (d, 1H, Ar), 7.06 (d, 1H, Ar), 7.2–7.38 (m, 6H, Ar), 8.57 (d, 1H, NH), 9.46 (s, 1H, $NHSO_2$). Anal. ($C_{22}H_{27}N_3O_3S$) C, H, N, S.

Method F. (*R*)-5-Isopropyl-*N*-[1-phenyl-2-(*N*-piperidinyl)ethyl]-2-benzoxazolamine Dihydrochloride (68a). To a suspension of 9.55 g (69.6 mmol) of (*R*)-(−)-2-phenylglycinol in 50 mL of CH_2Cl_2 at 0 °C was added 19.2 mL (18.23 g, 83.5 mmmol) of di-*tert*-butyl dicarbonate under anhydrous conditions. The reaction mixture was removed from the ice bath and stirred for 2 h at room temperature. The reaction mixture was then concentrated, and the residue was treated with ether giving a white crystalline product which was filtered to afford a 13-g first crop and a 1.9-g second crop. A total of 14.8 g (90% yield) of (*R*)-(−)-*N*-(*tert*-butoxycarbonyl)-2-phenylglycinol was collected as a white crystalline solid, mp 135–138 °C. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 2.4 (br, 1H, OH), 3.83 (t, 2H, CH_2), 4.78 (m, 1H, CH), 5.3 (br, 1H, NH), 7.27 (m, 5H, Ar).

Methanesulfonyl chloride (4.78 g, 41.7 mmol) was added dropwise to a solution of 9.0 g (37.9 mmol) of (*R*)-(−)-*N*-(*tert*-butoxycarbonyl)-2-phenylglycinol and 5.8 mL (4.22 g, 41.7 mmol) of Et_3N in 90 mL of CH_2Cl_2 at −10 °C under anhydrous conditions. After 1.5 h at 0 °C, the reaction was quenched with ice–H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with dilute HCl, dilute Na_2CO_3, and brine and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to afford 11.8 g of a white solid. The solid was recrystallized from CH_2Cl_2/petroleum ether to give 11.47 g (96%) of the mesylate as a white crystalline solid (96% yield), mp 112–114 °C. ^1H NMR ($CDCl_3$): δ 1.4 (s, 9H, tBu), 2.89 (s, 3H, CH_3SO_3), 4.41 (m, 2H, CH_2OSO_2), 5.0 (m, 1H, CH), 5.2 (br, 2H, NH), 7.3 (m, 5H, Ar).

A solution of 2.0 g (6.34 mmol) of the above mesylate and 2.7 g (31.7 mmol) of piperidine in 20 mL of freshly distilled THF was refluxed under argon for 5 h. The piperidinium sulfonate salt was precipitated by the addition of ether and removed by filtration. The filtrate was concentrated to give 1.9 g of oil. Flash column chromatography of the oil on silica gel and elution with 5% acetone in petroleum ether afforded 960 mg (50%) of (*R*)-*N*-(*tert*-butoxycarbonyl)-1-phenyl-2-piperidinylethylamine as a white crystalline solid, mp 83–84 °C. ^{1}H NMR ($CDCl_3$): δ 1.4 (m, 9H, tBu), 1.6 (m, 6H, 3 CH_2), 2.28 (m, 2H, CH_2N), 2.5 (m, 4H, CH_2NCH_2), 4.6 (m, 1H, CH), 5.5 (br, 1H, NH), 7.3 (m, 5H, Ar).

A solution of 940 mg (3.09 mmol) of the protected amine obtained above was stirred in 2 mL of TFA and 2 mL of CH_2Cl_2 at room temperature for 1.5 h under anhydrous conditions. The reaction was quenched with H_2O, and the pH was adjusted to 8 by the addition of saturated Na_2CO_3. The aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 600 mg (95%) of (*R*)-(−)-1-phenyl-2-piperidinylethylamine as a yellow oil. Without further purification, this oily product was used directly in the following reaction. ^{1}H NMR ($CDCl_3$): δ 1.4–1.6 (m, 6H, CH_2), 1.9 (s, 2H, NH_2), 2.3 (m, 4H, 2 CH_2N), 2.55 (m, 2H, CH_2N), 4.1 (dd, 1H, CH), 7.3 (m, 5H, Ar).

To a solution of 600 mg (2.94 mmol) of (*R*)-(−)-1-phenyl-2-piperidinylethylamine in 3 mL of DMSO was added 130 mg (3.23 mmol) of powdered NaOH. After 10 min of stirring, 690 mg (3.52 mmol) of 2-chloro-5-isopropylbenzoxazole was added. The resulting mixture was stirred at 60 °C for 3 h. The reaction was quenched with H_2O after cooling. The aqueous phase was extracted with EtOAc. The combined EtOAc extracts were extracted with 2 N HCl. The combined HCl extracts were washed with EtOAc and then treated with 2 N NaOH to adjust the pH to 8–9. The alkaline aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to give 540 mg of an oily residue. Flash column chromatography on silica gel, eluting with 1% MeOH in CH_2Cl_2, provided 460 mg (46%) of oil. The oil was treated with ethereal HCl to give a precipitate which was recrystallized from CH_2Cl_2/ether to afford 500 mg of **68a** (37%) as a white crystalline solid after drying in a vacuum at 50 °C overnight, mp 180 °C dec. ^{1}H NMR for the free base: δ 1.2 (d, 6H, 2 CH_3), 1.5–1.7 (m, 6H, 3 CH_2), 2.5–3.0 (m, 7H, CH of iPr, 3 CH_2N), 5.0 (dd, 1H, CH), 6.8–7.4 (m, 9H, Ar, NH). Anal. ($C_{23}H_{29}N_3O\cdot 2HCl\cdot H_2O$) C, H, N.

The preparation of **68b** (mp 185 °C dec) was carried out by following the same scheme and procedures, starting with (*S*)-(+)-phenylglycinol. The NMR spectrum was identical to that of **68a**.

Method G. 5-Chloro-*N*-[1-phenyl-2-(*S*,*S*-dioxo-*N*-thiomorpholino)ethyl]benzoxazolamine (71). To a 0 °C solution of the HCl salt of thiomorpholine (4.72 g, 34 mmol) in 40 mL of AcOH was added 30% H_2O_2 (14 mL). After the addition was complete, the reaction mixture was warmed to 100 °C and stirred overnight. The mixture was concentrated under reduced pressure and then recrystallized from EtOH to afford the thiomorpholinedioxide (3.4 g, 40%), mp 250 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.32 (d, 4H), 3.25 (d, 4H).

To a solution of the above thiomorpholinedioxide (0.40 g, 3.0 mmol) in 15 mL of toluene were added iPr_2NEt (0.34 g, 3.0 mmol) and α-chloroacetophenone (0.46 g, 3.0 mmol). The mixture was refluxed for 6 h and cooled and then eluted through a silica gel column with EtOAc:hexane (2:1) to obtain pure α-(*S*,*S*-dioxothiomorpholino)acetophenone (326.0 mg, 43%) as a white solid, a portion of which was taken on to the next reaction. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 2H, ArH), 7.58–7.65 (m, 1H, ArH), 7.50 (t, 2H, ArH), 4.05 (s, 2H, CH_2CO), 3.13 (br q, 8H, CH_2).

To a solution of α-(*S*,*S*-dioxothiomorpholino)acetophenone (248 mg, 0.98 mmol) in MeOH (10 mL) and a few drops of $CHCl_3$ was added NH_4OAc (85.0 mg, 11.0 mmol) followed by a solution of $NaCNBH_3$ (200 mg, 3.2 mmol) in MeOH (1 mL). After the mixture was stirred for 2 days at room temperature, the reaction was quenched with concentrated HCl and the mixture basified with KOH (s) and diluted with H_2O and then extracted with $CHCl_3$ (5 × 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated and then eluted through a silica column with 10% MeOH–CH_2Cl_2 to yield 1-phenyl-2-(*S*,*S*-dioxothiomorpholino)ethylamine, 115 mg (46%). ^{1}H NMR ($CDCl_3$): δ 7.30–7.41 (m, 5H, ArH), 4.20 (dd, 1H, CH), 2.90–3.21 (m, 8H), 2.55–2.72 (m, 2H), 2.0 (br s, 2H, NH_2).

A mixture of 2,5-dichlorobenzoxazole (44 mg, 0.23 mmol), 1-phenyl-2-(*S*,*S*-dioxothiomorpholino)ethylamine (60 mg, 0.24 mmol), and iPr_2NEt (37 mg, 0.29 mmol) in 3 mL of dichloroethane was heated to reflux and stirred overnight. After cooling to room temperature, the mixture was concentrated, taken up in a small amount of CH_2Cl_2, and eluted through a silica gel column with EtOAc:hexane (3:2) to obtain an oil, which was triturated with Et_2O and dissolved in EtOAc and then precipitated with hexanes. Filtration and recrystallization from EtOAc afforded 44 mg (47%) of 71, mp 189–191 °C. ^{1}H NMR ($CDCl_3$): δ 7.26–7.42 (m, 6H, ArH), 7.21 (d, 1H, ArH), 7.0 (dd, 1H, ArH), 5.78 (d, 1H, NH), 4.98 (q, 1H, CH), 2.83–3.23 (m, 10H, CH_2). Anal. ($C_{19}H_{20}ClN_3O_3S$) C, H, N.

Chiral HPLC Separation of 26a. (−)- and (+)-*N*-(2-Cyclohexyl-1-phenylethyl)-2-benzoxazolamine (26b,c). An 80-mg sample of **26a** was dissolved in 20 mL of mobile phase (hexane:iPrOH:Et_2NH, 990:10:1). Multiple injections of up to 5 mL on a semipreparative Chiralcel OG (Daicel) column (25 cm × 20 mm) were made at ambient temperature, with a flow rate of 9.0 mL/min. The detector was set at 280 nM. The first fraction, (+)-**26c**, had a retention time of 11.7 min and was isolated in >99% purity (37 mg). The second fraction, (−)-**26b**, had a retention time of 14.87 min and was isolated in 99% purity (37 mg).

Chiral HPLC Separation of 58a. (−)- and (+)-5-Chloro-*N*-[2-(4-fluorophenyl)-1-(2-pyridyl)ethyl]-2-benzoxazolamine (58b,c). A 10-mg sample of **58a** was dissolved in 5 mL of mobile phase (hexane:iPrOH:Et_2NH, 990:10:1). Multiple injections of up to 100 μL on an analytical Chiralcel OD (Daicel) column (25 cm × 4.6 mm) were made at ambient temperature, with a flow rate of 1.0 mL/min. The detector was set at 254 nM. The first fraction, (−)-**58b**, eluted at 22.35 min, while (+)-**58c** eluted at 29.78 min. A total of 3.8 and 3.0 mg, respectively, was isolated, both >99% pure.

Biological Methods. Inhibition of LTB_4 Biosynthesis in Human PMNs. Human polymorphonuclear leukocytes were obtained from the heparinized blood of healthy, medication-free donors by dextran sedimentation and Ficoll–Paque separation.[32] Compound solutions were prepared from DMSO stock solutions and diluted into Dulbecco's phosphate-buffered saline without Ca^{2+} and Mg^{2+}, by a robotic sample processor (Tecan/RSP 505).[33] Buffer solutions of compound and cells (2.5×10^6 cells/mL in Dulbecco's PBS with Ca^{2+} and Mg^{2+}) were incubated at 28 °C for 15 min with shaking prior to the addition of calcium ionophore A23187 (2.5 μM final concentration). After 10 min, the reaction was terminated by adding EGTA (10 mM final concentration), the solution centrifuged (300*g*, 7 min, 10 °C), and the supernatant analyzed for LTB_4 by commercially available RIA reagents (Advanced Magnetics, Cambridge, MA, and New England Nuclear, Boston, MA).

Acknowledgment. We acknowledge Tracy Saboe and Scot Campbell for NMR support in structure determination, Regina Mucci for technical assistance in in vitro screening, and Edward Graham and Tapon Roy for statistical analysis.

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