A Novel Series of [2-[Methyl(2-phenethyl)amino]-2-oxoethyl]benzene-Containing Leukotriene B_4 Antagonists: Initial Structure−Activity Relationships

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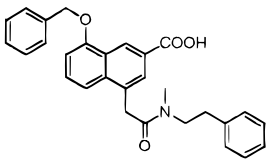
Received September 25, 1995⊗

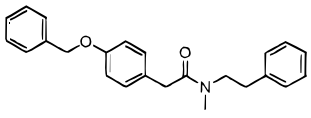
This report describes the synthesis of a new class of LTB_4 receptor antagonists containing [2-[methyl(2-phenethyl)amino]-2-oxoethyl]benzene as a key binding domain for interaction with high-affinity LTB_4 receptors. In addition to this binding domain, two other structural features, an acid function and a lipophilic group, are also required by these compounds for high binding affinity. Our studies indicate that maximal binding affinity in this series is controlled by the spatial relationship of these groups relative to one another. The structure−activity relationships are discussed. The most potent compound in this chemical series, (*E*)-5-[2-[methyl(2-phenethyl)-amino]-2-oxoethyl]-2-(benzyloxy)cinnamic acid (**32**), has an IC_{50} of 2 nM in a guinea pig spleen cell membrane assay. In the whole-cell human neutrophils binding assay, (*Z*)-5-[2-[methyl-(2-phenethyl)amino]-2-oxoethyl]-2-(benzyloxy)cinnamic acid (**30**) was the most potent compound with an IC_{50} of 50 nM.

Introduction

Leukotriene B_4 (LTB_4), a product of the 5-lipoxygenase pathway of arachidonic acid metabolism, is a potent chemotactic factor for neutrophils and has been postulated to play an important role in a variety of pathological conditions.[1] The search for potent and selective LTB_4 antagonists thus represents a novel approach to inflammatory diseases. During the last several years, a number of LTB_4 antagonists with different structural types have been reported.[2] Recently, we reported that RG 14893 is a potent LTB_4 receptor antagonist with oral activity.[3] The synthesis of this compound evolved from our initial observation that a simple phenylacetamide derivative **2** displayed moderate competitive antagonist activity with an IC_{50} of 4.7 μM in a broken-cell human polymorphonuclear leukocyte (PMN) LTB_4 binding assay. This unexpected activity led us to speculate that **2** had unusual structural features which could contribute to the binding affinity to the LTB_4 receptor. Such an interpretation prompted our research efforts in this area, which eventually led to the development of a series of [2-[methyl(2-phenethyl)amino]-2-oxoethyl]aryl-containing compounds as new, high affinity leukotriene B_4 receptor antagonists.



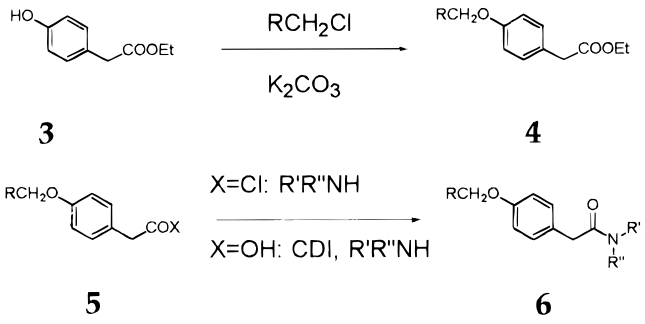
1



2

We report herein the initial structure−activity relationship studies that led to the characterization of 2-[methyl(2-phenethyl)amino]-2-oxoethyl group as a critical pharmacophore responsible for the LTB_4 receptor binding activity. Additional structural features required for enhanced binding affinity are also discussed.

Scheme 1



Chemistry

Most of the compounds listed in Tables 1−3 are synthesized according to Scheme 1−5. The formation of phenolic ether linkages were usually accomplished by reacting phenol derivatives with the appropriate halo compounds in the presence of K_2CO_3 in acetone or DMF. The amide bond was formed either by reacting the appropriate acid chloride with amines or by coupling the carboxylic acids with appropriate amines using 1,1′-carbonyldiimidazole (CDI).

The synthesis of the biphenyl compounds **16** is illustrated in Schemes 1 and 2. The Suzuki coupling reaction[4] of methyl 2-bromo-5-methoxybenzoate (**7**) with phenylboronic acid gave **8**. After demethylation of **8** with HBr in acetic acid, the resulting phenol **9** was converted to the triflate **11**. Palladium-catalyzed vinylation of **11** with vinyltrimethyltin[5] gave **12**. Hydroboration of **12** with 9-BBN followed by oxidation of **13** with Jones reagent provided **14**, which upon coupling with *N*-methylphenethylamine followed by base hydrolysis gave **16**.

A variation of the synthesis described above was used for the synthesis of **22a** (Scheme 3). Reduction of the ester **12** with DIBAL-H gave the corresponding benzyl

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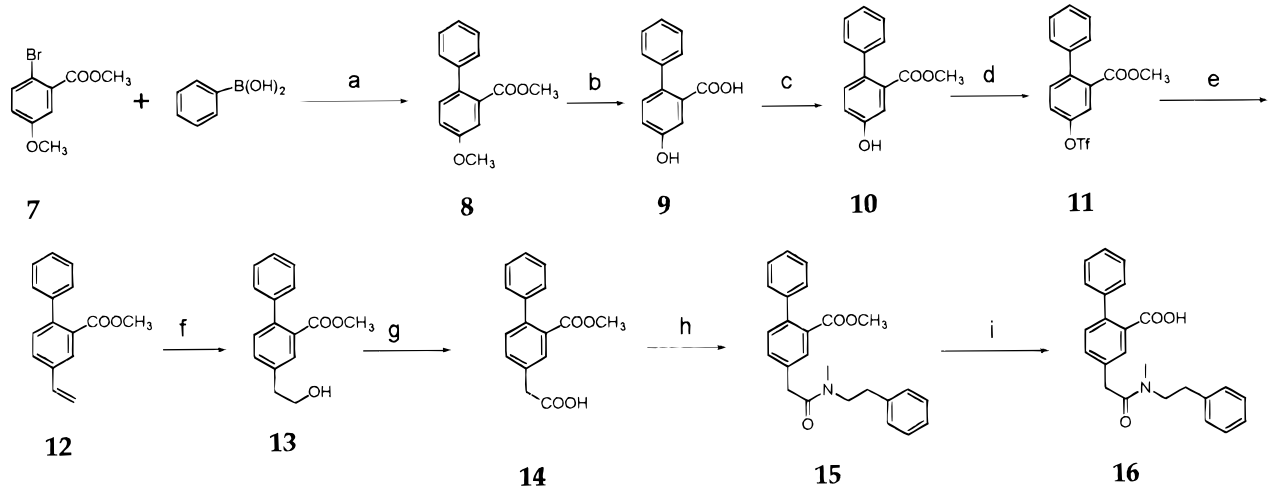
⊗ Abstract published in *Advance ACS Abstracts,* August 15, 1996.

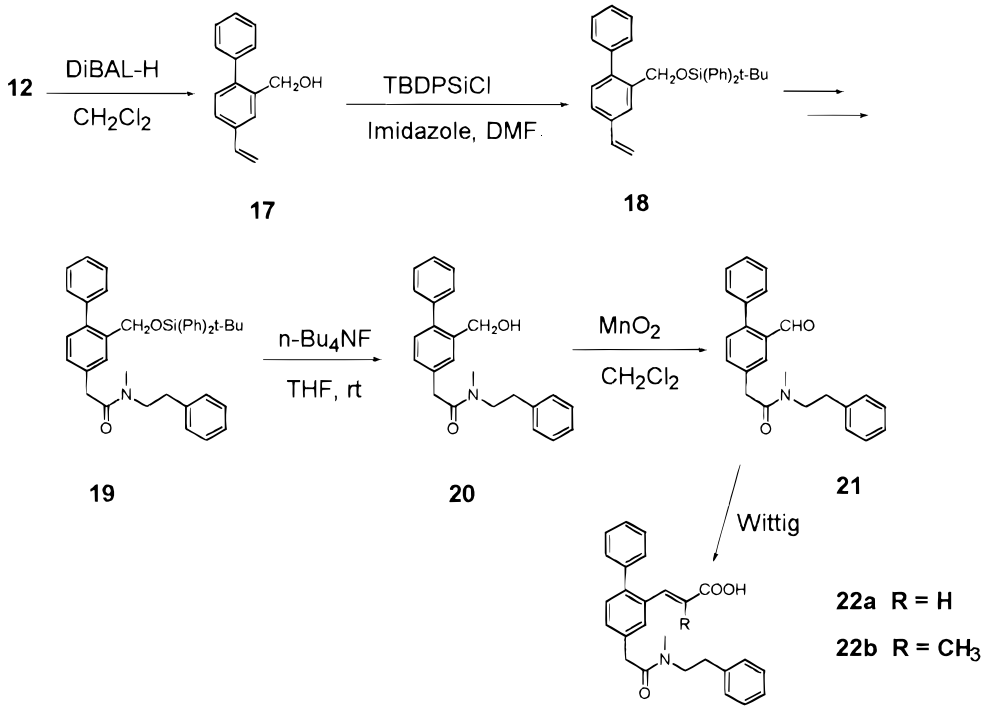
S0022-2623(95)00698-4 CCC: $12.00

Scheme 2[a]



[a] Reagents: (a) K_2CO_3, MeOH:H_2O, toluene, 80 °C, 94%; (b) HBr:AcOH, 118 °C, 60%; (c) HCl:MeOH, room temperature, 81%; (d) Tf_2O, Py, CH_2Cl_2, 90%; (e) $H_2C{=}CHSn(Me)_3$, $PdCl_2(Ph_3P)_2$, LiCl, DMF, room temperature, 96%; (f) (1) 9-BBN, THF; (2) H_2O_2, NaOH, 93%; (g) Jones reagent, acetone, O °C; (h) CDI, amine, CH_2Cl_2, room temperature; (i) LiOH, MeOH:H_2O:T.

Scheme 3



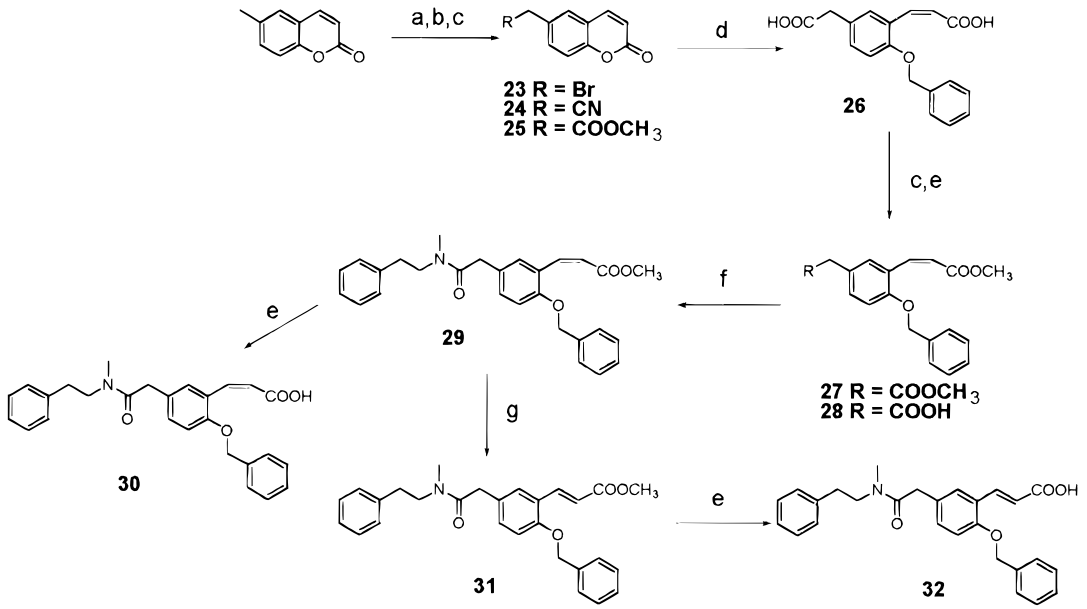
alcohol **17**. The silyl ether derivative **18** was then converted to **19** through a sequence of reactions analogous to the conversion of **12** to **15**. After oxidation of the deprotected alcohol **20** to **21**, the aldehyde was then converted to the target compounds **22a** and **22b** by the Wittig reactions.

The synthesis of **30** and **32** is shown in Scheme 4. The key intermediate **28** was prepared from 6-methylcoumarin through a series of reactions. Displacement of the bromide **23**, derived by NBS bromination of 6-methylcoumarin, with NaCN in DMSO gave **24**. Acid hydrolysis of **24** afforded **25**. This was followed by ring opening of **25** with base, alkylation with benzylbromide, and esterification to give the diester **27**. Selective hydrolysis of **27** gave **28**, which was then converted to the amide **29** in the usual manner. The conversion of the (*Z*)-isomer **29** to the (*E*)-isomer **31** was affected by catalytic amount of iodine. Finally, base hydrolysis of **29** and **31** gave **30** and **32**, respectively. The stereochemistry of these compounds was confirmed by NMR.

Starting from methyl 2-(benzyloxy)-5-bromobenzoate, **33** was synthesized through a sequence of reactions analogous to those for the conversion of **11** to **15**. Compound **34** was synthesized from 3,5-bis(benzyloxy)-phenylacetic acid through a sequence of reactions involving (1) amide formation using CDI, (2) selective debenzylation using BBr_3, (3) alkylation with ethyl bromoacetate, and (4) base hydrolysis.

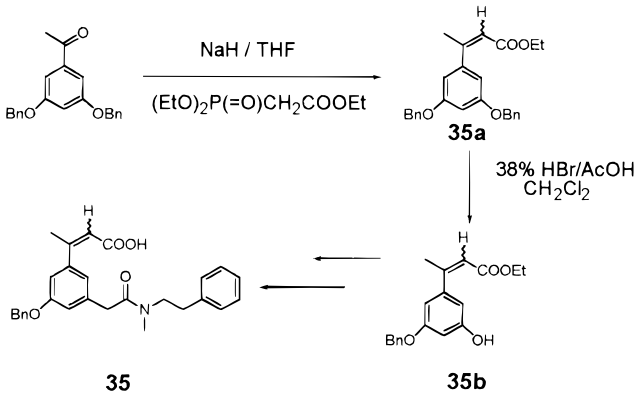
The synthesis of **35** is shown in Scheme 5. The Wittig−Horner reaction of 3′,5′-bis(benzyloxy)acetophenone with triethyl phosphonoacetate gave **35a**. Selective cleavage of **35a** with HBr/AcOH followed by chromatographic purification gave the monobenzylated derivative **35b**. The conversion of **35b** to **35** was accomplished through a sequence of reactions similar to those for the conversion of **10** to **15**.

Scheme 4[a]



[a] Reagents: (a) NBS, CCl_4, reflux/4.5 h; (b) NaCN:DMSO, room temperature, 2 h; (c) HCl:MeOH; (d) NaOH, EtOH, reflux, 12 h, then BnBr, reflux, 3 h; (e) LiOH, MeOH:THF:H_2O; (f) CDI, CH_2Cl_2, *N*-methylphenethylamine; (g) I_2, $CHCl_3$.

Scheme 5



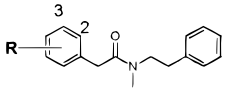
Results and Discussion

The LTB_4 receptor binding data obtained from the radioligand binding assay using guinea pig (GP) spleen cell membrane[6] are summarized in Tables 1−3. Most of these compounds were tested at 30 nM vs 0.5 nM [^{3}H]-LTB_4, and IC_{50} values were determined for the more potent compounds. A few selected compounds were also tested on intact human neutrophils.[7] Lead compound **2** exhibited IC_{50} values of 66 and 900 nM, respectively, in the GP spleen cell membrane and intact human PMN binding assay.

In order to characterize the structural features that were responsible for antagonist activity, we independently modified the benzyloxy and the acetamide groups of **2**. Initially, studies was focused on the effect of replacing the benzyloxy group with other lipophilic groups while the amide group was kept intact. As shown in Table 1, a number of such modifications offered no advantage over **2**. The 3-benzyloxy isomer **2a** was also about 4-fold less potent than **2** in the GP spleen binding assay.

Subsequent efforts were directed toward examining the effect on the binding affinity of modifying the amide group while the benzyloxy group was kept intact. Surprisingly, none of these modifications proved productive (Table 2). Replacing the phenyl ring of the *N*-phenethyl group with a pyridine (**2h**) or an indole (**2i**) ring led to compounds with lower affinity. The conformationally more restricted analog **2j** exhibited no activity at 30 nM. When the linkage between the center phenyl ring and the amide functionality was changed from methylene to ethylene (**2l**) and ethenylene (**2m**), the resulting compounds were also less active. A similar outcome resulted when the *N*-phenethyl group was changed to a *N*-benzyl group (**2k**). These results clearly indicate that the 2-[methyl(2-phenethyl)amino]-2-oxoethyl group is the key binding domain of the LTB_4 receptor for this class of compounds.

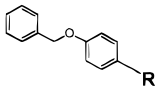
Table 1. Effect of Variation of the Lipophilic Group on Binding Affinity

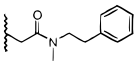
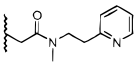
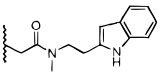
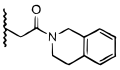
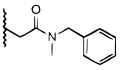
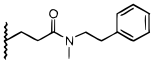
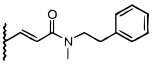
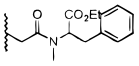
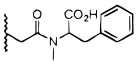
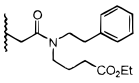
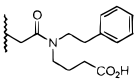


compd	R	IC_{50} (nM) or % I (nM)[a] GP spleen
2	4-BnO-[b]	65.6±6.8 (5)
2a	3-BnO-	225 ± 38 (2)
2b	4-(Quinolinyl-2-methoxy)	24 % (30 nM)
2c	4- 	12 % (30 nM)
2d	4-(4-BnO-)BnO-	9 % (30 nM)
2e	3-(Naphthyl-2-methoxy)	24 % (30 nM)
2f	3-CH_2COOH	39 % (30 nM)
2g	4-BnO-3-F-	37 % (30 nM)

[a] Radioligand binding assay on guinea pig spleen membranes or human PMN whole cells. Compounds were tested at multiple concentrations for competition with 0.2 nM [^{3}H]LTB_4. Values are means ± SEM of (*N*) separate experiments or percent inhibition at indicated concentration. [b] BnO = benzyloxy.

Table 2. Variation of Different Amide Groups



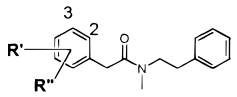
compd	R	IC_{50} (nM) or % I (nM)[a] GP spleen
2		65.6±6.8 (5)
2h		13 % (30 nM)
2i		0 % (30 nM)
2j		0 % (30 nM)
2k		13 % (30 nM)
2l		0 % (30 nM)
2m		2 % (30 nM)
2n		0 % (30 nM)
2o		0 % (30 nM)
2p		20 % (30 nM)
2q		20 % (30 nM)

[a] See Table 1.

With the key structural feature for antagonistic activity characterized, the task became how to improve overall binding affinity. Since the chemical structure of the LTB_4 molecule includes a carboxylic acid group, it is conceivable that the addition of such a group to **2** would be beneficial. As shown in Table 3, such modifications indeed improved the binding affinity although the location of the acid function seemed to be important. For example, the addition of a carboxylic acid group at the meta position to the amide group of **2** (compound **33,** IC_{50} = 15 nM) enhanced the binding affinity 4-fold. In contrast, the addition of a carboxylic acid functionality at another part of the molecule, such as **2o** and **2q** (Table 2), adversely affected the biological activity.

The substitution pattern of the groups on the phenyl ring seem to play an important role in determining biological activity. The results in Table 3 show that compounds with 1,3,4-substitution pattern (**30**, **32**, and **33**) exhibited higher binding affinity than those with 1,2,5- (**37**) or 1,3,5-patterns (**34**−**36**). The relative

Table 3. Disubstituted Phenylacetamide Derivatives



compd	R′ and R″	IC50 (nM) or % *I* (concn, nM)[a] GP spleen	Hu PMN
1		0.36 ± 0.03 (25)	4.7 ± 0.8 (5)
2	4-BnO	66	900
33	3-COOH 4-BnO	15	NT[b]
32	3-(*E*)-CH=CHCOOH 4-BnO	2.27 ± 0.5 (3)	27 (300)
30	3-(*Z*)-CH=CHCOOH	5.3 ± 1.2 (2)	50
34	3-OCH_2COOH 5-OBn	53.3 ± 9.5 (4)	NT
35	3-$C(CH_3)$=CHCOOH 5-OBn	143 ± 24 (4)	29 (300)
36	3-CH_2COOH 5-OBn	200 ± 71 (2)	NT
37	2-COOH 5-OBn	250 ± 35 (2)	28 (300)
38	3-CH_2COOH 5-OCH_2CH=CHPh	1200 ± 375 (2)	16 (300)
15	3-COOMe 4-Ph	37 (300)	0 (300)
16	3-COOH 4-Ph	27.0 ± 9.2 (2)	500
20	3-CH_2OH 4-Ph	21 (30)	18 (300)
22a	3-(*E*)-CH=COOH 4-Ph	44.6 ± 11.8 (5)	200
22b	3-CH=$C(CH_3)$COOH 4-Ph	65.0 ± 3.5 (2)	NT

[a] See Table 1. [b] NT = not tested

distance between the lipophilic group and the carboxylic function also affects the binding affinity. Thus, extending the distance of the carboxylic function of **33** from the center phenyl ring with an ethylene linkage improved the IC_{50} value of **32** to 2.3 nM. However, when the benzyloxy group of **32** was replaced with a phenyl ring as in **22a**, the binding affinity was reduced by 20-fold.

Most of the compounds discussed here display differential binding affinity toward the GP spleen cell membrane and intact human PMN. Generally, these compounds exhibit lower binding affinity in the human PMN assay. Compound **32** is a typical example. It had an IC_{50} of 5 nM in the GP spleen cell assay, but exhibited an IC_{50} of 50 nM in the intact human PMN binding assay. It is also interesting to note that while both **30** and **32** displayed similar affinity toward GP spleen LTB_4 receptors, the (*Z*)-isomer **30** (IC_{50} = 50 nM) was much more potent in the human PMN assay than the (*E*)-isomer **32** (IC_{50} > 300 nM).

Previously, we reported that **1** inhibited the GP spleen membrane and intact human PMN binding resulting in IC_{50} values of 0.4 nM (vs 0.5 nM ligand) and 4.7 nM (vs 0.5 nM ligand), respectively.[3] In addition, **1** also exhibited an IC_{50} of 0.96 nM in a GP whole cell PMN binding assay and, in a functional assay, it inhibited 1 nM LTB_4-induced GP PMN aggregation with an IC_{50} of 0.8 nM. The strong correlation between the binding affinity and functional antagonistic activity demonstrated that this compound is both a receptor binder and functional antagonist. On the basis of the results that **1** displayed similar affinity toward GP spleen and GP whole cell PMN, the observed differential binding affinity for certain compounds in the GP spleen and

human PMN assays is likely due to the variability among species of the LTB_4 receptors.[8]

In summary, we have developed a new class of LTB_4 receptor binders with a 2-[methyl(2-phenethyl)amino]-2-oxoethyl group as the key binding domain of the LTB_4 receptor. In addition, the results show that this class of LTB_4 receptor binder also needs an acid function and a lipophilic group for better binding affinity. The most potent compound in this chemical series is **32**, which had an IC_{50} of 2 nM in the GP spleen cell LTB_4 binding assay. It was 30 times more potent than the original lead **2**. In the human PMN binding assay, **30**, with an IC_{50} of 50 nM, was the most potent compound. Finally, we have obtained important SAR information that prove useful for the development of more potent LTB_4 receptor antagonists.[1] In the accompanying article, we describe the SAR studies which led to the synthesis of **1** as a high affinity and also functional antagonist of LTB_4 receptors.[9]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structure. Proton NMR were recorded on a Varian EM-390 (90 MHz) or a Bruker ACF-300 (300 MHz) spectrometer.

4-(Benzyloxy)-[2-[methyl(2-indolylethyl)amino]-2-oxoethyl]benzene (2i). To a solution of 4-(benzyloxy)phenylacetyl chloride (0.43 g, 1.65 mmol) in 10 mL of CH_2Cl_2 was added dropwise a solution of *N*-methyltryptamine (0.632 g, 3.64 mmol) in 20 mL of CH_2Cl_2. After 1 h of stirring, the organic solution was washed with water and the organic solvent was dried and removed under reduced pressure. Purification of the residue by flash chromatography (1:1:1 CH_2Cl_2:EtOAc:hexane) gave 0.62 g (94.3%) of **2i**: mp 133−134 °C. Anal. ($C_{26}H_{26}N_2O_2$) C, H, N.

4-(Benzyloxy)-[2-[3-carbethoxypropyl(2-phenethyl)amino]-2-oxoethyl]benzene (2p). (a). N-(3-carbethoxypropyl)phenethylamine. To a solution of 2.8 g (23.07 mmol) of phenethylamine in 10 mL of EtOH was added dropwise 1.5 g (7.69 mmol) of ethyl 4-bromobutyrate over a period of 10 min. After the mixture was stirred overnight at room temperature and EtOH evaporated, the residue was purified by flash chromatography (10:1 CH_2Cl_2:EtOH) to give 0.79 g (43.7%) of liquid product.

(b). A solution of 0.79 g (3.34 mmol) of the amine obtained above and 0.44 g (4.34 mmol) of triethylamine in 5 mL of CH_2Cl_2 was added to a solution of 4-(benzyloxy)phenylacetyl chloride (0.88 g, 3.34 mmol) in 10 mL of CH_2Cl_2. The reaction mixture was stirred overnight at room temperature, and then the solvent was removed. The residue was extracted with Et_2O, and the organic solution was washed well with water. After the solution was dried with $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatograph (20:1:1 $CHCl_3$:Hex:EtOAc) to give 0.51 g (33.2%) of **2p** as a liquid.

4-(Benzyloxy)-[2-[(3-carbethoxypropyl)(2-phenethyl)amino]-2-oxoethyl]benzene (2p). To a solution of 0.38 g (0.83 mmol) of **2p** in 5 mL of 80% aqueous EtOH was added 0.06 g (0.91 mmol) of KOH pellet, and the reaction mixture was then stirred overnight at room temperature. Most of the ethanol was removed under reduced pressure, and the aqueous solution was extracted with Et_2O (2 × 10 mL). The aqueous solution was then acidified to pH 3 and extracted with Et_2O (2 × 10 mL). The combined ethereal solution was washed with H_2O, dried, and evaporated to dryness to give 0.22 g (30%) of oily **2q**.

Compounds **2** and **2a**−**q** were prepared according the synthesis of **2i** (acid chloride method) described above or **15** (CDI method) described below.

Methyl 4-Methoxy-2-phenylbenzoate (8). To a solution of methyl 2-bromo-4-methoxybenzoate (10.0 g, 40.8 mmol), phenylboronic acid (7.46 g, 61.2 mmol), K_2CO_3 (11.28 g, 81.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (4.71 g, 4.06 mmol) in 50 mL of dry toluene were added 40 mL of methanol and 10 mL of H_2O. After being heated at 80 °C for 24 h under argon, the reaction mixture was cooled to room temperature and poured into 200 mL of water. The aqueous layer was separated from the organic layer and then extracted three times with 100 mL of EtOAc. The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (9:1 hexane:EtOAc) to give 8.98 g (91%) of **8** as white solid: ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3 H), 3.86 (s, 3 H), 7.05−7.45 (m, 8 H).

Methyl 5-Hydroxy-2-phenylbenzoate (10). The biphenyl compound **8** (8.9 g, 36.76 mmol) in 50 mL of HBr:AcOH was heated at 118 °C for 24 h. After removal of AcOH under reduced pressure, the residue was taken up in 200 mL of EtOAc and washed with water. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. Purification by flash chromatography (1:1 EtOAc:hexane) gave 4.66 g (60%) of acid **9**. **9** was esterified with CH_3OH:HCl and then purified by flash chromatography to give 3.85 g (81%) of **10**.

Methyl 5-[[(Trifluoromethyl)sulfonyl]oxy]-2-phenylbenzoate (11). To a solution of **10** (3.85 g, 16.87 mmol) in 30 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of 5.23 g (18.55 mmol) of trifluoromethanesulfonic anhydride in 10 mL of CH_2Cl_2 over 20 min. The reaction mixture was slowly warmed to room temperature, stirred for an additional 2 h, and then poured into 100 mL of H_2O and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography (9:1 hexane:EtOAc) gave 6 g (98.7%) of **11**.

Methyl 2-Phenyl-5-vinylbenzoate (12). A mixture of **11** (2.0 g, 5.55 mmol), vinyltrimethyltin (1.94 g, 6.11 mmol, 1.79 mL), LiCl (0.71 g, 16.65 mmol), and bis(triphenylphosphine)-dichloropalladium (0.08 g, 0.11 mmol) in 20 mL of DMF was stirred at room temperature for 12 h under argon. The reaction mixture was poured into 150 mL of H_2O and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Purification by flash chromatography (9:1 hexane:EtOAc) gave 1.03 g (78%) of **12** as colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3 H), 5.33 (d, 1 H), 5.84 (d, 1 H), 6.76 (dd, 1 H), 7.29−7.85 (m, 7 H).

Methyl 5-(2-Hydroxyethyl)-2-phenylbenzoate (13). To a stirred solution of **12** (1.01 g, 4.25 mmol) in 15 mL of dry THF was added 1.14 g (4.67 mmol) of 9-BBN, and then the mixture was stirred for 12 h at room temperature. Excess 9-BBN was quenched by 1 mL of H_2O, followed by 4 mL of 1 N NaOH. The mixture was stirred for 15 min, and then 50 mL of 30% H_2O_2 was added slowly to the reaction. After 30 min, the reaction mixture was poured into 100 mL of H_2O and extracted with EtOAc (3 × 75 mL). The organic solution was dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. Purification by flash chromatography (1:1 hexane:EtOAc) gave 1.01 g (93%) of **13**: ^{1}H NMR ($CDCl_3$) δ 2.94 (t, 2 H), 3.63 (s, 3 H), 3.92 (t, 2 H), 7.28−7.70 (m, 8 H).

Methyl 5-(Carboxymethyl)-2-phenylbenzoate (14). To a solution of **13** (2.27 g, 8.86 mmol) in 50 mL of acetone at 0 °C was added Jones reagent slowly until the brown color remained. The excess reagent was quenched with 2-propanol. The reaction mixture was poured into 100 mL of H_2O and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried, filtered, and evaporated to dryness. The crude **14** thus obtained was used for the next reaction without further purification.

Methyl 5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylbenzoate (15). To a solution of **14** (2.39 g, 8.86 mmol) in 30 mL of CH_2Cl_2 was added 1.58 g (9.75 mmol) of CDI in one portion. After the mixture was stirred at room temperature for 1 h, *N*-methylphenethylamine (1.8 g, 13.29 mmol, 1.93 mL) was added, and then the mixture was stirred for 24 h. The solvent was removed, and the residue was taken up in 50 mL of EtOAc, which was washed with 100 mL of 1 N

HCl solution and 100 mL of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography to give 3.15 g of **15**: ^{1}H NMR ($CDCl_3$) δ 2.86 (m, 2 H), 2.91 (s, 3 H), 3.02 (s, 3 H), 3.42 (s, 2 H), 3.60 (m, 2 H), 3.62 (s, 3 H), 3.74 (s, 2 H), 7.15−7.70 (m, 13 H). Anal. ($C_{25}H_{25}NO_3$) C, H, N.

5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylbenzoic Acid (16). A solution of **15** (250 mg, 0.65 mmol) in 10 mL of THF:H_2O (4:1) and $LiOH\cdot H_2O$ (135.4 mg, 3.23 mmol) was stirred for 48 h. The mixture was poured into 50 mL of H_2O, acidified with aqueous HCl solution, and then extracted with EtOAc. The organic solution was dried and removed under reduced pressure. Trituation with ether gave 144 mg (59%) of **16** as white solid: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 2.84 (m, 2 H), 2.92 (s, 3 H), 3.02 (s, 3 H), 3.42 (s, 2 H), 3.61 (m, 2 H), 3.74 (s, 2 H), 7.13−7.81 (m, 13 H). Anal. ($C_{24}H_{23}NO_3\cdot 0.25H_2O$) C, H, N.

2-Phenyl-5-vinylbenzyl Alcohol (17). A solution of **12** (1.8 g, 7.55 mmol) in 15 mL of dry CH_2Cl_2 at −78 °C under argon was treated with 18.9 mL of DIBAL-H (1 M, 18.8 mmol) via syringe. The reaction mixture was stirred at −78 °C for 2 h and then slowly warmed to room temperature, and stirring was continued for 4 h. After the reaction was quenched with 1 mL of CH_3OH and 4 mL of H_2O, the mixture was stirred for 30 min then poured into 50 mL of 1 N NaOH solution. The aqueous solution was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic layers were dried over anhydrous $NaSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude **17** thus obtained was used for the next reaction without purification.

2-Phenyl-5-vinylbenzyl *tert*-Butyldiphenylsilyl Ether (18). A solution of **17** (1.59 g, 7.55 mmol), imidazole (1.29 g, 18.88 mmol), and *tert*-butyldiphenylsilyl chloride (3.11 g, 11.33 mmol) in 25 mL of DMF was stirred at room temperature for 12 h. The reaction mixture was poured into 100 mL of H_2O, and the aqueous solution was extracted with 1:1 Et_2O:hexane (3 × 60 mL). The combined organic solution were dried and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (2% Et_2O:hexane) gave 2.7 g (80%) of **18**: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 4.64 (s, 2 H), 5.27 (d, 1 H), 5.79 (d, 1 H), 6.77 (dd, 1 H), 6.72−7.67 (m, 18 H).

5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylbenzyl *tert*-Butyldiphenylsilyl Ether (19). 18 was converted to **19** through a sequence of reactions: (a) hydroboration, (b) Jones oxidation, and (c) amide formation similar to the conversion of **12** to **15** described above: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 2.85 (m, 2 H), 2.88 and 3.01 (s, 3 H), 3.62 (m, 2 H), 3.55 and 3.77 (s, 2 H), 4.79 (s, 2 H), 7.10−7.90 (m, 23 H).

5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylbenzyl Alcohol (20). To a solution of **19** (2.0 g, 5.02 mmol) in 10 mL of THF was added 5.02 mL (1.0 M, 5.02 mmol) of tetrabutylammonium fluoride solution, and then the mixture was stirred for 12 h. The reaction mixture was poured into 50 mL of H_2O and extracted with EtOAc (3 × 25 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure. Purification by flash chromatography (2:1 hexane:EtOAc) gave 1.54 g (85.6%) of **20**: ^{1}H NMR ($CDCl_3$) δ 1.07 (bs, 1 H), 2.84 (m, 2 H), 2.94 (s, 3 H), 3.01 (s, 3 H), 3.46 (s, 2 H), 3.61 (m, 2 H), 3.73 (s, 2 H), 4.57 (s, 2 H), 4.61 (s, 2 H), 7.12−7.42 (m, 8 H). Anal. ($C_{14}H_{25}NO_2\cdot 0.25H_2O$) C, H, N.

5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylbenzaldehyde (21). To a stirred solution of **20** (1.54 g, 4.28 mmol) in 20 mL of CH_2Cl_2 was added 1.86 g (21.42 mmol) of activated MnO_2, and the resulting slurry was stirred for 48 h at room temperature. The reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure to give 1.45 g (95%) of **21**, which was used without further purification.

2-Methyl-3-[5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylphenyl]propenoic Acid (22b). To a solution of 0.73 g (0.7 mL, 3.08 mmol) of triethyl 2-phosphonopropionate in 20 mL of dry THF was added 0.092 g(3.08 mmol) of 80% sodium hydride oil dispersion under argon. After the mixture was stirred at room temperature for 1 h, 1.0 g (2.8 mmol) of **21** in 10 mL of THF was added, and stirring was continued for 12 h. The reaction mixture was poured into 100 mL of 1 N HCl solution and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (2:1 hexane:EtOAc) gave 0.99 g (80%) of the ethyl ester of **22b**. ^{1}H NMR ($CDCl_3$) δ 1.24 (dt, 3 H), 1.97 (dd, 3 H), 2.82 (m, 2 H), 2.92 and 3.02 (dd, 3 H), 3.45 and 3.72 (s, 2 H), 3.61 (m, 2 H), 4.12 (dq, 2 H), 6.98−7.40 (m, 13 H), 7.52 (d, 1 H).

The ester obtained above (0.99 g, 2.24 mmol) in 10 mL of THF and 1 mL of H_2O was treated with 0.47 g (11.21 mmol) of lithium hydroxide, and the solution was stirred at room temperature for 12 h. The reaction mixture was then poured into water and acidified to pH 1 using concentrated HCl. The aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Recrystallization from Et_2O yielded 0.6 g (64%) of **22b**: mp 130−132 °C. ^{1}H NMR ($CDCl_3$) δ 1.97 (d, 3 H), 2.81 (m, 2 H), 2.89 and 3.01 (d, 3 H), 3.60 (m, 2 H), 3.46 and 3.75 (s, 2 H), 7.05−7.40 (m, 13 H), 7.61 (d, 1 H), 10.32 (bs, 1 H). Anal. ($C_{26}H_{25}NO_3$) C, H, N.

3-[5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-phenylphenyl]propenoic Acid (22a). This compound was synthesized according to the procedure described above, except triethyl phosphonoacetate was used.

6-(Bromomethyl)coumarin (23). A mixture of 6-methylcoumarin (20 g, 124.87 mmol) and NBS (22.23 g, 124.87 mmol) in 700 mL of CCl_4 was refluxed under a sun lamp for 4.5 h. After filtration, the filtrate was concentrated under reduced pressure. The residue was triturated with EtOAc, and the resulting solid was collected on a filter to yield 16.0 g (54%) of crude **23**. **23** thus obtained was used for the next reaction without further purification.

6-(Cyanomethyl)coumarin (24). A solution of **23** (8.43 g, 35.27 mmol) and NaCN (1.73 g, 35.27 mmol) in 60 mL of DMSO was stirred at room temperature for 2 h. The reaction mixture was poured into 700 mL of H_2O and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with water (2 × 150 mL) and brine (150 mL), dried, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (1:1 EtOAc:hexane) gave 2.58 g (40%) of **24** as an oil.

6-(Carbomethoxymethyl)coumarin (25). A stream of dry HCl gas was bubbled into a solution of **24** (2.58 g, 13.95 mmol) in 70 mL of CH_3OH at 0 °C for 10 min, and the reaction mixture was then stirred at room temperature for an additional 12 h. After concentration under reduced pressure, the residue was dissolved in 100 mL of EtOAc, and the solution was washed with H_2O (2 × 50 mL), and brine (1 × 50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield 2.88 g (95%) of **25**.

Methyl (*Z*)-2-(Benzyloxy)-5-(carbomethoxymethyl)cinnamate (27). A solution of **25** (2.63 g, 12.06 mmol) in 20 mL of EtOH was treated with an aqueous NaOH solution (prepared from 5.0 g, 200 mmol, of NaOH and 10 mL of H_2O). After the mixture was heated under reflux for 12 h, 2.85 mL (24 mmol) of benzyl bromide was added to the reaction mixture, and refluxing was continued for an additional 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in H_2O, washed with EtOAc (2 × 20 mL), and acidified to pH 3 with concentrated HCl. The precipitated solid (**26**), collected on a filter (2.42 g, 64% yield), was converted to the diester without further purification.

A stream of dry HCl gas was bubbled into a solution of **26** (1.82 g, 5.82 mmol) in 70 mL of MeOH for 10 min, and then the mixture was stirred at room temperature for 3 h. After concentration under reduced pressure, the residue was dissolved in 70 mL of EtOAc, and the organic solution was washed with $NaHCO_3$, H_2O, and brine, dried over anhydrous $MgSO_4$, and concentrated to yield 1.86 g (94%) of **27**.

Methyl (*Z*)-2-(Benzyloxy)-5-(carboxymethyl)cinnamate (28). A mixture of **27** (1.86 g, 5.49 mmol) and 230 mg (5.49 mmol) of $LiOH\cdot H_2O$ in 50 mL of a 1:1:1 MeOH:THF:H_2O

solution was stirred at room temperature for 12 h. After concentration *in vacuo*, the residue was taken up into water and the aqueous solution was washed with EtOAc, acidified to pH 3 with 1 N HCl, and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated to give 1.8 g (100%) of **28** as an oil. The crude acid was used without further purification.

Methyl (*Z*)-5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-(benzyloxy)cinnamate (29). To a solution of **28** (1.86 g, 5.49 mmol) in 50 mL of dry CH_2Cl_2 was added 1.02 g (6.26 mmol) of CDI in one portion under argon. The reaction mixture was stirred at room temperature for 20 min, and then *N*-methylphenethylamine (827 μL, 5.69 mmol) was added. After 8 h, the reaction mixture was diluted with EtOAc, and the organic solution was washed with 1 N HCl, 1 N NaOH, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography yielded **29** (1.35 g, 54%).

(*Z*)-5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-(benzyloxy)cinnamic Acid (30). A reaction mixture of **29** (150 mg, 0.34 mmol) and 71 mg (1.7 mmol) of $LiOH \cdot H_2O$ in 12 mL of a 1:1:1 MeOH:THF:H_2O solution was stirred at room temperature for 24 h. The reaction mixture was diluted with 50 mL of H_2O, and the aqueous solution was washed with Et_2O (2 × 20 mL) and then acidified to pH 3 with a 1 N HCl solution. The white precipitate was collected on a filter and recrystallized from EtOAc/hexane to give 100 mg (69%) of **30**: mp 48−51 °C; ^{1}H NMR ($CDCl_3$) δ 7.0−7.5 (m, 12 H), 6.86 (m, 2 H), 5.95 (m, 1 H), 5.07 (d, 2 H), 3.55 (m, 4 H), 2.75 (m, 5 H). Anal. ($C_{27}H_{27}NO_4 \cdot 0.5H_2O$) C, H, N.

Methyl (*E*)-5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-2-(benzyloxy)cinnamate (31). A solution of **28** (1.24 g, 2.81 mmol) and iodine (284 mg, 1.12 mmol) in 50 mL of $CHCl_3$ was refluxed for 12 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2, the organic solution was washed with $Na_2S_2O_3$ solution (2 × 25 mL) and brine (2 × 50 mL), dried with $MgSO_4$, and filtered, and the filtrate was concentrated *in vacuo* to yield crude **31** (1.24 g, 100% yield) as an oil.

(*E*)-5-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-2-(benzyloxy)cinnamic Acid (32). A mixture of **31** (160 mg, 0.36 mmol) and $LiOH \cdot H_2O$ (76 mg, 1.8 mmol) in 10 mL of a 1:1:1 THF:H_2O:MeOH solution was stirred at room temperature overnight. The reaction mixture was poured into 50 mL of water, and the aqueous solution was washed with Et_2O (2 × 25 mL) and then acidified to pH 3 with 1 N HCl solution. The precipitated product was collected on a filter and recrystallized from EtOAc:hexane to give 20 mg (77%) of **32**: mp 56−58 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (m, 1 H), 7.0−7.4 (m, 12 H), 6.92 (m, 1 H), 6.54 (m, 1 H), 5.16 (d, 2 H), 3.6 (m 4 H), 2.75 (m, 5 H). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

3,5-Bis(benzyloxy)-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]benzene (34a). To a stirred solution of 3,5-bis-(dibenzyloxy)phenylacetic acid (4.4 g, 12.59 mmol) in 30 mL of CH_2Cl_2 was added 2.25 g (13.85 mmol) of CDI in one portion. After the mixture was stirred at room temperature for 30 min, 1.87 g (13.85 mmol) of *N*-methylphenethylamine was added, and stirring was continued for 2 h. After concentration, the residue was partitioned between EtOAc and 1 N HCl solution. The organic layer was separated, dried, and concentrated. Purification by flash silica gel column chromatography (1:3 EtOAc:hexane) gave 4.02 g (68.6%) of product as a clear oil.

3-(Benzyloxy)-5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenol (34b). A solution of 3.72 g (7.99 mmol) of **34a** and 2.66 mL (2.66 mmol, 1 M) of BBr_3 in 50 mL of CH_2Cl_2 was stirred at room temperature for 72 h. After concentration, the reaction mixture was partitioned between EtOAc and 1 N HCl and worked up as usual. Purification by flash column chromatography (3:7 EtOAc:hexane) gave 0.8 g (27%) of **34b** as a clear oil.

Ethyl 3-(Benzyloxy)-5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenoxyacetate (34c). A mixture of 0.8 g (2.13 mmol) of **34b**, 0.36 g (2.13 mmol) of ethyl bromoacetate, and 0.29 g (2.13 mmol) of K_2CO_3 in 50 mL of acetone was refluxed for 18 h. The reaction mixture was poured into water and extracted with EtOAc (2 × 50 mL). The combined extracts were dried, concentrated, and purified by flash column chromatography (2:3 EtOAc:hexane) to give 0.86 g (87.6%) of **34c** as a colorless oil.

3-(Benzyloxy)-5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenoxyacetic Acid (34). A solution of 0.85 g (1.85 mmol) of **34c** and 2.23 mL (2,23 mmol) of 1 N NaOH in 30 mL of EtOH was stirred at room temperature for 1.5 h. The reaction mixture was poured into 50 mL of H_2O, acidified to pH 2 with 1 N HCl solution and extracted with EtOAc. The organic solution was dried and concentrated. The resulting oil was triturated with Et_2O, and the precipitate was filtered to give 0.485 g (60.2%) of **34** as a white powder: mp 112−115 °C.

Ethyl 3-[3,5-Bis(benzyloxy)phenyl]-3-methylpropenoate (35a). To a solution of 4.05 g (3.58 mL, 18.05 mmol) of triethyl phosphonoacetate in 20 mL of THF under argon was added 0.54 g (18.05 mmol) of 80% NaH in oil dispersion at room temperature. After the mixture was stirred for 1.5 h, 5.0 g (15.04 mmol) of 3′,5′-bis(benzyloxy)acetophenone was added, and the reaction mixture was stirred for an additional 72 h at room temperature. The reaction mixture was poured into water and extracted with EtOAc (3 × 50 mL). The combined extracts were dried, filtered, and concentrated to give 6.5 g of yellow oil. The crude product thus obtained was used for the next reaction without further purification.

Ethyl 3-(3-Benzyloxy-5-hydroxyphenyl)-3-methylpropenoate (35b). To a solution of 3.7 g of crude **35a** in 50 mL of CH_2Cl_2 at 0 °C was added 1.97 mL of 30% HBr in AcOH. After being stirred at 0 °C for 1 h and then for 18 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and water, and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (1:9 EtOAc:hexane) gave 0.775 g (26%) of **35b**.

3-[3-(Benzyloxy)-5-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenyl]-3-methylpropenoic Acid (35). 35b was converted to **35** as a mixture of (*E*)- and (*Z*)-isomers, according to the procedures described above for the conversion of **11**−**16**: ^{1}H NMR ($CDCl_3$) δ 2.53 and 2.55 (s, 3 H), 2.73 and 2.84 (t, 2 H), 2.87 and 3.0 (s, 3 H), 3.39 and 3.68 (s, 2 H), 3.51 and 3.61 (t, 2 H), 5.05 (d, 2 H), 6.14 (d, 2 H), 6.77−7.42 (m, 10 H).

Methyl 5-(Benzyloxy)-3-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenylacetate (36a). A mixture of 2.32 g (7.73 mmol) of 5-(benzyloxy)-1,3-phenylenediacetic acid and 2.65 g (16.34 mmol) of CDI in 20 mL of CH_2Cl_2 was stirred at room temperature for 20 min, and then *N*-methylphenethylamine (1.12 mL, 7.73 mmol) was added. After the mixture was stirred for an additional 12 h, 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) and MeOH (0.31 mL, 7.73 mmol) were added to the reaction mixture, and stirring was continued for another 3 h. The reaction mixture was concentrated, the residue was dissolved in 70 mL of EtOAc, and the organic solution was washed with H_2O and 1 N HCl solution, dried, and then evaporated to dryness. Purification by flash chromatography (35:75 EtOAc:hexane) gave 1.76 g (53%) of **36a**.

5-(Benzyloxy)-3-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]phenylacetic Acid (36). A mixture of 1.75 g (4.08 mmol) of **36a** in 60 mL of a 1:1:1 MeOH:THF:H_2O solution and $LiOH \cdot H_2O$ (356 mg, 8.48 mmol) was stirred at room temperature for 1.5 h. The reaction mixture was then diluted with 50 mL of H_2O, acidified to pH 2 with 1 N HCl solution, and extracted with EtOAc (3 × 30 mL). The combined extracts were concentrated and filtered to give 1.63 g (96%) of **36** as white solid: mp 49−52 °C; ^{1}H NMR (acetone-d_6) δ 2.7−2.85 (m, 5 H), 2.9 and 2.92 (s, 3 H), 3.44 and 3.65 (s, 2 H), 3.5−3.6 (m, 4 H), 5.06 and 5.08 (s, 2 H), 6.85 (m, 1 H), 6.8−6.9 (m, 2 H), 7.1−7.5 (m, 8 H). Anal. ($C_{26}H_{27}NO_4 \cdot {}^1/_4\ H_2O$) C, H, N.

LTB_4 Receptor Ligand Binding Assays. The guinea pig spleen assay was purchased as a kit from NEN/DuPont.[6] The kit supplied guinea pig spleen homogenate, unlabeled LTB_4, and assay buffer (10 mM Na_2HPO_4, pH 7.5, 138 mM NaCl, 5 mM EDTA, 10 mM $MgCl_2$, 0.1% w/v bacitracin). Compounds were solublized in DMSO, and further dilution was made in assay buffer. Assay tubes were kept on ice. Compound (50 μM) was added first, followed by 0.5 nM [^{3}H]LTB_4 (50 μL) and then the spleen membrane suspension (400 μL), resulting in a final assay volume of 0.5 mL. The tubes were vortexed for

10 s and incubated at 4 °C for 2 h. Separation of bound [^{3}H]-LTB_4 from free LTB_4 was performed by rapid filtration through GF/B glass fiber filters and washing with three 6 mL aliquots of cold saline. Radioactivity remaining on the filters was quantitated by liquid scintillation spectrometry. Specific binding was defined as that displaced by 3 μM unlabeled LTB_4. The activity of a compound was determined as the percent inhibition of specific binding.

The human PMN whole cell binding assay used PMNs isolated from whole blood. Blood was collected in plastic, with the anticoagulant acid−citrate−dextrose, from human volunteers and used within 2 h of collection. The PMNs were isolated by dextran sedimentation followed by separation on Histopaque 1077. The remaining erythrocytes were hypotonically lysed. The resulting pellet was suspended in Hanks buffer, 5 mM HEPES (pH 7.4), and 1% ovalbumin. The assay tubes were kept on ice. Compound was dissolved in DMSO, and 5 μL of compound or DMSO was added to the appropriate tubes. To complete the mixture, 0.5 nM [^{3}H]LTB_4 and 3×10^6 PMN/mL were added to a total volume of 0.5 mL. The tubes were incubated for 20 min at 4 °C. Separation of bound [^{3}H]LTB_4 from free [^{3}H]LTB_4 was performed by rapid filtration through GF/B glass fiber filters and washing with three 6 mL aliquots of cold saline. Radioactivity remaining on the filters was measured by liquid scintillation spectrometry. Specific binding was defined as that displaced by 1 μM unlabeled LTB_4. Compounds were tested at multiple concentrations, and the activity of a compound was determined as the percent inhibition of specific binding or as IC_{50} value.

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JM9506985