Structure−Activity Relationships Study of Two Series of Leukotriene B_4 Antagonists: Novel Indolyl and Naphthyl Compounds Substituted with a 2-[Methyl(2-phenethyl)amino]-2-oxoethyl Side Chain

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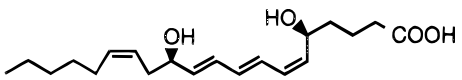
N-Methyl-*N*-phenethylphenylacetamide has been reported to be a key binding domain to LTB_4 receptors. Here we describe the synthesis and structure−activity relationship (SAR) studies of two new series of LTB_4 receptor antagonists in which the phenyl ring of this receptor binding domain is replaced with indole and naphthalene, respectively. Results of these studies indicate that, in addition to the 2-[methyl(2-phenethyl)amino]-2-oxoethyl moiety, the presence of an acid group and a lipophilic side chain, as well as the spatial relationship of these three functions, is crucial for high binding affinity with LTB_4 receptors. Our SAR studies also reveal that an arenecarboxylic acid, or an enoic acid in which the carboxyl group is conjugated with the central ring, is the preferred polar group. The lipophilic side chain of the naphthyl series was found to tolerate minor variations, ranging from a phenylmethoxy group to phenyl and alkyloxy groups. The most active compounds are 2-ethyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoic acid (**4g**) of the indolyl series and 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid (**2a**) or the naphthyl series, with IC_{50} of 8 and 4.7 nM respectively, in the receptor binding assay using intact human neutrophils.

Introduction

Leukotriene B_4 (LTB_4, **1**) is a metabolite of the 5-lipoxygenase arachidonic acid peroxidation pathway and has been implicated as a mediator of inflammatory diseases such as allergic asthma, psoriasis, gout, and ulcerative colitis. Discovery of specific LTB_4 receptor antagonists as therapeutic agents for treatment of LTB_4-mediated diseases has been a topic of intense research interest in recent years.[1] We have reported the synthesis RG 14893 (**2a**), a potent competitive LTB_4 receptor antagonist with oral inhibitory activity of the chemotaxis of PNMs to the LTB_4-induced wheals in guinea pigs.[2] In the preceding paper[3] we have also described the development and structure−activity relationship study of a class of LTB_4 antagonists based on the phenylacetamide **3**. Our study established that three structural features, namely (a) the 2-[methyl(2-phenethyl)amino]-2-oxoethyl side chain, (b) an acid function, and (c) an additional lipophilic group, are required for high binding affinity with LTB_4 receptors.[3]

In the phenylacetamide series of LTB_4 receptor antagonists, the central phenyl ring appears to mimic part of the triene system of the natural ligand, LTB_4, and to act as template for the attached side chains. Thus, we decided to investigate if other aromatic systems could better serve these two functions. Moreover, since the more active phenylacetamides were found to bind with human LTB_4 receptors with an IC_{50} of about 50 nM,[3] it was also our objective to develop novel compounds with



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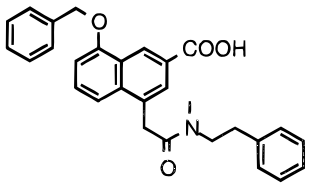
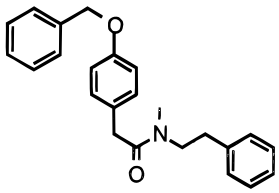


2a



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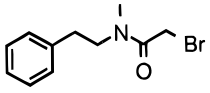
improved activity in binding assay using intact human cells. In this report, we describe the synthesis and the SAR studies of two series of high-affinity LTB_4 receptor antagonists based on the indolyl and naphthyl central ring. This research effort eventually led to the discovery of **2a**.

Chemistry

Most of the indoles listed in Table 1 are synthesized according to Scheme 1. *N*-Methyl-*N*-phenethylbromoacetamide (**9**) was prepared from bromoacetyl bromide or



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chloride and *N*-methyl-*N*-phenethylamine in the presence of triethylamine. Phosphonate esters (**10**) were either obtained commercially or prepared from triphenyl phosphite and the corresponding α-bromo ester.[4] The

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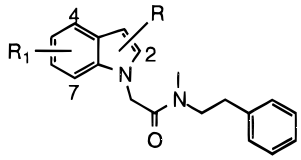
Table 1. LTB_4 Receptor Binding Data of Substituted Indoles



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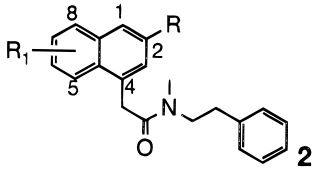
			IC_{50} ±SEM (*N*), nM	
compd	R	R_1	GP spleen	human intact PMN
4a	3-CH=CHCO$_2$H	5-BnO[a]	4.3 ± 0.49 (20)	53 ± 34.5(17)
4b	3-CH=CHCO$_2$H	6-BnO	>300 (1)	NT[b]
4c	3-CH=CHCO$_2$H	7-BnO	>300 (1)	NA[c]
4d	3-CH=CHCO$_2$H	4-BnO	1.0 ± 0.25 (3)	16.5 ± 1.5(2)
6a	3-CHO	5-BnO	80 (1)	>300 (1)
7a	3-CH=CHCO$_2$Et	5-BnO	>300 (1)	NT
4e	3-(CH=CH)$_2$CO$_2$H	5-BnO	8 (1)	19.0 ± 9(2)
4f	3-CH=C(Me)CO$_2$H	5-BnO	5 (1)	11.0 ± 2.1(6)
4g	3-CH=C(Et)CO$_2$H	5-BnO	1.3 (1)	7.6 ± 1.7 (6)
4h	3-CH$_2$CH$_2$CO$_2$H	5-BnO	40 (1)	NT
4i	3-CH$_2$CO$_2$H	5-BnO	30 (1)	NT
4j	3-CO$_2$H	5-BnO	1.5 ± 0.5 (2)	26.3 ± 3.1 (3)
4k (2-Me)	3-CO$_2$H	5-BnO	5 (1)	90 (1)
4l	2-CO$_2$H	5-BnO	2.5 ± 0.5 (3)	11.2 ± 2.8 (6)
4m	3-CO(C$_6$H$_4$-*m*-CO$_2$H)	5-BnO	12 (1)	8.5 (1)
4n	3-CH=CH(5-tetrazolyl)	5-BnO	4.5 (1)	19 (1)
4o	3-(CH=CH)$_2$CO$_2$H	4-BnO	1.5 (1)	15 (1)
4p	3-CH=C(Me)CO$_2$H	4-BnO	2.33 ± 0.34 (4)	24.5 ± 4.5 (2)
4q	3-CH=C(Et)CO$_2$H	4-BnO	1.5 (1)	35 ± 5 (2)
4r	3-CH(Ph)CO$_2$H	4-BnO	2.5 (1)	19 (1)
4s	3-CO$_2$H	4-BnO	1.45 ± 0.35 (2)	20.3 ± 3.2 (3)

[a] BnO = phenylmethoxy. [b] NT = not tested. [c] NA = no activity.

Table 2. Binding Data of the Naphthyl Series of LTB_4 Receptor Antagonists



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			IC_{50} ± SEM (N), nM	
compd	R	R_1	GP spleen	human intact PMN
2a	CO$_2$H	8-BnO[a]	0.36 ± 0.03 (25)	4.7 ± 0.8 (5)
2b	CO$_2$H	7-BnO	1.07 ± 0.33 (3)	7.75 ± 1.52 (4)
2c	CO$_2$H	1-BnO	6.5 (1)	80 (1)
2d	CH=CHCO$_2$H	8-BnO	0.58 ± 0.07 (5)	3.55 ± 0.61 (10)
2e	(CH=CH)$_2$CO$_2$H	8-BnO	1 (1)	8 (1)
2f	(CH$_2$)$_2$CO$_2$H	8-BnO	NT[b]	10 (1)
2g	(CH$_2$)$_4$CO$_2$H	8-BnO	2.8 (1)	100 (1)
2h	CH=C(Et)CO$_2$H	8-BnO	0.8 (1)	50 (1)
2i	CH=CH-(5-tetrazolyl)	8-BnO	3 (1)	5 (1)
2j	CON(Me)OH	8-BnO	10 (1)	60 (1)
2k	CO$_2$H	8-OC$_6$H$_5$	1.5 (1)	25 (1)
2l	CO$_2$H	8-C$_6$H$_5$	0.45 ± 0.05 (2)	8.25 ± 1.44 (4)
2m	CO$_2$H	8-OMe	>30 (1)	700 (1)
2n	CO$_2$H	8-O(CH$_2$)$_4$CH$_3$	0.6 (1)	9.0 ± 1.53 (3)
2o	CH=CHCO$_2$H	8-C$_6$H$_5$	1 (1)	50 (1)
2p	(CH$_2$)$_2$CO$_2$H	8-C$_6$H$_5$	3.5 (1)	40 (1)
2q	CH=CHCO$_2$H	8-OC$_6$H$_5$	2 (1)	20 (1)
2r	(CH$_2$)$_2$CO$_2$H	8-OC$_6$H$_5$	20 (1)	250 (1)

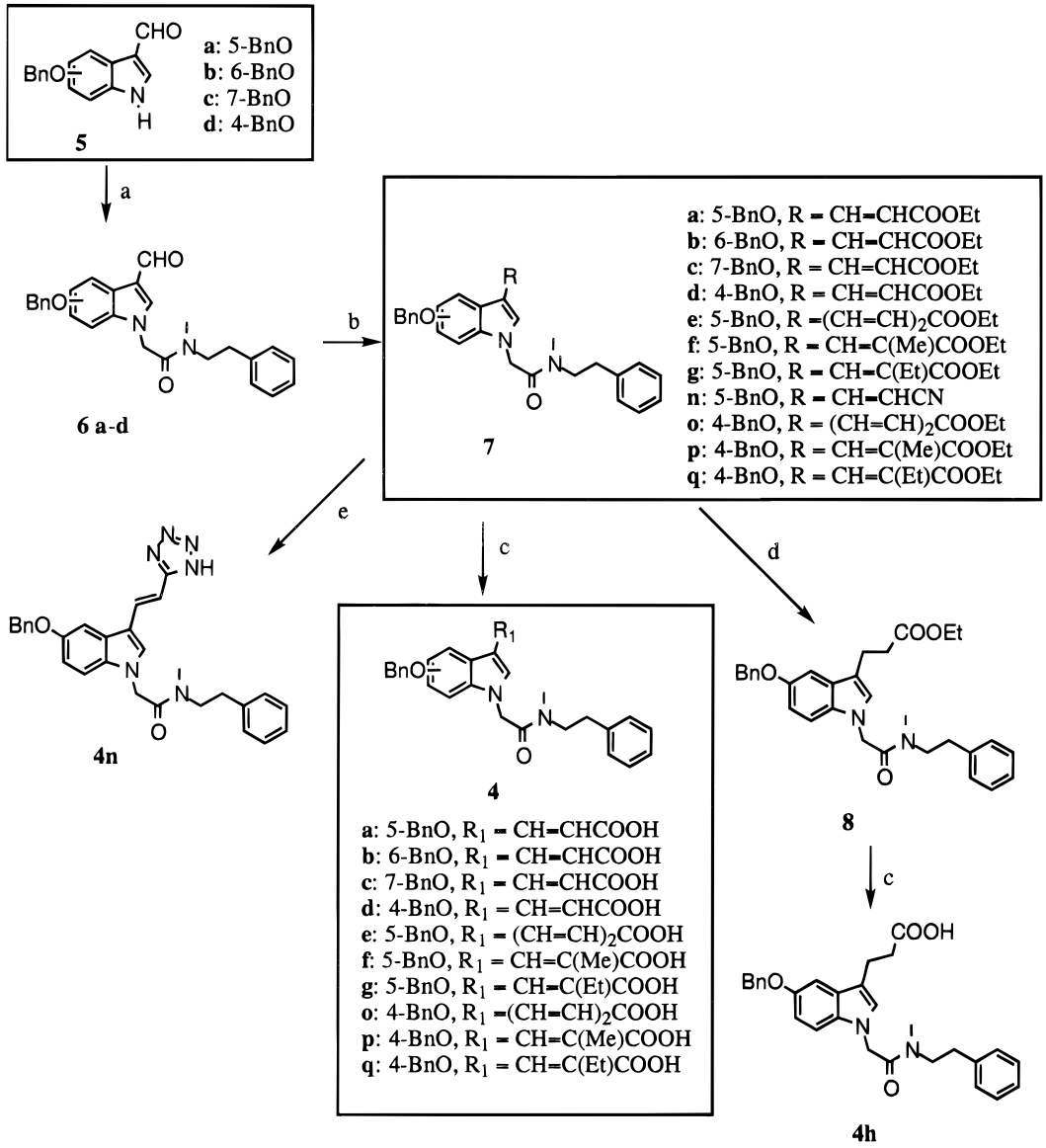
[a] BnO = phenylmethoxy. [b] NT = not tested.

only problematic step in Scheme 1 was the hydrolysis of the esters **7** to the acid **4**. This reaction proceeded slowly at room temperature and gave the diacid side product at a reaction temperature higher than ~50 °C. The α-methyl acids, **4f** and **4p**, could be synthesized directly from **6a** and **6d**, respectively, by treating the indolecarboxaldehydes with methylmalonic acid in the presence of morpholine.[5]

The indolecarboxylic acids **4i**−**m** and **4r**−**s** of Table 1 were prepared by N-alkylation of the corresponding indolecarboxylates with **9** in a manner similar to the synthesis of **6** from **5** described in Scheme 1. Most of the starting indolecarboxylates were obtained commercially. The precursors for **4m** and **4r** were synthesized according to known procedures. These N-alkylated indolecarboxylates were then hydrolyzed to the desired acids.

The syntheses of **2a** and **2k**−**n** of the naphthyl series (Table 2) are illustrated in Scheme 2. The Stobbe condensation of **11** with dimethyl succinate gave **12** as

Scheme 1[a]

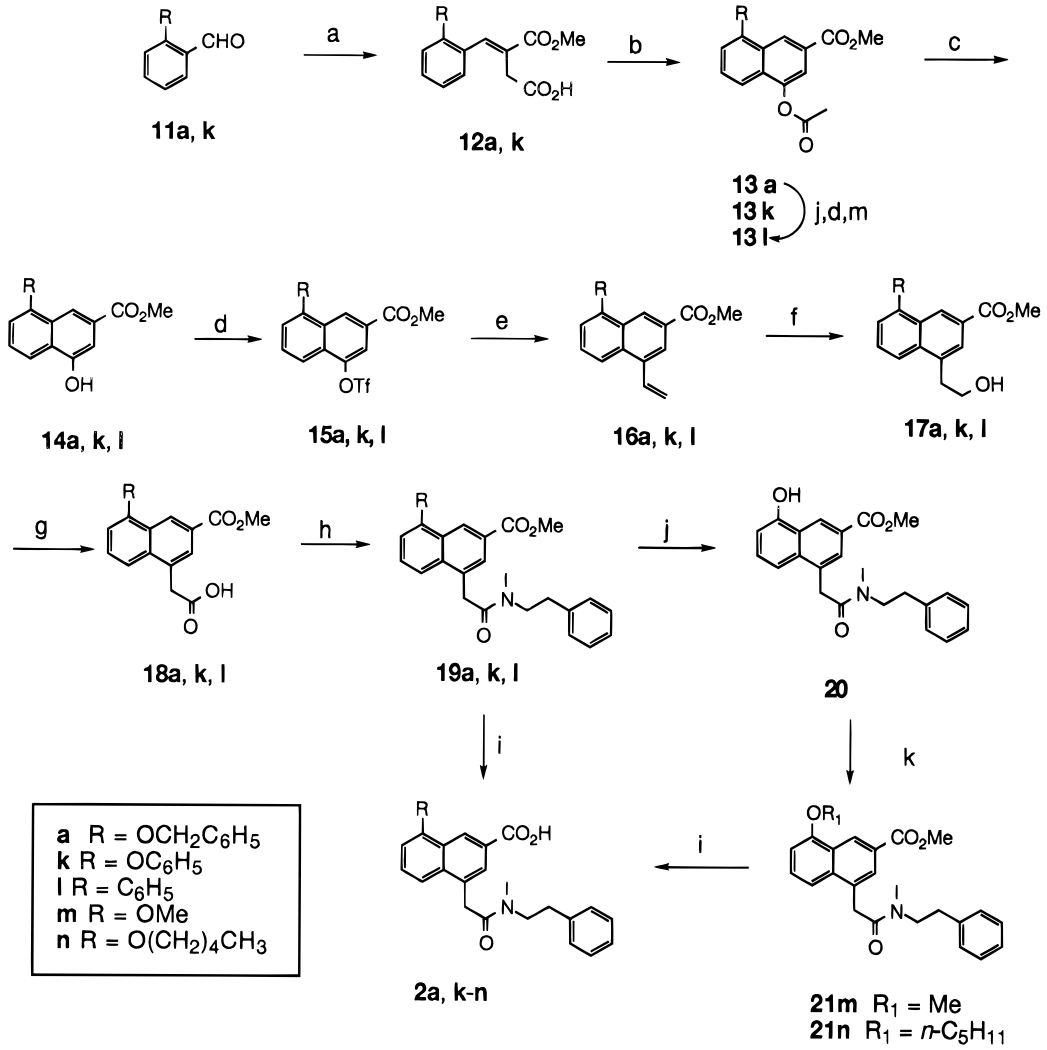


[a] Reagents: (a) **9**, NaH, THF, 0 °C-r.t., 18h, 97.9% (from **5a**); (b) **10**, NaH, THF; 0 °C-r.t., 8 h, 88% (from **6a**); (c) KOH, EtOH/H_2O, r.t.-50 °C, 6-72 h, 40% (from **7a**), quantitative (from **8**); (d) H_2, Pd/C, EtOH, 30 min., 90% (from **7a**); (e) NaN_3, NH_4Cl, DMF, 11.7% (from **7n**).

mixtures of *E* and *Z* isomers, which were cyclized directly with Ac_2O:NaOAc to give the naphthadenecarboxylate **13a** and **13k**.[6] The intermediate **13l** was obtained from **13a** via a three-step procedure (hydrogenolysis, conversion of the resulting naphthol to the triflate, and palladium-catalyzed phenylation of the triflate with phenylboric acid[7]). **13** was subjected to methanolysis, and the product **14** was converted to the triflate **15**. Palladium-catalyzed vinylation of **15** with vinyltributyltin afforded the 4-vinylnaphthalene **16**.[8] Hydroboration of **16** with 9-BBN gave the hydroxy intermediate **17**, which was oxidized with Jones reagent to the naphthaleneacetic acid **18**. Coupling of **18** with *N*-methylphenethylamine using 1,1'-carbonyldiimidazole (CDI) yielded the esters **19a** and **19k**−**l**. Hydrogenolysis of **19a** gave the naphthol **20**, which was alkylated to afford the esters **21**. Hydrolysis of **19** and **21** yielded the acids **2a** and **2k**−**n** as crystalline solid substances. The hydroxamic acid **2j** was prepared from the acid chloride of **2a**.

The reactions described in Scheme 2 proceeded quite well, with the exception of the oxidation of **17** to the naphthaleneacetic acid **18**. This reaction was rather slow, and the best yield was only about 60%. We, therefore, have explored other synthetic routes to the naphthaleneacetic acid. Two of these alternate ap-

Scheme 2[a]



[a] Reagents: (a) *t*BuOK, dimethyl succinate, 85% (from **11a**); (b) Ac_2O-NaOAc, reflux, 4 h, 43% (from **12a**) ; (c) NaOMe, MeOH, r.t., 2h, 98% (from **13a**); (d) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, 99% (from**14a**); (e) $H_2C{=}CHSnBu_3$, LiCl, $PdCl_2[P(C_6H_5)_3]_2$, 63% (from **15a**); (f) 9-BBN, H_2O_2, THF, (from **16a**); (g) Jones, acetone, 60% (from **17a**, minor impurities); (h) $C_6H_5CH_2CH_2NHCH_3$, CD DMAP, CH_2Cl_2, 57% (from **18a**); (i) $LiOH.H_2O$, THF:MeOH:H_2O, 89% (from **19a**); (j) H_2, Pd/C, 90% (from **19a**); (k) R_1Br, K_2CO_3, acetone, quantitative (for **21m**); (m) $C_6H_5B(OH)_2$, $[(C_6H_5)_3P]_4P$ K_3PO_4, dioxane, 86%.

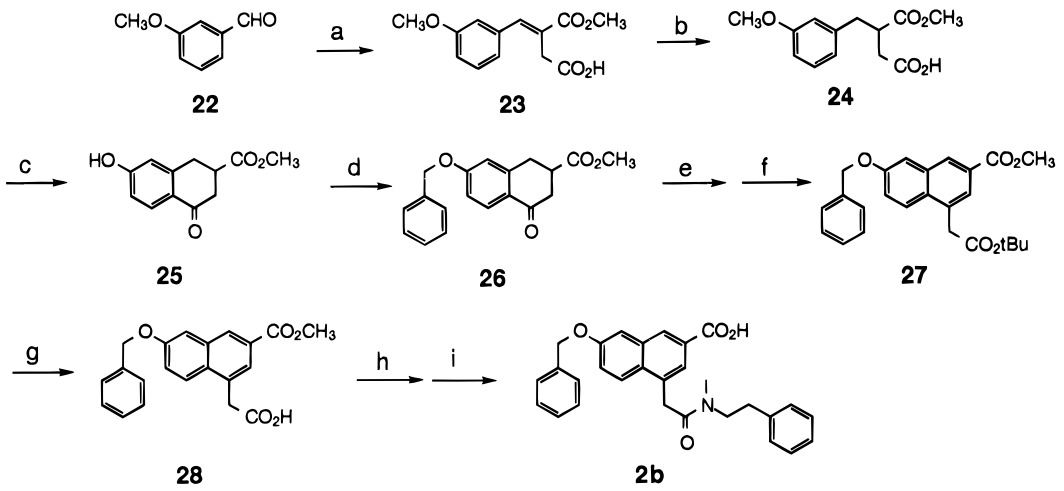
proaches are illustrated in Scheme 3 and 4, which also depict the syntheses of two of the isomers of **2a** (**2b** and **2c**, respectively). Unfortunately these alternate synthetic routes did not offer an advantage over the original approach described in Scheme 2. More recently, Pendrak *et al.* has reported a new method for the preparation of the intermediate **18a**.[9]

Thus in Scheme 3, Stobbe condensation of **22** with methyl succinate afforded an *E*/*Z* mixture of **23**, which was reduced directly to **24**. Conversion of **24** to its acid chloride, followed by intramolecular Friedel−Crafts acylation, afforded the α-tetralone **25**. The methoxy group of **24** was also cleaved during this process. The phenolic function of **25** was benzylated to afford **26**. **26** was reacted with *tert*-butyl (diethylphosphono)acetate in a Wittig reaction, and the product was treated with DDQ to afford the *tert*-butyl ester **27**. The *tert*-butyl group of **27** was removed under acidic condition to give the naphthaleneacetic acid **28**. The conversion of **28** to **2b** was achieved by using procedures similar to those used for the preparation of **2a** from **19a**.

In Scheme 4, benzylation of commercially available **29** gave 4-bromonaphthalene **30**. Palladium-catalyzed ethynylation of **30**,[10] followed by transesterification, afforded the 4-ethynylnaphthalene **31**. Oxidation of the geminal diboron intermediate of **31** gave naphthaleneacetic acid **32**.[11] Conversion of **32** to **2c** following similar procedures described for the preparation of **2a**.

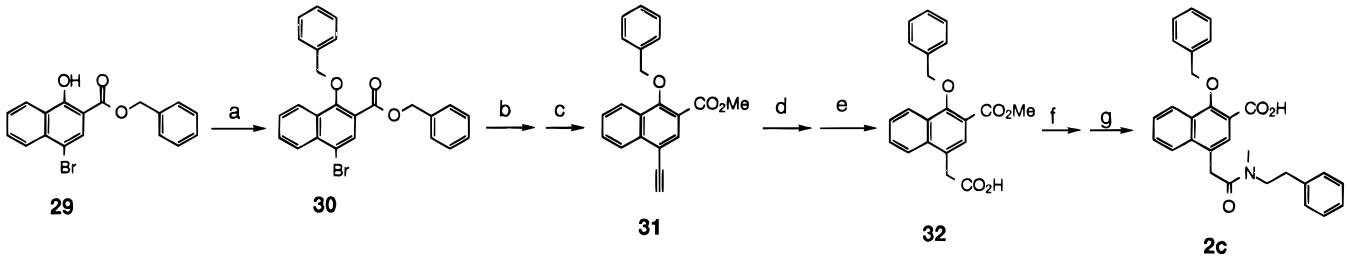
The rest of the compounds listed in Table 2 were derived by modification of the acid group of **2a** and **2k**−**l**. These compounds were prepared from the corresponding naphthalenecarboxaldehydes. As an illustration, the synthesis of **2q** is shown in Scheme 5. Thus, a reduction−oxidation reaction sequence converted the intermediate **17k** of Scheme 2 to the naphthalenecarboxaldehyde **33**. Conversion of **33** to the key intermediate **36**, and the subsequent transformation of **36** to **2q**, followed similar procedures described in Schemes 1 and

Scheme 3[a]



[a] Reagents: (a) $MeOCOCH_2CH_2COOMe$, *t*BuOH/KO*t*Bu; (b) H_2, 10% Pd/C, HOAc, 82% (from crude **23**); (c) $SOCl_2$, CH_2Cl_2, $AlCl_3$, $ClCH_2CH_2Cl$, 22%; (d) $C_6H_5CH_2Br$, K_2CO_3, DMF, 77%; (e) $(EtO)_2P(O)CH_2COOtBu$, NaH, 83%; (f) DDQ, C_6H_6, 56%; (g) CF_3CO_2H, CH_2Cl_2, quantitative; (h) $C_6H_5CH_2CH_2NHCH_3$, CDI, DMAP; (i) $LiOH.H_2O$, THF:MeOH:H_2O.

Scheme 4[a]



[a] Reagents: (a) $C_6H_5CH_2Br$, K_2CO_3, DMF, 29%; (b) trimethylsilylacetylene, Et_3N, $Pd(OAc)_2[P(C_6H_5)_3]_2$; (c) MeOH, K_2CO_3, 14% (from **30**); (d) BH_3, $(CH_3)_2C{=}C(CH_3)_2$, THF, MCPBA; (e) Jones, 17.7% (from **31**, crude); (f) $C_6H_5CH_2CH_2NHCH_3$, CDI, DMAP, CH_2Cl_2; (g) $LiOH.H_2O$, THF:MeOH:H_2O.

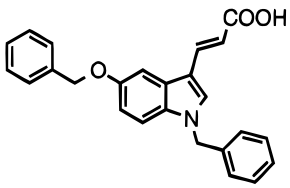
2. Intermediates **17** were used as the starting material predominantly because they were available at the time.

All of the compounds bearing an enoic carboxylic acid side chain consisted of a mixture of *cis*−*trans* isomers (by NMR). No attempts were made to separate these geometric isomers, and the biological data obtained for these compounds were those of the isomeric mixtures.

Results and Discussion

The LTB_4 receptor binding data, obtained from radioligand binding assay using either guinea pig spleen cell membrane[12] or intact human neutrophils[13] are listed in Tables 1 and 2. The lead compound **2a** had IC_{50} values of 0.36 and 4.7 nM respectively, in the GP spleen cell membrane and intact human PMN binding assay.

Our interest in the indole series originated from an initial observation that both the indoleacrylic acid **37**[14] and the phenylacetamide **3** bound to LTB_4 receptors of a cell membrane preparation of GP PMNs with similar activity.[15] This result prompted us to replace one of the two phenylmethyl groups of **37** with the 2-[methyl(2-phenethyl)amino]-2-oxoethyl moiety of **3**. The resulting hybrid molecule **4a** was found to have a high affinity for LTB_4 receptors, with IC_{50}s of 4 and 55 nM in binding assays using GP spleen cell membrane and intact human neutrophils, respectively (Table 1).



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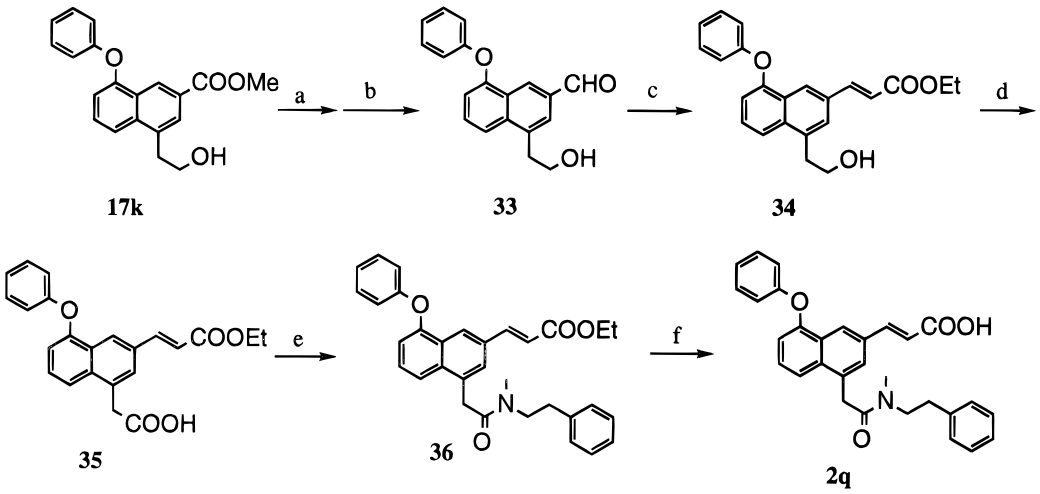
The locations of the phenylmethoxy group of **4a** was found to be crucial for receptor affinity. Thus, the 6- and 7-phenylmethoxy analogs, **4b** and **4c**, were less active, whereas the 4-phenylmethoxy analog **4d** was more active than **4a**. These results suggest that the spatial relationship of the three side chains, which to a large extend is determined by their substitution pattern on the central indole ring, is an important factor in determining the affinity of these molecules with LTB_4 receptors.

We have found from SAR study of the phenylacetamide series that modification on either the amide or phenylmethoxy group led to compounds of lower activity,[3] therefore our SAR study of **4a** was directed mainly toward the modification of its acid side chain. The importance of this carboxylic acid function was demonstrated by the lower receptor affinity of the aldehyde **6a** and ester **7a**, and the comparable activity of the corresponding tetrazole **4n**. Varying the length of the

Scheme 5[a]



[a]Reagents: (a) LAH, Et_2O, O °C-r.t.; (b) MnO_2, CH_2Cl_2, 18 h, 56% (from **17k**); (c) **10a**, NaH, THF, 0° C-r.t., 6 h; (d) Jones, acetone; (e) $C_6H_5CH_2CH_2NHCH_3$, CDI, DMAP, CH_2Cl_2; (f) $LiOH.H_2O$, THF:MeOH:H_2O.

carboxylic acid function afforded somewhat more potent compounds (**4e** and **4j**), especially in the human whole cell assay. On the other hand, analogs of **4a** having a saturated acid side chain (**4h** and **4i**) were at least 7-fold less active than **4a**. These data suggested that the length of the acid side chain, at least within the range of one to five carbon atoms, was not a significant factor in determining the binding affinity of these compounds. Instead, conjugation of the carboxyl group with the central aromatic ring was a prerequisite for strong binding to LTB_4 receptors. The binding affinity of **4a** was also found to improve noticeably, especially in the human whole cell binding assay, by substituting the carbon atom next to the carboxyl function with a lower alkyl group (**4f** and **4g**). In fact, **4g** was the lead compound of the indole series, with an IC_{50} value of 1.3 and 7.6 nM respectively in the GP spleen cell membrane and intact human PMN binding assay.

Similar acid group modifications of the 4-(phenylmethoxy)indole **4d**, however, did not improve activity (**4o**−**q** and **4s**, Table 1). It is noteworthy that the phenylacetic acid derivative **4r** was quite active, even though its carboxylic group was not conjugated with either the indole or phenyl ring.

Other modifications on the acid side chain of **4a**, such as transposition of the acid group from the 3 to the 2 position on the indole ring (**4l**), or replacing the enoic acid group with the carboxybenzoyl moiety found in LY223982,[16] a potent LTB_4 receptor antagonist (**4m**), also improved binding affinity. **4m** in particular was one of the two indoles that have IC_{50} values of less than 10 nM in the intact human PMN binding assay.

The LTB_4 receptor binding data of the naphthyl compounds are shown in Table 2. One of the initial compounds synthesized in this series, 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid (**2a**) was found to bind with human neutrophil LTB_4 receptors with an IC_{50} value of 4.7 nM. By Scatchard analysis, **2a** exhibited K_is of 0.14 and 2 nM for guinea pig and human PMN LTB_4 receptors, respectively.[2]

SAR study of **2a** was carried out in a manner similar to that described for **4a**, and in general the results paralleled those obtained for the indole series. Thus, compounds **2b** and **2c** again demonstrated the importance of the substitution pattern on the central ring. The saturated acids (**2f** and **2g**) were again less active. The propenoic acid **2d** and its tetrazolyl derivative **2i** had binding affinity comparable to that of **2a**, whereas the hydroxamic acid **2j** was less active. We also carried out a limited study on the modification of the phenylmethoxy group of **2a**. The phenyl (**2l**) and short chain alkyloxy (**2n**) analogs were found to retain the receptor affinity of the parent compound, whereas the activities of the methoxy (**2m**) and the phenoxy (**2k**) analogs were significantly reduced.

The guinea pig aggregation assay[17] was used to determine, *in vitro*, whether compounds active in the binding assay were LTB_4 receptor agonists or antagonists. Thus, **4a** and **2a** were found to inhibit LTB_4-induced (1 nM) aggregation of guinea pig PMNs with IC_{50} values of 1.5 and 0.85 nM, respectively. In addition, these agents were found to be pure LTB_4 antagonists due to their complete lack of agonist activity in this assay.[18] These results indicated a good correlation between the binding affinity and functional antagonist activity of **4a** and **2a** against LTB_4 high-affinity receptors in guinea pigs. *In vivo*, the po administration of **2a** to guinea pigs, 1 h prior to LTB_4 challenge, resulted in a dose-related reduction in LTB_4-induced bronchoconstriction with an ED_{50} value of 1.7 mg/kg.[18] This result confirmed that **2a** was a potent, orally active antagonist of LTB_4 high-affinity receptors.

In summary, we have achieved the main objectives for this study, namely, to develop novel LTB_4 receptor ligands based on central aromatic systems other than benzene and to improve activity of these compounds in the intact human neutrophil binding assay. Some of these compounds, such as **2a**,**b**,**d**,**e**,**i**,**l**,**n** and **4g**,**m**, were found to bind to LTB_4 receptors of human neutrophil with IC_{50} of less than 10 nM. Our SAR studies, based on *in vitro* receptor binding assays, established that (1) the spatial relationship among the three side chains on the central aromatic ring, as determined by their substitution pattern, is crucial for receptor binding, (2) the one-carbon carboxylic and the propenoic acid side

chains are preferred over propanoic or pentadienoic acids, (3) alkylation on the α carbon of the propenoic acid can enhance potency, and (4) naphthalene is preferred over indole as the aromatic central ring.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and were uncorrected. Mass and proton NMR spectra were recorded for all compounds and were consistent with assigned structures. ^{1}H NMRs were recorded on a Varian EM-390 (90 MHz) or a Bruker ACF-300 (300 MHz) spectrometer in $CDCl_3$ solution unless indicated otherwise.

***N*-Methyl-*N*-(2-phenethyl)-2-bromoacetamide (9).** To a solution of 34.7 g (171.95 mmol) of bromoacetyl bromide in 100 mL of CH_2Cl_2, cooled to −25 °C by an external cooling bath, was added dropwise a solution of 46.5 g (343.9 mmol) of *N*-methylphenethylamine in 50 mL of CH_2Cl_2 over a period of 1 h. The reaction mixture was stirred at −25 °C for an additional 15 min and allowed to equilibrate to room temperature. The mixture was diluted with CH_2Cl_2 and washed successively with H_2O, 1 N aqueous HCl solution, and saturated salt solution. After being dried over $MgSO_4$, the organic layer was concentrated *in vacuo* to give quantitatively **9** as a beige oil: ^{1}H NMR δ 2.86, 2.9 (2 t, 2 H), 2.95, 3.0 (2 s, 3 H), 3.6, 3.64 (2 t, 2 H), 3.7, 4.07 (2 s, 2 H), 7.34 (m, 5 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indole-3-carboxaldehyde (6a). A suspension of NaH (0.9 g of 80% dispersion in mineral oil, 30 mmol) in 120 mL of anhydrous tetrahydrofuran (THF) in a round bottom flask was cooled in an ice bath, and 7.46 g (29.7 mmol) of 5-(phenylmethoxy)indole-3-carboxaldehyde (**5a**) was added in portions with stirring . The mixture was stirred in the cooling bath for additional 10 min, and 9.13 g (35.64 mmol) of **9** was added. The reaction mixture was stirred at room temperature for 18 h. H_2O and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. This oil was chromatographed on silica gel using CH_2Cl_2:EtOAc (2:1) as the eluent to give 12.4 g (29.07 mmol, 97.9% yield) of **6a** as a beige solid: ^{1}H NMR δ 1.27 (t, 3 H), 2.88 (m, 2 H), 2.9, 3.04 (2 s, 3 H), 3.6 (m, 2 H), 4.3, 4.77 (2 s, 2 H), 5.18, 5.22 (2 s, 2 H), 6.7−7.73 (m, 13 H), 8.0 (m, 1 H), 10.04, 10.1 (2 s, 1 H). Anal. ($C_{27}H_{26}N_2O_3 \cdot 0.25H_2O$) C, H, N.

Ethyl 3-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoate (7a). A suspension of NaH (0.84 g of 80% dispersion in mineral oil, 28 mmol) in 80 mL of anhydrous THF in a round bottom flask was cooled in a cold water bath (*ca.* 10 °C), and 5.6 mL (27.2 mmol) of triethyl phosphonoacetate (**10a**) was added dropwise at 0 °C. After the mixture was stirred for an additional 10 min, a solution of 7.74 g (18.15 mmol) of **6a** in 40 mL of anhydrous THF was added. The reaction mixture was stirred at room temperature for 5 h. H_2O and EtOAc were added, and the layers were separated. The organic layer was washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to give 11.7 g of yellow solid substance. This crude product was chromatographed on silica gel using 10% EtOAc in CH_2Cl_2 as the eluent to give 7.93 g of **7a** as beige solid substance: ^{1}H NMR δ 1.34 (t, 3 H), 2.79, 3.00 (2 s, 3 H), 2.81 (m, 2 H), 3.53 (m, 2 H), 4.20, 4.63 (2 s, 2 H), 4.28 (q, 2 H), 5.10, 5.11 (2 s, 2 H), 6.30, 6.34 (2 d, 1 H), 6.67−7.50 (m, 14 H), 7.83, 7.87 (2 d, 1 H). Anal. ($C_{31}H_{32}N_2O_4$) C, H, N.

3-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoic Acid (4a). To a mixture of 7.4 g (14.95 mmol) of **7a** and 200 mL of EtOH was added a solution of 1.26 g (44.4 mmol) of KOH in 20 mL of H_2O. The mixture was heated at 50 °C for 3 days, and the suspension obtained was concentrated *in vacuo*. The concentrated reaction mixture was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2 N aqueous HCl solution to pH ∼7. The precipitate formed was collected and dried *in vacuo* to give 2.8 g (5.98 mmol, 40% yield) of **4a** as light beige powder: ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.9 (m, 2 H), 2.97, 3.08 (2 s, 3 H), 4.7, 5.1 (2 s, 2 H), 5.21 (bs, 2 H), 6.28, 6.34 (2 d, 1 H), 6.8−8.15 (m, 15 H). Anal. ($C_{29}H_{28}N_2O_4$) C, H, N.

Compounds **4b**−**g** and **4o**−**q** of Scheme 1, and the intermediates leading to them, were prepared according to the above procedures.

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-6-(phenylmethoxy)indole-3-carboxaldehyde (6b): ^{1}H NMR δ 2.9 (m, 2 H), 2.91, 3.05 (2 s, 3 H), 3.64 (m, 2 H), 4.26, 4.8 (2 s, 2 H), 5.12, 5.15 (2 s, 2 H), 6.4, 6.86 (2 s, 1 H), 7.0−7.66 (m, 12 H), 7.26 (m, 1 H), 10.0, 10.7 (2 s, 1 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-7-(phenylmethoxy)indole-3-carboxaldehyde (6c): ^{1}H NMR δ 2.4, 2.84 (2 s, 3 H), 2.76 (m, 2 H), 3.4 (m, 2 H), 4.48, 5.04 (2 s, 2 H), 5.05 (s, 2 H), 6.8−8.1 (m, 14 H), 10.0, 10.4 (2 s, 1 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indole-3-carboxaldehyde (6d): ^{1}H NMR δ 1.25 (t, 3 H), 2.89 (m, 2 H), 2.89, 3.01 (2 s, 3 H), 3.6 (m, 2 H), 4.31, 4.81 (2 s, 2 H), 5.0, 5.28 (2 bs, 2 H), 6.5−7.85 (m, 14 H), 10.4, 10.6 (2 s, 1 H).

Ethyl 3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-6-(phenylmethoxy)indol-3-yl]propenoate (7b): ^{1}H NMR δ 1.33 (t, 3 H), 2.78 (m, 2 H), 2.8, 3.0 (2 s, 3 H), 3.57 (m, 2 H), 4.25, 4.8 (2 s, 2 H), 4.3 (q, 2 H), 5.1, 5.15 (2 cs, 2 H), 6.4, 6.45 (2 d, 1 H), 6.75−7.6 (m, 13 H), 7.9 (m, 2 H).

Ethyl 3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-7-(phenylmethoxy)indol-3-yl]propenoate (7c): ^{1}H NMR δ 1.34 (t, 3 H), 2.43, 2.87 (2 s, 3 H), 2.7 (m, 2 H), 3.44 (m, 2 H), 4.3 (q, 2 H), 4.53, 5.05 (2 s, 2 H), 5.05, 5.08 (2 s, 2 H), 6.42, 6.5 (2 d, 1 H), 6.64 (m, 2 H), 7.07−7.8 (m, 12 H), 7.94, 8.0 (2 d, 1 H).

Ethyl 3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoate (7d): ^{1}H NMR δ 1.24 (t, 3 H), 2.80 (t, 2 H), 2.84, 3.00 (2 s, 3 H), 3.54 (q, 2 H), 4.15 (q, 2 H), 4.28, 4.70 (2 s, 2 H), 5.17, 5.20 (2 s, 2 H), 6.20, 6.23 (2 d, 1 H), 6.40−7.53 (m, 15 H), 7.27, 8.33 (2 d, 1 H).

Ethyl 5-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]-2,4-pentadienoate (7e): ^{1}H NMR δ 1.27 (t, 3 H), 2.66, 2.86 (2 s, 3 H), 2.70 (m, 2 H), 3.42 (m, 2 H), 3.81−4.53 (m, 4H), 4.99 (bs, 2 H), 5.77 (d, 1 H), 6.0−8.0 (m, 17 H).

Ethyl 2-methyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoate (7f): ^{1}H NMR δ 1.37 (t, 3 H), 2.10,2.14 (2 s, 3 H), 2.80 (m, 2 H), 2.84, 2.99 (2 s, 3 H), 3.54 (m, 2 H), 4.26 (q, 2 H), 4.26, 4.70 (2 s, 2 H), 6.60−7.73 (m, 14 H), 7.88 (d, 1 H).

Ethyl 2-ethyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-ly]propenoate (7g): ^{1}H NMR δ 1.20 (m, 6 H), 2.67 (m, 4 H), 2.86, 2.93 (2 s, 3 H), 3.42 (m, 2 H), 4.10 (q, 2 H), 4.17, 4.64 (2 s, 2 H), 4.99, 5.01 (2 s, 2 H), 6.60−7.40 (m, 14 H), 7.80 (d, 1 H).

Ethyl 2-methyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoate (7p): ^{1}H NMR δ 1.13 (t, 3 H), 2.11, 2.13 (2 s, 3 H), 2.82 (m, 2 H), 2.88, 3.02 (2 s, 3 H), 3.57 (m, 2 H), 4.1 (q, 2 H), 4.31, 4.8 (2 s, 2 H), 5.16 (bs, 2 H), 6.43−7.6 (m, 14 H), 8.53 (bs, 1 H).

Ethyl 2-ethyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoate (7q): ^{1}H NMR δ 0.99 (t, 3 H), 1.20 (t, 3 H), 2.40 (m, 2 H), 2.86 (m, 2 H), 2.82, 2.99 (2 s, 3 H), 3.57 (m, 2 H), 4.20 (q, 2 H), 4.89, 5.20 (2 s, 2 H), 5.26 (bs, 2 H), 6.56−7.73 (m, 12 H), 7.81 (d, 1 H), 8.10 (s, 1 H), 8.70 (d, 1 H).

3-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-6-(phenylmethoxy)indol-3-yl]propenoic acid (4b): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.96 (m, 2 H), 2.97, 3.1 (2 s, 3 H), 4.74, 5.1 (2 s, 2 H), 6.16, 5.2 (2 s, 2 H), 6.35 (d, 1 H), 6.85−8.16 (m, 15 H). Anal. ($C_{29}H_{28}N_2O_4$) C, H, N.

3-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-7-(phenylmethoxy)indol-3-yl]propenoic acid (4c): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.48, 2.81 (2 s, 3 H), 2.63 (m, 2 H), 3.3 (m 2 H), 4.52, 5.0 (2 s, 2 H), 5.0 (bs, 2 H), 6.2, 6.26 (2 d, 1 H), 6.6−7.47 (m, 14 H), 7.95, 8.03 (2 d, 1 H). Anal. ($C_{29}H_{28}N_2O_4 \cdot 0.5H_2O$) C, H, N.

3-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoic acid (4d): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.86 (m, 2 H), 2.94, 3.0 (2 s, 3 H),

3.56 (m, 2 H), 4.47, 4.88 (2 s, 2 H), 4.7, 4.75 (2 s, 2 H), 6.14, 6.2 (2 d, 2 H), 6.43−7.74 (m, 14 H), 8.07, 8.15 (2 d, 1 H). Anal. ($C_{29}H_{28}N_2O_4$) C, H, N.

5-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]-2,4-pentadienoic acid (4e): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.9 (m, 2 H), 2.99, 3.13 (2 s, 3 H), 3.8 (m 2 H), 4.82, 5.17 (2 s, 2 H), 5.3 (s, 2 h), 6.03 (d, 1 H),7.0−7.7 (m, 17 H). Anal. ($C_{31}H_{30}N_2O_4\cdot0.25H_2O$) C, H, N.

2-Methyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoic acid (4f): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.06 (m, 3 H), 2.93 (m, 2 H), 2.93, 3.04 (2 s, 3 H), 4.66, 5.05 (2 s, 2 H), 5.05, 5.09 (2 s, 2 H), 6.80−6.90 (m, 2 H), 7.06−7.50 (m, 12 H), 7.70 (bs, 1 H). Anal. ($C_{30}H_{30}N_2O_4$) C, H, N.

2-Ethyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propenoic acid (4g): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 1.13−1.47 (m, 6 H), 2.46, 2.87 (2 s, 3 H), 2.56−3.00 (m, 4 H), 3.45 (m, 2 H), 4.27 (m, 2 H), 4.36, 4.76 (2 s, 2 H), 5.16, 5.20 (2 s, 2 H), 6.86−7.65 (m, 14 H), 8.17 (d, 1 H). Anal. ($C_{31}H_{32}N_2O_4\cdot0.2H_2O$) C, H, N.

5-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]-2,4-pentadienoic acid (4o): ^{1}H NMR δ 2.75 (m, 2 H), 2.91, 3.05 (2 s, 3 H), 3.56 (m, 2 H), 4.26, 4.35, 4.81, 4.89 (4 s, 2 H), 5.16, 5.20, 5.23 (3 s, 2 H), 5.59−8.0 (m, 18 H). Anal. ($C_{31}H_{30}N_2O_4\cdot0.25H_2O$) C, H, N.

2-Methyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoic acid (4p): ^{1}H NMR δ 2.1 (bs, 3 H), 3.65 (t, 2 H), 4.4, 4.9 (2 s, 2 H), 5.22 (bs, 2 H), 6.5−7.7 (m, 14 H), 8.66 (bs, 1 H). Anal. ($C_{30}H_{30}N_2O_4$) C, H, N.

2-Ethyl-3-[1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]propenoic acid (4q): ^{1}H NMR δ 2.00, 2.10 (2 s, 3 H), 2.63−3.00 (m, 5 H), 3.50 (m, 2 H), 4.23, 4.29, 4.80, 4.87 (4 s, 2 H), 5.13 (m, 2 H), 6.43−7.54 (m 14 H), 7.76−8.88 (m, 1 H). Anal. ($C_{31}H_{32}N_2O_4$) C, H, N.

3-[1-[2-[Methyl(2-phenethyl)amino-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propanoic Acid (4h). A mixture of 0.93 g of **7a**, 0.5 g of 10% palladium on activated carbon, and 150 mL of EtOH was shaken under 40 psi of hydrogen in a Parr apparatus for 30 min. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue obtained was chromatographed on silica gel using EtOAc:hexane (2:1) as the eluent to give in over 90% yield ethyl 3-[1-[2-[methyl(2-phenethyl)amino-2-oxoethyl]-5-(phenylmethoxy)indol-3-yl]propanoate (**8)** as a white powder: ^{1}H NMR δ 1.24 (t, 3 H), 2.56−3.14 (m, 6 H), 2.71, 2.95 (2 s, 3 H), 3.5 (m, 2 H), 4.16 (q, 2 H), 4.28, 4.61 (2 a, 2 H), 6.7−7.6 (m, 14 H). **8** was hydrolyzed to **4h** according to the procedure described for the synthesis of **4a**, except the reaction was conducted at room temperature in 6 h: ^{1}H NMR δ 2.75 (m, 4 H), 2.81, 2.03 (2 s, 3 H), 3.0 (m, 2 H), 3.6 (m, 2 H), 4.36, 4.76 (2 s, 2 H), 5.18 (bs, 2 H), 6.72−7.7 (m, ∼13 H), 8.2 (m, ∼1 H). Anal. ($C_{29}H_{30}N_2O_4$) C, H, N.

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-3-(2-tetrazol-5-ylvinyl)-5-(phenylmethoxy)indole (4n). 3-(2-Cyanovinyl)-1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indole (**7n**) was prepared from **6a** and **10e** according to the procedure for the synthesis of **7a**: ^{1}H NMR δ 2.9 (m, 2 H), 2.91, 3.04 (2 s, 3 H), 3.6 (m, 2 H), 4.23, 4.86 (2 s, 2 H), 5.06, 5.12 (2 s, 2 H), 5.49, 5.56 (2 d, 1 H), 6.3−7.5 (m, 15 H). A mixture of 0.845 g (1.88 mmol) of **7n**, 0.37 g (5.64 mmol) of sodium azide, and 0.3 g (5.64 mmol) of ammonium chloride in 5 mL of DMF was heated in an oil bath of 100 °C for 18 h. The reaction mixture was cooled and poured into 200 mL of cold water. Two milliliters of 1 N aqueous NaOH solution was added, and the aqueous mixture was extracted with Et_2O. The aqeous layer was acidified to pH ∼4 with 1 N HCl solution. The precipitate formed was collected by filtration and dissolved in ∼200 mL of EtOAc. The solution was stirred for 0.5 h and filtered to remove undissolved substances. The filtrate was concentrated *in vacuo,* and the residue was triturated in EtOAc to give 108 mg of **4n** as white solid powder: ^{1}H NMR δ 2.85, 2.96 (2 t, 2 H), 3.02, 3.07 (2s, 3 H), 3.59, 3.69 (2 t, 2 H), 4.5, 4.9 (2 s, 2 H), 5.13, 5.16 (2 s, 2 H), 6.75−7.85 (m, 16 H). Anal. ($C_{29}H_{28}N_6O_2\cdot0.5H_2O$) C, H, N.

Methyl 1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-3-indoleacetate (ester of 4i): ^{1}H NMR δ 2.74 (m, 2 H), 2.82, 2.98 (2 s, 3 H), 3.46 (m, 2 H), 3.51−3.71 (m, 5 H), 4.47, 4.71 (2 s, 2 H), 5.08, 5.12 (2 s, 2 H), 6.74−7.5 (m, 13 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-3-indoleacetic acid (4i): ^{1}H NMR (C_6D_6:DMSO-d_6, 9:1) δ 2.62 (m, 2 H), 2.67, 2.69 (2 s, 3 H), 3.36 (m, 2 H), 3.61, 3.62 (2 s, 2 H), 4.45, 4.72 (2 s, 2 H), 4.90, 4.92 (2 s, 2 H), 6.77−7.39 (m, 13 H). Anal. ($C_{27}H_{26}N_2O_4$) C, H, N.

Ethyl 1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-3-indolecarboxylate (ester of 4j): ^{1}H NMR δ 1.34 (t, 3 H), 2.80 (m, 2 H), 2.75, 2.94 (2 s, 3 H), 3.46 (m, 2 H), 4.16, 4.57 (2 s, 2 H), 4.28, 4. 30 (2 q, 2 H), 5.04, 5.06 (2 s, 2 H), 6.53−7.90 (m, 14 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxotheyl]-5-(phenylmethoxy)-3-indolecarboxylic acid (4j): ^{1}H NMR δ 2.86 (m, 2 H), 3.50 (m, 2 H), 4.40, 4.86 (2 s, 2 H), 5.06 (bs, 2 H), 6.60−7.80 (m, 14 H). Anal. ($C_{27}H_{26}N_2O_4$) C, H, N.

Ethyl 2-methyl-1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-3-indolecarboxylate (ester of 4k): ^{1}H NMR δ 1.37, 1.41 (2 t, 3 H), 2.38, 2.56 (2 s, 3 H), 2.84 (m, 2 H), 2.9, 3.01 (2 s, 3 H), 3.65 (t, 2 H), 4.3, 4.61 (2 s, 2 H), 4.41, 4.45 (2 q, 2 H), 6.64 (d, 1 H), 6.6−8.37 (m, 12 H).

2-Methyl-1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-3-indolecarboxylic acid (4k): ^{1}H NMR δ 2.4, 2.63 (2s, 2 H), 2.87, 2.96 (2 t, 2 H), 3.03, 3.05 (2 s, 3 H), 3.69,3.71 (2 t, 2 H), 4.36, 4.79 (2 s, 2 H), 5.08, 5.11 (2 s, 2 H), 6.52−7.83 (m, 13 H). Anal. ($C_{28}H_{28}N_2O_4$) C, H, N.

Ethyl 1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)-2-indolecarboxylate (ester of 4l): ^{1}H NMR δ 1.35, 1.39 (2 t, 3 H), 2.94 (m, 2 H), 3.03, 3.06 (2 s, 3 H), 3.74 (m, 2 H), 4.38, 4.42 (2 q, 2 H), 5.2 (s, 2 H), 5.22, 5.46 (2 s, 2 H), 6.8−7.65 (m, 14 H).

1-[2-[Methyl(2-phenethyl)amino]2-oxoethyl]-5-(phenylmethoxy)-2-indolecarboxylic acid (4l): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.9 (m, 2 H), 2.9, 3.1 (2 s, 3 H), 3.6 (m, 2 H), 5.17 (s, 2 H), 5.23, 5.54 (2 s, 2 H), 6.87−7.6 (m, 13 H), 8.05 (s, 1 H). Anal. ($C_{27}H_{26}N_2O_4\cdot0.25H_2O$) C, H, N.

3-(3-Carboxybenzoyl)-1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-5-(phenylmethoxy)indole (4m). To a solution of 2.23 g (10 mmol) of 5-(phenylmethoxy)indole in 15 mL of THF, stirred under nitrogen in a round bottom flask that was cooled in an ice bath, was added 6.15 mL (12 mmol) of a 2 M solution of CH_3MgBr in Et_2O. The mixture was stirred in the ice bath for another 15 min, and a solution of 2.38 g (12 mmol) of isophthalic acid, monomethyl ester monochloride was added. The reaction mixture was stirred at room temperature for 18 h and poured into cold water. The aqueous mixture was extracted with EtOAc. The combined extracts were washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue obtained was chromatographed on silica gel using 25% EtOAc in hexane as eluent to give 0.4 g of 3-(3-carbomethoxybenzoyl)-5-(phenylmethoxy)indole. This intermediate was alkylated with reagent **9** to give the methyl ester of **4m**. Alkaline hydrolysis of this ester gave **4m** as beige powder: ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.90 (m, 2 H), 2.91, 3.03 (2 s, 3 H), 4.06 (m, 2 H), 4.66, 5.1 (2 s, 2 H), 5.1 (s, 2 H), 6.83−8.3 (m, 18 H). Anal. ($C_{34}H_{30}N_2O_5\cdot0.2H_2O$) C, H, N.

2-[1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)indol-3-yl]phenylacetic Acid (4r). To a solution of 1 g (4.48 mmol) of 4-(phenylmethoxy)indole in 10 mL of Et_2O, stirred under nitrogen in an ice bath, was added dropwise 1.5 mL (4.48 mmol) of a 3 M solution of CH_3MgBr in Et_2O, followed by 1.31 g (5.37 mmol) of ethyl 2-bromophenylacetate. The reaction mixture was stirred at room temperature for 18 h and at reflux for 6 h. The reaction mixture was poured into cold water, and the aqueous mixture was extracted with EtOAc. The combined extracts were washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel using 20% EtOAc in hexane as eluent to yield 0.45 g of ethyl 2-[4-(phenylmethoxy)indol-3-yl]phenylacetate as an off-while powder: mp 126−128 °C; ^{1}H NMR δ 1.10 (t, 3 H), 4.10 (q, 2 H), 5.20 (s, 2 H), 5.81 (s, 1 H), 6.60 (d, 2 H), 6.90-7.20 (m, 3 H), 7.40 (s, 5

H), 7.50 (s, 5 H), 8.23 (bs, 1 H). This intermediate was N-alkylated with **9** to afford 0.44 g of the ester of **4r**: ^{1}H NMR δ 1.06 (t, 3 H), 2.69, 2.90 (2 s, 3 H), 2.71 (m, 2 H), 3.42 (m, 2 H), 4.01 (m, 2 H), 4.18, 4.55 (2 s, 2 H), 5.02 (s, 2 H), 5.56, 5.62 (2 s, 1 H), 6.39 (m, 2 H), 6.60−7.25 (m, 17 H). Hydrolysis of the ester gave **4r** as white crystalline substance: ^{1}H NMR δ 2.71 (m, 2 H), 2.31, 2.93 (2 s, 3 H), 3.46, 3.54 (2 t, 2 H), 4.14, 4.18, 4.26, 4,3 (4 s, 2 H), 4.7 (bs, 1 H), 5.04 (m, 2 H), 5.55, 5.63 (2 s, 1 H), 6.31−7.26 (m, 13 H). Anal. ($C_{34}H_{32}N_2O_4$) C, H, N.

Ethyl 1-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)-3-indolecarboxylate (ester of 4s): ^{1}H NMR δ 1.20 (t, 3 H), 2.73, 2.90 (2 s, 3 H), 2.76 (m, 2 H), 4.17, 4.56 (2 s, 2 H), 4.20 (m, 2 H), 5.14, 5.16 (2 s, 2 H), 6.30−7.60 (m, 14 H).

1-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-4-(phenylmethoxy)-3-indolecarboxylic acid (4s): ^{1}H NMR δ 2.86 (m, 2 H), 2.89, 2.98 (2 s, 3 H), 3.55 (m, 2 H), 4.24, 4.75 (2 s, 2 H), 5.20, 5.24 (2 s, 2 H), 6.43 (d, 2 H), 6.80 (m, 2 H), 6.94−7.30 (m, 10 H), 7.46, 7.79 (2 s, 1 H). Anal. ($C_{27}H_{26}N_2O_4$) C, H, N.

3-Carbomethoxy-4-[2-(phenylmethoxy)phenyl]-3-butenoic Acid (12a). A solution of 210.7 g (0.99 mol) of 2-(phenylmethoxy)benzaldehyde (**11a**) and 173.65 g (1.19 mol) of dimethyl succinate in 500 mL of *t*-BuOH was added dropwise within 3 h to a refluxing mixture of 166.1 g (1.48 mol) of KO-*t*-Bu and 1000 mL of *t*-BuOH. Reflux was continued for another 3 h, and *t*-BuOH was removed *in vacuo*. The residue obtained was dissolved in 1000 mL of 1 N aqueous HCl, and the aqueous solution was extracted with three 250-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield an oily crude product. This oil was stirred in a solvent mixture of hexane: Et_2O (9:1, v/v) overnight, and the solid substance formed was collected and dried under reduced pressure to give 275 g (0.848 mol) of **12a**: ^{1}H NMR δ 3.55 (s, 2 H), 3.82 (s, 3 H), 5.12 (s, 2 H), 6.60−7.50 (m, 9 H), 8.10 (s, 1 H).

Methyl 4-Acetoxy-8-(phenylmethoxy)-2-naphthalenecarboxylate (13a). A solution of 275 g (0.848 mol) of **12a** in 1000 mL of acetic anhydride was heated at reflux for 6 h. After cooling, the mixture was concentrated *in vacuo*, and the residue was dissolved in toluene. The toluene solution was concentrated *in vacuo*. This process was repeated one more time, and the residue was dissolved in Et_2O. After the mixture stood at room temperature overnight, a solid precipitate formed was collected by filtration to give 75 g of **13a** as yellow solid. The filtrate was concentrated *in vacuo* and dissolved in a CH_3OH:H_2O solvent mixture and cooled to 0 °C. The crystalline substance formed was collected by filtration to give another batch of **13a**. The filtrate was purified on a short silica gel column using 10% acetone in hexane as eluent to afford an additional quantity of the product. The total yield of **13a** was about 127 g: ^{1}H NMR δ 2.41 (s, 3 H), 3.95 (s, 3 H), 5.28 (s, 2 H), 6.92 (d, 1 H), 7.30−7.51 (m, 7 H), 7.85 (s, 1 H), 9.00 (s, 1 H).

Methyl 4-Hydroxy-8-(phenylmethoxy)-2-naphthalenecarboxylate (14a). Sodium (12.49 g, 0.543 mol) was added in portions within 1 h under argon to 1000 mL of anhydrous CH_3OH. To this mixture was added 126.93 g of **13a** (0.362 mol) in one portion. The reaction mixture was stirred for 1 h and acidified to pH ∼3 with 1 N HCl solution (∼800 mL). The precipitate formed was collected by filtration and dissolved in EtOAc. The organic solution was dried ($MgSO_4$), and solvent was removed *in vacuo* to give 109.38 g of **14a** as a pale yellow solid: ^{1}H NMR δ 3.89 (s, 3 H), 5.30 (s, 2 H), 7.11 (d, 1 H), 7.30−7.59 (m, 7 H), 7.87 (d, 1 H), 8.55 (s, 1 H), 9.40 (bs, 1 H).

3-Carbomethoxy-5-(phenylmethoxy)-1-naphthyl Trifluoromethanesulfonate (15a). Pyridine (144 mL, 1.77 mol) was added to a solution of 109.4 g (0.355 mol) of **14a** in 800 mL of anhydrous CH_2Cl_2. The mixture was cooled in an ice bath and 71.7 mL (0.426 mol) of triflic anhydride was added dropwise within 0.5 h. The reaction mixture was stirred in the cooling bath for an additional 1 h, and solvent was removed *in vacuo*. The residue was diluted with 1 N HCl solution and extracted with three 250-mL portions of EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 155.1 g of **15a** as light brown solid substance: ^{1}H NMR δ 3.89 (s, 3 H), 5.31 (s, 2 H), 7.03 (d, 1 H), 7.35−7.70 (m, 7 H), 8.02 (s, 1 H), 9.11 (s, 1 H).

Methyl 8-(Phenylmethoxy)-4-vinyl-2-naphthalenecarboxylate (16a). A mixture of 100.44 g (0.288 mol) of **15a**, 48.34 g (1.14 mol) of lithium chloride, 3.2 g (4.56 mmol) of bis-(triphenylphosphine)palladium(II) chloride, and ∼600 mL of anhydrous DMF was stirred at room temperature under an argon atmosphere for 15 min. Next, 79.55 g (0.251 mol) of vinyltributyltin was added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into 1000 mL of water and extracted with four 200-mL portions of EtOAc. The organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was taken up in 500 mL of Et_2O and treated with 2 equiv of a solution of KF in water. The precipitate formed (Bu_3SnF) was removed by filtration. The filtrate was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography using 5% EtOAc in hexane as eluent to yield 57.89 g of **16a**: ^{1}H NMR δ 3.93 (s, 3 H), 5.25 (s, 2 H), 5.51 (d, 1 H), 5.88 (d, 1 H), 6.90 (d, 1 H), 7.31−7.52 (m, 6 H), 7.66 (d, 1 H), 8.22 (s, 1 H), 9.05 (s, 1 H).

Methyl 4-(2-Hydroxyethyl)-8-(phenylmethoxy)-2-naphthalenecarboxylate (17a). To a solution of 57.89 g (0.182 mol) of **16a** in 500 mL of THF, stirred at room temperature under argon, was added 44.45 g (0.364 mol) of 9-BBN. The reaction mixture was stirred for 48 h, cooled in an ice bath, and treated with 100 mL each of H_2O and 30% H_2O_2. The mixture was stirred for an hour each in the ice bath, and at room temperature. The mixture was again cooled in an ice bath and 27.3 mL of 2 N aqueous NaOH solution was added. After bein stirred in the cooling bath for 4 h, the mixture was extracted with four 150-mL portions of EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed on a silica gel using a solvent mixtures of 15−50% ethyl acetate in hexane as the eluent to afford 40.5 g of **17a**: ^{1}H NMR δ 3.32 (t, 2 H), 3.91 (s, 3 H), 3.98 (t, 2 H), 6.90 (d, 1 H), 7.31−7.57 (m, 7 H), 7.61 (d, 1 H), 7.98 (s, 1 H), 9.01 (s, 1 H). Five grams of unreacted starting material **16a** was also recovered.

3-Carbomethoxy-5-(phenylmethoxy)-1-naphthaleneacetic Acid (18a): To a suspension of 64.03 g (0.19 mol) of **17a** in 1500 mL of acetone was added dropwise at 0 °C 50 mL of Jones reagent. The mixture was stirred at ∼0 °C for 38 h, and during this period a total of 130 mL of Jones reagent in three portions was added at intervals. The mixture was then diluted with H_2O and extracted with EtOAc. The organic extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was triturated with Et_2O to give **18a** as light brown solid substance. The concentrated mother liquor was triturated again in Et_2O. This procedure was repeated twice to yield additional crops of the product. Total yield of **18a** was 40.2 g (with minor impurities): ^{1}H NMR δ 3.98 (s, 3 H), 4.11 (s, 2 H), 5.32 (s, 2 H), 6.93 (d, 1 H), 7.32−7.54 (m, 7 H), 8.04 (s, 1 H), 9.10 (s, 1 H).

Methyl 4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylate (19a). To a solution of 40.2 g (0.115 mol) of **18a** in 100 mL of CH_2Cl_2 was added 27.91 (0.172 mol) of CDI. The mixture was stirred at room temperature for 1 h, and 23.27 g (0.172 mol) of *N*-methylphenethylamine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added. The mixture was stirred at room temperature for 18 h and concentrated *in vacuo*. The residue obtained was diluted with EtOAc, and the organic solution was washed with 1 N HCl solution, saturated aqueous Na_2CO_3 solution, and H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel using 30−50% EtOAc in hexane as the eluent to afford 30.8 g of **19a** as a beige oily substance: ^{1}H NMR δ 2.30, 2.89 (2 t, 2 H), 2.92, 3.02 (2 s, 3 H), 3.59, 3.63 (2 t, 2 H) 3.75, 4.07 (2 s, 2 H), 3.92, 3.94 (2 s, 3 H), 5.25, 5.28 (2 s, 2 H), 6.89, 6.91 (2 d, 1 H), 7.05−7.54 (m, 7 H), 7.78, 7.95 (2 s, 1 H), 9.03, 9.07 (2 s, 1 H).

4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic Acid (2a). To a solution of 30.8 g (65.87 mmol) of **19a** in 450 mL of a solvent mixture of THF:CH_3OH:H_2O (1:1:1) was added 13.82 (0.329

mol) of LiOH·H_2O. This mixture was stirred overnight at room temperature and acidified to pH ~3 with 1 N HCl solution. The precipitate formed was extracted into EtOAc. The organic extracts were washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was triturated with Et_2O to afford 26.7 g of **2a** as white powder: ^{1}H NMR δ 2.88, 2.91 (2 t, 2 H), 2.98, 3.08 (2 s, 3 H), 3.67 (m, 2 H), 3.79, 4.12 (2 s, 2 H), 5.29, 5.31 (2 s, 2 H), 6.91, 6.93 (2 d, 1 H), 7.12−7.56 (m, 7 H), 7.82, 8.01 (2 s, 1 H), 9.12, 9.14 (2 s, 1 H). Anal. ($C_{29}H_{27}NO_4$) C, H, N.

The 2-naphthalenecarboxylic acids **2k**−**n**, and the intermediates leading to them, were prepared by the procedures described above, with the exception of intermediates **13l**, **20**, and **21**.

Methyl 4-acetoxy-8-phenoxy-2-naphthalenecarboxylate (13k): ^{1}H NMR δ 2.52 (s, 3 H), 4.03 (s, 3 H), 6.98−7.82 (m, 8 H), 8.07 (d, 1 H), 9.18 (d, 1 H).

Methyl 4-Acetoxy-8-phenyl-2-naphthalenecarboxylate (13l). A mixture of 3.55 g of **13a** (10.1 mmol), 1.5 g of 10% Pd/C, and 240 mL of EtOH was shaken in a Parr apparatus under 35 psi of H_2 for 2.5 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give methyl 4-acetoxy-8-hydroxy-2-naphthalenecarboxylate in quantitative yield: ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 2.54 (s, 3 H), 4.02 (s, 3 H), 7.12 (dd, 1 H), 7.50 (m, 1 H), 7.81 (d, 1 H), 7.98 (d, 1 H), 9.16 (d, 1 H), 10.34 (s, 1 H). To a solution of 2.578 g (9.9 mmol) of methyl 4-acetoxy-8-hydroxy-2-naphthalenecarboxylate in 30 mL of pyridine was added dropwise at room temperature 2 mL (3.35 g, 11.88 mmol) of trifluoromethanesulfonic anhydride. The reaction mixture was stirred for 18 h and concentrated *in vacuo*. The residue was dissolved in EtOAc, and the organic solution was washed with 1 N aqueous HCl solution and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed on silica gel using 20% EtOAc in hexane as the eluent to give 2.1 g of the triflate as yellow solid: ^{1}H NMR δ 2.47 (s, 3 H), 4.00 (s, 3 H), 7.50−7.60 (m, 2 H), 7.83−7.95 (m, 2 H), 8.69 (d, 1 H). To a solution of 7.32 g (18.7 mmol) of the triflate in 50 mL of dioxane was added 5.94 g (28 mmol) of K_3PO_4, 2.5 g (20.5 mmol) of phenylboric acid (97%), and 0.54 g (0.47 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was stirred in an oil bath of 85 °C for 18 h, cooled, and poured into ~500 mL of cold H_2O. EtOAc was added, and the gray solid Pd catalyst was removed by filtration. The layers were separated, and the aqueous layer was extracted with additional amount of EtOAc. The combined extracts were washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was triturated in acetone:Et_2O to give **13l** as grayish powder. The mother liquor was concentrated, and the residue was purified on a silica gel column, using 10% EtOAc in hexane as the eluent, to afford additional amount of product. Total yield of **13l** was 5.2 g: ^{1}H NMR δ 2.46 (s, 3 H), 3.86 (s, 3 H), 7.34−7.90 (m, 9 H), 8.50 (d, 1 H).

Methyl 4-hydroxy-8-phenoxy-2-naphthalenecarboxylate (14k): ^{1}H NMR δ 3.34 (s, 3 H), 6.95 (d, 1 H), 7.04 (m, 2 H), 7.16 (t, 1 H), 7.34−7.48 (m, 4 H), 7.96 (d, 1 H), 8.31 (bs, 1 H).

Methyl 4-hydroxy-8-phenyl-2-naphthalenecarboxylate (14l): ^{1}H NMR (5−10% DMSO-d_6 in $CDCl_3$) δ 3.85 (s, 3 H), 7.33−7.60 (m, 3 H), 7.33 (s, 5 H), 8.08 (bs, 1 H), 8.28 (d, 1 H).

3-Carbomethoxy-5-phenoxy-1-naphthyl trifluoromethanesulfonate (15k): ^{1}H NMR δ 4.12 (s, 3 H), 7.08−8.05 (m, 8 H), 8.29 (d, 1 H), 9.36 (d, 1 H).

Methyl 8-phenoxy-4-vinyl-2-naphthalenecarboxylate (16k): ^{1}H NMR δ 4.02 (s, 3 H), 5.60 (d, 1 H), 5.94 (d, 1 H), 6.96−8.00 (m, 9 H), 8.39 (s, 1 H), 9.19 (s, 1 H).

Methyl 8-phenyl-4-vinyl-2-naphthalenecarboxylate (16l): ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 5.66 (dd, 1 H), 5.95 (dd, 1 H), 7.0−7.87 (m, 8 H), 8.28 (d, 1 H), 8.33 (bs, 1 H).

Methyl 4-(2-hydroxyethyl)-8-phenoxy-2-naphthalenecarboxylate (17k): ^{1}H NMR δ 3.40 (t, 2 H), 4.02 (s, 3 H), 4.06 (t, 3 H), 7.02 (d, 1 H), 7.20−7.70 (m, 7 H), 7.98 (d, 1 H), 8.16 (s, 1 H), 9.16 (s, 1 H).

Methyl 4-(2-hydroxyethyl)-8-phenyl-2-naphthalenecarboxylate (17l): ^{1}H NMR δ 3.4 (t, 2 H), 3.9 (s, 3 H), 4.05 (t, 2 H), 7.26−7.9 (m, 7 H), 8.17 (m, 2 H), 8.66 (bs, 1 H).

3-Carbomethoxy-5-phenoxy-1-naphthaleneacetic acid (18k): ^{1}H NMR δ 3.95 (s, 3 H), 4.14 (s, 2 H), 6.95 (d, 1 H), 7.13 (d, 2 H), 7.21 (t, 1 H), 7.42 (m, 2 H), 7.6 (t, 1 H), 7.77 (d, 1 H), 8.0 (s, 1 H), 8.86 (s, 1 H).

3-Carbomethoxy-5-phenyl-1-naphthaleneacetic acid (18l): ^{1}H NMR δ 3.87 (s, 3 H), 4.16 (s, 2 H), 7.23−7.74 (m, 8 H), 7.97 (m, 2 H), 8.6 (bs, 1 H).

Methyl 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenoxy-2-naphthalenecarboxylate (19k): ^{1}H NMR δ 2.91 (m, 2 H), 3.06, 3.12 (2 s, 3 H), 3.73 (m, 2 H), 3.86, 4.20 (2 s, 2 H), 4.03 (s, 3 H), 7.07 (d, 1 H), 7.24−7.93 (m, 12 H), 7.91, 8.10 (2 s, 1 H), 9.11, 9.17 (2 s, 1 H).

Methyl 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenyl-2-naphthalenecarboxylate (19l): ^{1}H NMR δ 2.84, 2.86 (2 t, 2 H), 3.0, 3.06 (2 s, 3 H), 3.66 (t, 2 H), 3.87 (s, 3 H), 3.87, 4.13 (2 s, 2 H), 7.0−8.0 (m, 14 H), 8.56 (bs, 1 H).

Methyl 8-hydroxy-4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-2-naphthalenecarboxylate (20) was prepared from **19a** in a manner similar to the preparation of methyl 4-acetoxy-8-hydroxy-2-naphthalenecarboxylate from **13a** (see synthesis of **13l** from **13a**): ^{1} H NMR δ 2.99 (t, 2 H), 3.07, 3.14 (2 s, 3 H), 3.74, 4.03 (2 s, 2 H), 3.75 (t, 2 H), 3.94, 3.96 (2 s, 3 H), 6.2 (m, 1 H), 6.78, 6.95 (2 d, 1 H), 7.01 (m, 1 H), 7.21−7.43 (m, 5 H), 7.6, 7.81 (2 d, 1 H), 7.96, 8.06 (2 bs, 1 H), 8.52, 8.55 (2 d, 1 H).

Methyl 8-Methoxy-4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-2-naphthalenecarboxylate (21m). A mixture of 0.125 g (0.33 mmol) of **20**, 56 mg (0.397 mmol) of CH_3I, 46 mg (0.33 mmol) of K_2CO_3, and 25 mL of 2-butanone was heated to reflux under nitrogen for 18 h. Water and CH_2Cl_2 were added to the reaction mixture, and the layers were separated. The organic layer was washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography, using 10% EtOAc in CH_2Cl_2 as the eluent, to give 130 mg (0.33 mmol) of **21m** as a yellow oil: ^{1}H NMR δ 2.8, 2.89 (2 t, 2 H), 2.93, 3.04 (2 s, 3 H), 3.58, 3.64 (2 t, 2 H), 3.75, 4.06 (s, 2 H), 3.94, 3.95 (2 s, 3 H), 4.0, 4.02 (2 s, 3 H), 6.85 (t, 1 H), 7.13 (d, 1 H), 7.16−7.55 (m, 6 H) 7.78, 7.96 (2 s, 1 H), 8.95, 9.02 (2 s, 1 H).

Methyl 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(pentyloxy)-2-naphthalenecarboxylate (21n) was prepared according to the above procedure: ^{1}H NMR δ 0.97 (m, 3 H), 1.5 (m, 4 H), 1.94 (m, 2 H), 2.8, 2.86 (2 t, 2 H), 2.88, 3.0 (2 s, 3 H), 3.59, 3.64 (2 t, 2 H), 3.74, 4.06 (2 s, 2 H), 3.92, 3.93 (2 s, 3 H), 4.11 (m, 2 H), 6.84 (t, 1 H), 7.1−7.54 (m, 7 H), 7.79, 7.94 (2 s, 1 H), 8.97, 9.02 (2 s, 1 H).

4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenoxy-2-naphthalenecarboxylic acid (2k): ^{1}H NMR δ 2.79−3.10 (m, 2 H), 2.98, 3.03 (2 s, 3 H), 3.57−3.84 (m, 3 H), 4.13 (m, 2 H), 6.70−7.66 (m, 13 H), 7.79, 7.98 (2 s, 1 H), 9.02, 9.06 (2 s, 1 H). Anal. ($C_{28}H_{25}NO_4$·0.25H_2O) C, H, N.

4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenyl-2-naphthalenecarboxylic acid (2l): ^{1}H NMR δ 2.92 (m, 2 H), 3.03, 3.09 (2 s, 3 H), 3.70 (t, 3 H), 3.83, 4.17 (2 s, 2 H), 7.18−7.77 (m, 13 H), 7.94 (m, 1 H), 8.63, 8.69 (2 bs, 1 H). Anal. ($C_{28}H_{25}NO_3$) C, H, N.

8-Methoxy-4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-2-naphthalenecarboxylic acid (2m): ^{1}H NMR δ 2.79 (m, 2 H), 2.9, 2.96 (2 s, 3 H), 3.55 (m, 2 H), 3.66, 4.02 (2 s, 2 H), 3.94, 3.95 (2 s, 3 H), 6.8 (t, 1 H), 7.04−7.48 (m, 7 H), 7.69, 7.88 (2 s, 1 H), 8.86, 8.92 (2 s, 1 H). Anal. ($C_{23}H_{23}NO_4$·0.2H_2O) C, H, N.

4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(pentyloxy)-2-naphthalenecarboxylic acid (2n): ^{1}H NMR (DMSO-d_6) δ 0.92 (m, 3 H), 1.44 (m, 4 H), 1.87 (m, 2 H), 2.76, 2.84 (2 t, 2 H), 2.88, 3.04 (2 s, 3 H), 3.53, 3.66 (2 t, 2 H), 3.85, 4.12 (2 s, 2 H), 4.16 (m, 2 H), 7.0 (m, 1 H), 7.15−7.56 (m, 7 H), 7.67, 7.83 (2 s, 1 H), 8.75, 8.78 (2 s, 1 H). Anal. ($C_{27}H_{31}NO_4$·0.25H_2O) C, H, N.

N-Methyl-4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)naphthalene-2-hydroxamic Acid (2j). To a solution of 0.5 g (1.1 mmol) of **2a** in 10 mL of CH_2Cl_2, stirred under argon in an ice bath, were added 0.24 mL (2.76

mmol) of oxalyl chloride and a drop of DMF. The reaction mixture was stirred in the cooling bath for 1 h and was allowed to warm to room temperature. This mixture was added with stirring to a cooled (ice bath) mixture of 0.38 g (98% reagent, 4.41 mmol) of *N*-methylhydroxylamine hydrochloride, 0.9 mL of triethylamine, 5 mL of THF, and 1 mL of H_2O. The reaction mixture was stirred at room temperature for 2 h and poured into 100 mL of a 1 N aqueous HCl solution. CH_2Cl_2 was added, and the layers were separated. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified on a silica gel column, using 20−30% EtOAc in CH_2Cl_2 as the eluent, to yield 210 mg of **2j** as an off-white foam: ^{1}H NMR δ 2.85 (m, 2 H), 2.85, 2.98 (2 s, 3 H), 3.61 (m, 1 H), 3.74, 4.00 (2 s, 2 H), 5.27 (s, 2 H), 6.97−8.10 (m, 14 H), 8.74 (bs, 1 H). Anal. ($C_{30}H_{30}N_2O_4 \cdot 0.5H_2O$) C, H, N.

3-Carbomethoxy-4-(3-methoxyphenyl)butyric Acid (24). 3-Carbomethoxy-4-(3-methoxyphenyl)-3-butenoic acid (**23**) was prepared from *m*-anisaldehyde and methyl succinate according to the procedure described for the preparation of **12a**. Next, 21.1 g (~84.4 μmol) of crude 23, a yellow oil, was dissolved in 100 mL of HOAc, and 2.11 g of 10% Pd/C was added. The mixture was shaken under 50 psi of H_2 for 4 h and filtered to remove the catalyst. The filtrate was concentrated *in vacuo* to give 17.6 g of **24** as yellow oil: ^{1}H NMR δ 2.25−3.24 (m, 5 H), 3.63 (s, 3 H), 3.73 (s, 3 H), 6.67−7.25 (m, 4 H).

3-Carbomethoxy-6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (25). A solution of 27 g (106.8 mmol) of **24** and 15.6 mL (213.6 mmol) of thionyl chloride in CH_2Cl_2 was heated to reflux for 18 h. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in 100 mL of 1,2-dichloroethane, and this solution was added dropwise to a suspension of 57 g (427.3 mmol) as $AlCl_3$ in 300 mL of 1,2-dichloroethane. The reaction mixture was stirred at room temperature for 18 h and poured into cold water. The aqueous mixture was acidified with 150 mL of concentrated HCl and filtered. The filtrate was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel using 50% EtOAc in hexane as the eluent to give 5.3 g of **25** as a brown crystalline solid: ^{1}H NMR δ 2.8 and 3.15 (m, 5 H), 3.7 (s, 3 H), 6.73 (d, 1 H), 6.81 (dd, 1 H), 7.95 (d, 1 H).

3-Carbomethoxy-6-(phenylmethoxy)-3,4-dihydro-1(2*H*)-naphthalenone (26). A solution of 5.3 g (24.1 mmol) of **25** and 4.3 mL (35.1 mmol) of benzyl bromide in 30 mL of DMF was heated at 75 °C with 6.65 g (48.1 mmol) of anhydrous K_2CO_3 for 18 h. EtOAc and H_2O were added, and the layers were separated. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel using 25% EtOAc in hexane as the eluent to give 5.8 g of **26** as a brown solid: ^{1}H NMR δ 2.88 (m, 2 H), 3.17 (m, 3 H), 3.73 (s, 3 H), 5.12 (s, 2 H), 6.8 (d, 1 H), 6.92 (dd, 1 H), 7.4 (m, 5 H), 8.0 (d, 1 H).

***tert*-Butyl 3-Carbomethoxy-6-(phenylmethoxy)-1-naphthaleneacetate (27).** To a solution of 17.03 mL (72.5 mmol) of *tert*-butyl (diethylphosphono)acetate in 100 mL of THF was added in portions 2.17 g of NaH (72.5 mmol, 80% oil dispersion). After the mixture was stirred for 2 h at room temperature, 4.5 g (14.5 mmol) of **26** was added, and the reaction mixture was stirred at room temperature for 18 h. Water and EtOAc were added, and the layers were separated. The organic layer was washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography, using 6% EtOAc in hexane as the eluent, to afford 4.95 g (12.1 mmol) of the Wittig product as a yellow oil. This material and 4.13 g (18.18 mmol) of DDQ were dissolved in 20 mL of benzene, and the solution was heated at 60 °C for 2 h. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash silica gel chromatography, using 6% EtOAc in hexane as eluent, to give 2.75 g of **27** as yellow oil. The product was contaminated by a small amount of the ethyl ester formed via transesterification during the workup: ^{1}H NMR δ 1.43 (s, 9 H), 3.94 (s, 3 H), 5.21 (s, 2 H), 7.86 (m, 7 H), 7.84 (s, 1 H), 7.95 (d, 1 H), 8.41 (s, 1 H).

3-Carbomethoxy-6-(phenylmethoxy)-1-naphthaleneacetic acid (28). A solution of 1 g (2.5 mmol) of **27** and 3 mL of trifluoroacetic acid in 30 mL of CH_2Cl_2 was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* to afford 0.9 g of **28** as a white solid: ^{1}H NMR δ 3.94 (s, 3 H), 4.03 (s, 2 H), 5.16 (s, 2 H), 7.42 (m, 6 H), 7.85 (m, 2 H), 8.4 (s, 1 H).

4-[Methyl(2-phenethyl)amino]-2-oxoethyl]-7-(phenylmethoxy)-2-naphthalenecarboxylic acid (2b) was prepared from **28** according to the procedure described for the preparation of **2a** from **18a** (Scheme 2): ^{1}H NMR δ 2.9 (m, 2 H), 3.0 and 3.06 (s, 3 H), 3.64 (q, 2 H), 3.77 and 4.12 (s, 2 H), 5.18 and 5.2 (s, 2 H), 7.15−7.91 (m, 14 H), 8.42 and 8.47 (s, 1 H). Anal. ($C_{29}H_{27}NO_4$) C, H, N.

Benzyl 4-Bromo-1-(phenylmethoxy)-2-naphthalenecarboxylate (30). A solution of 5 g (14.57 mmol) of benzyl 4-bromo-1-hydroxy-2-naphthalenecarboxylate (**29**) (Alfred Bader Chemicals) and 2.08 mL (17.48 mmol) of benzyl bromide in 45 mL of a solvent mixture of acetone:DMF (8:1, v/v) was heated to reflux in the presence of 4.03 g (29.14 mmol) of anhydrous K_2CO_3 for 2 h. Water and EtOAc were added to the reaction mixture, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography, using 5% EtOAc in hexane as eluent, to give 1.9 g of **30** as a white solid. ^{1}H NMR δ 5.13 (s, 2 H), 7.2 (m, 12 H), 8.08 (m, 2 H), 8.26 (s, 1 H).

Methyl 3-Ethynyl-1-(phenylmethoxy)-2-naphthalenecarboxylate (31). A mixture of 1.9 g (4.38 mmol) of **30**, 1 mL (0.686 g, 7.02 mmol) of (trimethylsilyl)acetylene, 33 mg (0.044 mmol) of bis(triphenylphosphine)palladium(II) acetate, and 25 mL of triethylamine was heated at 100 °C for 4 h and then was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic layer was washed with saturated NH_4Cl solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in 50 mL of CH_3OH, and the solution was stirred at room temperature in the presence of 1 g of K_2CO_3 for 3 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography, using 5% EtOAc in hexane as eluent, to afford 0.2 g of **31** as an orange oil, which solidified after standing at room temperature for a few hours: ^{1}H NMR δ 3.34 (s, 1 H), 3.86 (s, 3 H), 5.08 (s, 2 H), 7.34 (m, 7 H), 8.04 (s, 1 H), 8.13 (m, 2 H).

3-Carbomethoxy-4-(phenylmethoxy)-1-naphthaleneacetic Acid (32). To a solution of 1.25 mL (1.25 mmol) of 2,3-dimethyl-2-butene in 20 mL of THF was added dropwise at 0 °C 1.25 mL (1.25 mmol) of a 1.0 M solution of borane−THF complex in THF. The mixture was stirred at 0 °C for 2 h, and a solution of 0.36 g (1.13 mmol) of **31** in 10 mL of THF was added. The mixture was stirred at 0 °C for another 2 h, and a solution of 0.88 g (5.12 mmol) of 3-chloroperoxybenzoic acid in 10 mL of THF was added. After being stirred for an additional 18 h at room temperature, the reaction mixture was treated with 2 N aqueous NaOH solution, H_2O, and Et_2O, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 30 mL of acetone, and Jones reagent was added at 0 °C until a green precipitate occurred. The reaction mixture was stirred in the cooling bath for another hour and then treated with EtOAc and H_2O, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was partitioned between EtOAc and saturated aqueous Na_2CO_3 solution. The aqueous layer was acidified with 1 N HCl to pH ~1. The precipitate that occurred was collected by filtration and dried to afford ~70 mg of crude **32** as a yellow solid. This substance was used for the preparation of **2c** without further purification.

4-[2-Methyl(2-phenethyl)amino]-2-oxoethyl]-1-(phenylmethoxy)-2-naphthalenecarboxylic acid (2c) was prepared from **32** according to the procedures described for the synthesis of **2a** from **18a** (Scheme 2). Methyl ester of **2c**: ^{1}H NMR δ 2.87 (m, 2 H), 3.0, 3.05 (2 s, 3 H), 3.66 (m, 2 H), 3.72, 4.05 (2 s, 2 H), 3.9 (s, 3 H), 5.13, 5.16 (2 s, 2 H), 7.15−7.65 (m, 11 H), 7.78 (s, 1 H), 7.9 (d, 1 H), 8.29 (d, 1 H), 8.34 (d, 1 H).

2c: ^{1}H NMR δ 2.9 (m, 2 H), 3.03, 3.06 (2 s, 3 H), 3.68 (m, 2 H), 3.73, 4.08 (2 s, 2 H), 5.15, 5.2 (2 s, 2 H), 7.14−7.93 (m, 13 H), 7.91 (s, 1 H), 8.29 (m, 1 H).

4-(2-Hydroxyethyl)-8-phenoxy-2-naphthaldehyde (33). To a solution of 4.86 g (15.1 mmol) of **17k** in 120 mL of THF cooled in a cold water bath (*ca.* 5−10 °C) was added in portions 1.2 g of LAH. The mixture was stirred in the cooling bath for 1 h, and 4.5 mL of H_2O was added slowly, followed by ∼1 mL of 1 N aqueous HCl. The solid substance occurred was removed by filtration. The filtrate was washed with saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to afford 4.4 g of 4-(2-hydroxyethyl)-8-phenoxy-2-naphthalenemethanol as a solid substance. Then 4.16 g (14.14 mmol) of the naphthalenemethanol was dissolved in 800 mL of CH_2Cl_2, and 7.25 g (83.43 mmol) of activated MnO_2 was added. The mixture was stirred at room temperature for 18 h and filtered. The filtrate was concentrated *in vacuo* to afford 2.5 g of **33**: ^{1}H NMR δ 3.16 (bs, 1 H), 3.40 (t, 2 H), 4.04 (t, 2 H), 7.03−8.06 (m, 9 H), 8.88 (s, 1 H), 10.26 (d, 1 H).

Ethyl 3-[4-(2-hydroxyethyl)-8-phenoxy-2-naphthyl]propenoate (34) was prepared from **33** according to the procedure described for the synthesis of **7a** from **6a** (Scheme 1), with the exception that 2.5 molar equiv of the reagent **10a** was used: ^{1}H NMR δ 1.35 (t, 3 H), 3.4 (t, 2 H), 4.1 (t, 2 H), 4.34 (q, 2 H), 6.7 (d, 1 H), 7.04−8.1 (m, 10 H), 8.54 (s, 1 H).

3-(2-Carbethoxyvinyl)-5-phenoxy-1-naphthaleneacetic acid (35) was prepared from **34** according to the procedure described for the synthesis of **18a** from **17a** (Scheme 2): ^{1}H NMR δ 1.4 (t, 3 H), 4.2 (s, 2 H), 4.36 (q, 2 H), 6.68 (d, 1 H), 7.04−8.1 (m, 10 H), 8.56 (bs, 1 H).

Ethyl 3-[4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenoxy-2-naphthyl]propenoate (36) was prepared from **35** according to the procedure described for the synthesis of **19a** from **18a** (Scheme 2): ^{1}H NMR δ 1.35 (t, 3 H), 2.94 (m, 2 H), 3.02, 3.11 (2 s, 3 H), 3.71 (m, 2 H), 3.84, 4.13 (2 s, 2 H), 4.34 (q, 2 H), 6.6, 6.64 (2 d, 1 H), 6.97−7.75 (m, 14 H), 7.94, 7.98 (2 d, 1 H), 8.46, 8.53 (2 bs, 1 H).

The following naphthyl carboxylic acids were prepared from the corresponding esters according to the procedure described for the synthesis of **2a** from **19a** (Scheme 2).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthyl]propenoic acid (2d): ^{1}H NMR δ 2.76 (t, 2 H), 2.91, 3.03 (2 s, 3 H), 3.56 (t, 2 H), 3.72, 4.02 (2 s, 2 H), 5.2 (s, 2 H), 6.46, 6.49 (2 d, 1 H), 6.8−7.54 (m, 14 H), 7.8, 7.84 (2 d, 1 H), 8.34, 8.38 (2 s, 1 H).

5-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthyl]-2,4-pentadienoic acid (2e): ^{1}H NMR δ 2.90 (m, 2 H), 2.98, 3.10 (2 s, 3 H), 3.60 (m, 2 H), 3.86, 4.14 (2 s, 2 H), 5.35 (s, 2 H), 6.10 (d, 1 H), 7.06−7.60 (m, 17 H), 8.46 (m, 1 H).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthyl]propanoic acid (2f): ^{1}H NMR δ 2.51 (m, 4 H), 2.9, 3.04 (2 s, 3 H), 2.9, 3.1 (2 t, 2 H), 3.54, 3.68 (2 t, 2 H), 3.76, 4.06 (2 s, 2 H), 5.24, 5.25 (2 s, 2 H), 6.89 (m, 1 H), 6.97−7.56 (m, 13 H), 8.1, 8.14 (2 s, 1 H).

5-[4-[2-Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthyl]pentanoic acid (2g): ^{1}H NMR δ 1.7 (m, 4 H), 2.3 (m, 2 H), 2.75 (t, 2 H), 2.76−2.91 (m, 2 H), 2.9, 3.05 (2 s, 3 H), 3.51, 3.67 (2 t, 2 H), 3.78, 4.06 (2 s, 2 H), 5.28, 5.3 (2 s, 2 H), 6.88 (m, 1 H), 7.04 (m, 1 H), 7.18−7.53 (m, 12 H), 8.06 (d, 1 H).

2-Ethyl-3-[4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthyl]propenoic acid (2h): ^{1}H NMR δ 1.24 (t, 2 H), 2.50−3.03 (m, 4 H), 2.97, 3.12 (2 s, 3 H), 3.64 (q, 2 H), 3.88, 4.16 (2 s, 2 H), 5.36 (s, 2 H), 7.07−7.80 (m, 14 H), 8.06 (d, 1 H), 8.64 (bs, 1 H).

4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-(2-tetrazol-5-ylvinyl)naphthalene (2i): ^{1}H NMR δ 3.06 (m, 2 H), 3.2 (s, 3 H), 3.64, 3.99 (2 s, 2 H), 3.86 (m, 2 H), 6.45 (d, 1 H), 6.5−7.55 (m, 15 H), 7.86 (d, 1 H).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenyl-2-naphthyl]propenoic acid (2o): ^{1}H NMR δ 2.85 (t, 2 H), 3.00, 4.13 (2 s, 3 H), 3.64 (t, 2 H), 3.80, 4.13 (2 s, 2 H), 6.36 (dd, 1 H), 6.94−7.64 (m, 15 H), 7.90 (m, 1 H).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenyl-2-naphthyl]propanoic acid (2p): ^{1}H NMR δ 2.54−3.04 (m, 4 H), 2.98, 3.10 (2 s, 3 H), 3.44−3.80 (m, 2 H), 3.80, 4.20 (2 s, 2 H), 7.13−7.86 (m, 14 H), 8.03 (m, 1 H).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenoxy-2-naphthyl]propenoic acid (2q): ^{1}H NMR δ 2.9 (m, 2 H), 3.03, 3.1 (2 s, 3 H), 3.68 (m, 2 H), 3.77, 4.1 (2 s, 2 H), 6.5, 6.55 (2 d, 1 H), 6.92 (t, 1 H), 7.03−7.6 (m, 14 H), 7.85, 8.0 (2 d, 1 H), 8.3, 8.36 (2 s, 1 H).

3-[4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-phenoxy-2-naphthyl]propanoic acid (2r): ^{1}H NMR δ 2.65 (m, 2 H), 2.83, 2.9 (2 t, 2 H), 3.0, 3.11 (2 s, 3 H), 3.06 (m, 2 H), 3.54, 3.61 (2 t, 2 H), 3.79, 4.12 (2 s, 2 H), 6.9 (m, 1 H), 7.0−7.62 (m, 13 H), 7.96, 8.1 (2 s, 1 H).

LTB_4 Receptor Ligand Binding Assays. For the protocols of the guinea pig spleen and human PMN whole cell binding assays, please see ref 3.

Guinea Pig PMN Aggregation Assay. Guinea pigs were injected ip with 6 mL of 6% sodium caseinate. Twenty-four hours later peritoneal PMNs were recovered by lavage with 7% sodium citrate in physiological saline. Cells were washed once in Hank's balanced salt solution and maintained at 1×10^5/mL on a rocking platform at room temperature in the absence of Ca^{2+} or Mg^{2+} (10 mM), preincubation at 37 °C for 5 min followed by addition of antagonist and, 2 min later, agonist (LTB_4). The ensuing aggregation was monitored for 5 min.

LTB_4-Induced Bronchoconstriction in Guinea Pigs. Male Hartley guinea pigs (350−400 g) were anesthetized with pentobartital (50 mg/kg, ip) and surgically prepared for measurement of airway function. A tracheal cannula was inserted, and a catheter was placed in the jugular vein to allow intravenous administration of drugs. Each animal was placed in a whole body plethysmograph and ventilated at the rate of 80 breaths/min and a tidal volume of 8 mL/kg. Changes in dynamic compliance (C_{dyn}) were measured using a Buxco pulmonary mechanics computer and Vlidyn differential pressure transducers. Spontaneous breathing was inhibited with gallamine triethiodide (15 mg/kg, iv) and sympatheitc modulation of airway tone was blocked with propranolol (1 mg/kg, iv). LTB_4 antagonist or vehicle was given orally 1 h before challenge with LTB_4. A DeVilbiss Pulmo-Sonic nebulizer, placed in-line between the ventilator and the animal, was used to give a continuous aerosol of LTB_4 for 3 min. Peak changes in C_{dyn} are measured at the 3 min time point. Mean (± SEM) values of the maximal responses for drug- and vehicle-treated groups were compared statistically using Student's *t*-test.

References

(1) For more information on the role of LTB4 and LTB4 antagonistis, see: Fird-Hutchinson, A. W. Leukotriene B_4 in Inflammation. *Crit. Rev. Immunol.* **1990**, *10*, 1−12. Djuric, S. W.; Fretland, D. J.; Penning, T. D. The Leukotriene B_4 Receptor Antagonists—A Most Discriminating Class of Antiinflammatory Agent? *Drugs Future* **1992**, *17*, 819−930. Cohen, N.; Yagaloft, K. Recent Progress in the Development of Leukotriene B_4 Antagonists. *Cur. Opin. Invest. Drugs* **1994**, *3*, 13−22.

(2) Huang, F. C.; Chan, W. K.; Warus, J.; Morrissette, M. M.; Moriarty, K.; Chang M. N.; Travis, J. J.; Mitchell, L. S.; Nuss, G. W.; Sutherland, C. A. 4-[2-(Methyl(2-phenethyl)amino)-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic Acid: A High Affinitiy, Competitive, Orally Active Leukotriene B_4 Receptor Antagonist. *J. Med. Chem.* **1992**, *35*, 4253-4255.

(3) Huang, F. C.; Chan, W. K.; Moriarty, K. J.; Poli, G.; Morrisette, M. M.; Galemmo, R. A.; Warus, J. D.; Dankulich, W. D.; Sutherland, C. A. A Novel Series of [2-[Methyl(2-phenethyl)-amino]-2-oxoethyl]benzene-Containing Leukotriene B_4 Antagonists: Initial Structure−Activity Relationships. *J. Med. Chem.* **1996**, *39*, 3748−3755.

(4) Loev, B.; Chan, W. K.; Jones, H. U.S. Patent 4,505,930, 1985.

(5) Reilly, L. Chemical Process & Development Department, Rhône-Poulenc Rorer Central Research, Collegeville, PA. Unpublished result.

(6) Baddar, F. G.; El-Assal, L. S.; Baghos, V. B. 1-Phenylnaphthalenes. Part II. The Cyclization of Ethyl Hydrogen rr-di-o-Methoxyphenyl and rr-di-p-Methoxyphenyl-Itaconate to the Corresponding 1-Phenylnaphthalenes. *J. Chem. Soc.* **1955**, 1714−1718.

(7) Takayuki, O.; Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reaction of Aryl or Vinylic Triflates with Organoboron Compounds. *Synlett* **1990**, 221−223.

(8) Scott, W. J.; Stille, J. K. Palladium-Catalyzed Coupling of Vinyl Triflates with Organostannanes. Synthetic and Mechanistic Studies. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.
(9) Pendrak, I.; Chambers, P. A. Improved Synthesis of RG-14893, a High-affinity Leukotriene B4 Receptor Antagonist, via a Photochemical Wolff Rearrangement. *J. Org. Chem.* **1995**, *60*, 3249−3251.
(10) Takahashi, S.; Kuroyama, Y.; Sonogashira, K,; Hagihara, N. A Convenient Synthesis of Ethynylarenes and Diethynylarenes. *Synthesis* **1980**, 627.
(11) Zweifel, G,; Arzoumanian, H. Geminal Organometallic Compounds. I. The Sythesis and Structure of 1,1-Diborohexane. *J. Am. Chem. Soc.* **1967**, *89*, 291.
(12) The guinea pig spleen cell membrane binding assay was purchased as a kit from New England Nuclear Research Products (Catalog No. NED-005A.)
(13) Lin, A.; Ruppel, P. L.; Gorman, R. R. Leukotriene B_4 Binding to Human Neutrophils. *Prostaglandins* **1984**, *28*, 837−849.
(14) Chan, W. K.; Lee, Thomas D. L.; Huang, F. C. U.S. Patent 4,758,586, 1988.
(15) Sutherland, C. A.; Chan, W. K.; Huang, F. C. Unpublished results.
(16) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. Benzophenone Dicarboxylic Acid Antagonists of Leukotriene B_4. 1. Structure-activity Relationships of the Benzophenone Nucleus. *J. Med. Chem.* **1990**, *33*, 2798−2807.
(17) Cunningham, F. M.; Shipley, M. E.; Smith, M. J. H. Aggregation of Rat Polymorphonuclear Leukocytes in vitro. *J. Pharm. Pharmacol.* **1980**, *32*, 377−380.
(18) Sutherland, C. A.; Mitchell, L.; Herczeg, T.; Yu, K. T.; Travis, J.; Sweeney, D.; Beale, L.; Chan, W. K.; Huang, F. C.; Chang, M.; Martin, G. E. Pharmacological Activity of RG 14893, A Novel Leukotriene B_4 Receptor Antagonist. Manuscript in preparation.

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