Discovery of Ecopladib, an Indole Inhibitor of Cytosolic Phospholipase $A_2\alpha$

Katherine L. Lee,*,† Megan A. Foley,† Lihren Chen,† Mark L. Behnke,† Frank E. Lovering,† Steven J. Kirincich,† Weiheng Wang,† Jaechul Shim,‖ Steve Tam,† Marina W. H. Shen,‡ SooPeang Khor,⊥ Xin Xu,⊥ Debra G. Goodwin,‡ Manjunath K. Ramarao,‡ Cheryl Nickerson-Nutter,‡ Frances Donahue,§ M. Sherry Ku,§ James D. Clark,‡ and John C. McKew†

Departments of Chemical and Screening Sciences, Inflammation, Drug Safety and Metabolism, and Chemical and Pharmaceutical Development, Wyeth Research, 200 CambridgePark Drive, Cambridge, Massachusetts 02140

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The synthesis and structure−activity relationship of a series of indole inhibitors of cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$, type IVA phospholipase) are described. Inhibitors of $cPLA_2\alpha$ are predicted to be efficacious in treating asthma as well as the signs and symptoms of osteoarthritis, rheumatoid arthritis, and pain. The introduction of a benzyl sulfonamide substituent at C2 was found to impart improved potency of these inhibitors, and the SAR of these sulfonamide analogues is disclosed. Compound **123** (Ecopladib) is a submicromolar inhibitor of $cPLA_2\alpha$ in the GLU micelle and rat whole blood assays. Compound **123** displayed *oral* efficacy in the rat carrageenan air pouch and rat carrageenan-induced paw edema models.

Introduction

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$,[a] type IVA phospholipase) catalyzes the selective release of arachidonic acid from the sn-2 position of glycerophospholipids to initiate the production of leukotrienes, prostaglandins, and thromboxanes. The 1-*O*-alkyl-2-OH-glycerophosphocholine remaining after arachidonic acid release can be acetylated to form another inflammatory mediator, platelet-activating factor (PAF). The release of arachidonic acid and PAF synthesis are linked as evidenced by studies in cells and animals where depletion of arachidonate at the sn-2 position of phospholipids results in lower levels of PAF synthesis.[1] In addition, the timecourse of synthesis of leukotrienes and PAF are the same.[2] Although the PLA_2 family is large and diverse,[3] $cPLA_2\alpha$ is the only lipase with significant selectivity for arachidonic acid[4,5] which originally suggested that it is the primary PLA_2 responsible for prostaglandin, leukotriene, and PAF production. Experiments with $cPLA_2\alpha$ deficient mice demonstrated that prostaglandin and leukotriene production was reduced by ~90%,[6,7] confirming the primacy of $cPLA_2\alpha$ in lipid mediator production.

$cPLA_2\alpha$ deficient mice are generally healthy with a defect in induction of labor that is also seen with the cyclooxygenase-1 (COX-1) deficient mice[8,9] and slightly reduced litter size, which was more pronounced in the COX-2 deficient mice.[10,11] The $cPLA_2\alpha$ deficient mice were resistant to disease in multiple models including an ova-induced anaphylaxis model of asthma,[6] a bleomycin-induced model of idiopathic pulmonary fibrosis,[8] acid and LPS-induced adult respiratory distress syndrome,[12] a collagen-induced arthritis model of rheumatoid arthritis,[13] an MPTP-induced Parkinson's model,[14] a model of colon cancer in the APC mouse,[15,16] an ischemia reperfusion model of stroke,[17] and a model of multiple sclerosis.[18] Deficiencies in COX-2,[19,20,21] 5-lipoxygenase (5-LO),[22,23] and 5-LO activating protein[24] each lead to resistance in a subset of these models, which demonstrates the position of $cPLA_2\alpha$ at the head of the biochemical pathway.

Several classes of $cPLA_2\alpha$ inhibitors have been reported in the literature,[25] and recently, reviews by Lehr[26] and Kokotos[27] have been published. Seno and co-workers at Shionogi have reported a class of pyrrolidine inhibitors represented in Chart 1 by compound **1**.[28,29] Indole inhibitors with a C2 carboxylic acid (e.g., **2**) have been reported by Lehr and co-workers.[30,31,32] Propanone inhibitors (e.g., **4**) have been described by Connolly and co-workers.[33] Dennis and co-workers have reported 2-oxoamide inhibitors represented by compound **5**[34] and showed efficacy in the rat carrageenan-induced edema assay with intraperitoneal dosing[35] and in models of pain with intrathecal dosing.[36] Recently, Lehr has reported potent in vitro activity with indolylpropanone inhibitors such as compound **6**.[37]

We evaluated some of these inhibitors (or a close analogue thereof, e.g., **3**) in our primary assays. In the GLU micelle assay, purified human $cPLA_2\alpha$ cleaves an artificial substrate, 7-hydroxycoumarinyl-γ-linolenate (GLU) that is presented in a high concentration of Triton micelles containing nonhydrolyzable 1,2-di-*O*-tetradecyl-*sn*-glycero-3-phosphocholine (DTPC) to promote calcium binding of the enzyme to the micelle. Of the compounds tested, compounds **1** and **4** displayed sub-micromolar activity in the GLU micelle assay. The second assay is the rat whole blood (RWB) assay, which is stringent due to both the presence of high lipid content and serum albumin. Only the Shionogi pyrrolidine **1** showed sub-micromolar activity in the RWB assay, as shown in Chart 1. Since clinically efficacious doses of NSAIDs, COX-2 inhibitors and 5-LO inhibitors give plasma levels comparable to the IC_{50}s in whole blood assays, it is likely that $cPLA_2\alpha$ inhibitors will need to show efficacy in whole blood assays.[38,39]

* To whom correspondence should be addressed. Phone: (617) 665-5664. Fax: (617) 665-5682. E-mail: klee@wyeth.com.
† Chemical and Screening Sciences, Cambridge, MA.
‖ Current address: Chemical and Screening Sciences, Pearl River, NY.
‡ Inflammation, Cambridge, MA.
⊥ Drug Safety and Metabolism, Andover, MA.
§ Chemical and Pharmaceutical Development, Pearl River, NY.

[a] Abbreviations: $cPLA_2\alpha$, cytosolic phospholipase $A_2\alpha$; PAF, platelet-activating factor; COX, cyclooxygenase; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 5-LO, 5-lipoxygenase; FLAP, 5-LO activating protein; GLU, 7-hydroxycoumarinyl-γ-linolenate; DTPC, 1,2-di-*O*-tetradecyl-*sn*-glycero-3-phosphocholine; RWB, rat whole blood; NSAID, nonsteroidal antiinflammatory drug; MC, methylcellulose; MCT, medium chain triglyceride; MAFP, methyl arachindonyl fluorophosphonate; PAPC, 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphocholine; PAPE, 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphoethanolamine; $sPLA_2$, secreted PLA_2; IgE, immunoglobulin E; PG, prostaglandin; LT, leukotriene; TX, thromboxane; HETE, hydroxyeicosatetraenoic acid; FT-ICR, Fourier transform ion cyclotron resonance; ESI, electrospray ionization; CPE, carrageenan paw edema.

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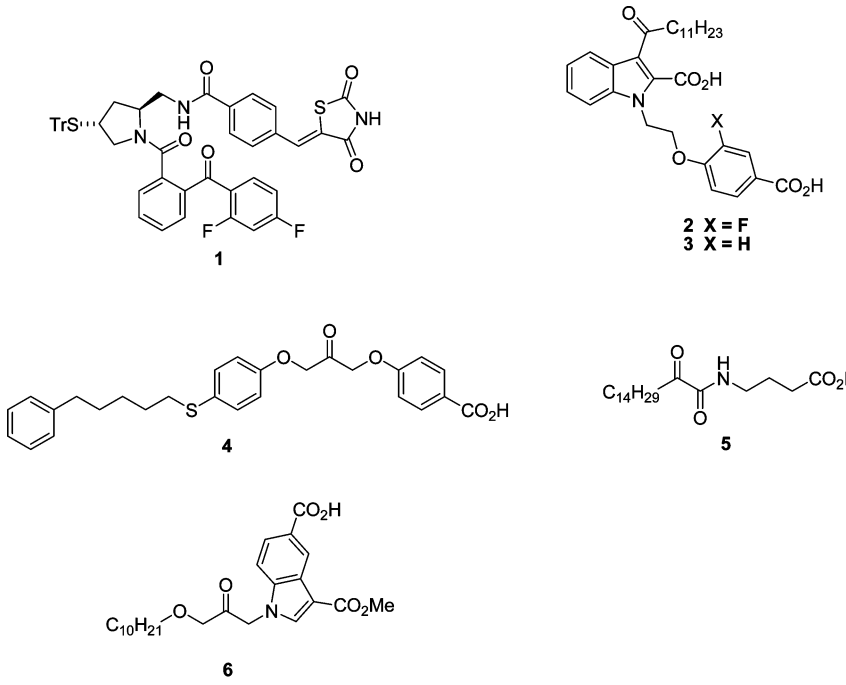
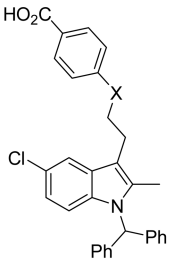
Chart 1. Examples of cPLA$_2$ Inhibitors



	GLU IC_{50} (μM)	RWB IC_{50} (μM)
1	0.11	0.25
2	NT	NT
3	-19% @ 10 μM	6% @ 50 μM
4	63% @ 0.04 μM	58% @ 12.5 μM
5	4.4	16% @ 10 μM
6	NT	NT

Chart 2. Wyeth's Indole Lead Compounds



	GLU IC_{50} (μM)	RWB IC_{50} (μM)	Rat IV Clearance (mL/min/kg)
7 X = O	3.0	7.0	3.2
8 X = SO_2	0.8	2.0	44

Our group has previously disclosed indole inhibitors of cPLA$_2\alpha$, including compounds **7** and **8** (Chart 2).[40,41] 2-Methylindoles **7** and **8** (Chart 2) are low micromolar inhibitors of cPLA$_2\alpha$ in the two primary assays. The IC_{50} values of **7** and **8** in the GLU micelle assay are 3.0 and 0.8 μM respectively, which for **7** corresponds to one inhibitor per >350 molecules of detergent and lipid. Thus, the inhibitor must be interacting with cPLA$_2\alpha$ and not be acting to disrupt the membrane surface. Compounds **7** and **8** have IC_{50}s of 7.0 and 2.0 μM, respectively, in the RWB assay.

Our efforts to synthesize more potent cPLA$_2\alpha$ inhibitors by increasing the substitution at C2 are reported here. We had defined a two-part pharmacophore for cPLA$_2\alpha$ inhibition in the *N*-benzhydryl group and C3 benzoic acid, and we sought to engineer a third interaction with the enzyme. Although compound **8** is more potent than **7**, we decided to focus our optimization efforts starting with **7** because it has a significantly lower clearance in rats (3.2 versus 44 mL/min/kg).

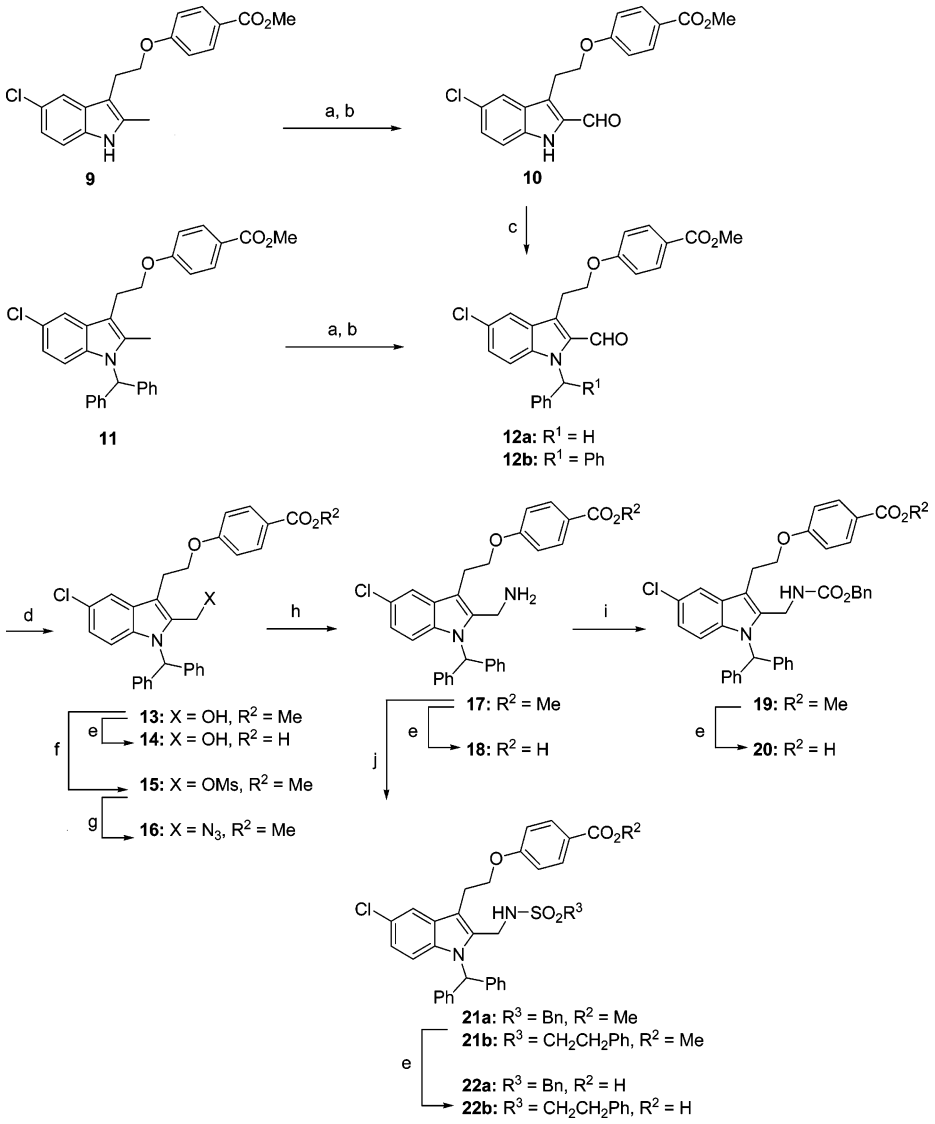
Chemistry

A variety of different substituents and linker lengths were required to adequately explore the SAR at the indole C2 position and several different routes were developed to deliver the diverse analogues required. Compounds with one-carbon substituents at C2 were synthesized as outlined in Scheme 1. A reductive alkylation method to install C3 substituents on indoles has previously been reported.[42,43] C2 methyl indole **9**[41] was converted to the dibromide and then treated with silver carbonate to afford aldehyde **10**. N-Alkylation with benzyl bromide then afforded compound **12a**. Indole **11**[41] was oxidized using a similar protocol to afford indole **12b**. Reduction of **12b** with $NaBH_4$ gave alcohol **13**, which was converted to amine **17** in a three-step procedure. Derivatization of the amine afforded carbamate **19** and sulfonamides **21a** and **21b**. Ester hydrolysis of selected compounds afforded the related carboxylic acids.

Alcohol **30** was synthesized as described in Scheme 2. 5-Chloroindole (**23**) underwent Friedel−Crafts acylation with oxalyl chloride and reduction with $LiAlH_4$. Alcohol **24** was activated as the mesylate and displaced with methyl 4-hydroxybenzoate. Indole **26** was then brominated at C2. N-Alkylation afforded benzhydryl derivative **28**. Ester hydrolysis afforded carboxylic acid **29**, which after treatment with excess *tert*-BuLi to make the dianion, was treated with ethylene oxide to afford alcohol **30**.

The syntheses of C2 aminoethyl derivatives are described in Scheme 3. Henry reaction of aldehydes **12a** and **12b** followed

Scheme 1[a]



[a] Reagents: (a) NBS, CCl_4; (b) Ag_2CO_3, acetone, H_2O; (c) NaH, BnBr, DMF; (d) $NaBH_4$, THF, MeOH; (e) 1 N NaOH, THF, MeOH; (f) MsCl, Et_3N, CH_2Cl_2; (g) NaN_3, DMF; (h) PPh_3, H_2O, THF; (i) BnOCOCl, Et_3N, CH_2Cl_2; (j) R^3SO_2Cl, sat. $NaHCO_3$, CH_2Cl_2.

by Zn(Hg) reduction[44,45] of the nitroolefins afforded amines **32a** and **32b**. The use of THF instead of MeOH as the solvent for the reduction minimized the formation of undesired byproducts. Carbamoylation and acylation of amine **32b** and ester hydrolysis yielded carbamate **35** and amide **37**, respectively. Reductive amination of **32b** with phenylacetaldehyde and subsequent ester hydrolysis afforded phenethylamine **39**.

As shown in Scheme 4, reaction of amine **32b** with various sulfonyl chlorides followed by ester hydrolysis provided sulfonamides **41a**, **41b**, **41d**, and **41e**, while a similar sequence with *N*-benzyl indole **32a** afforded **41c**. N-Methylation of sulfonamide **40d** using silver(I) oxide in neat MeI followed by ester hydrolysis yielded compound **43**. Using palladium catalysis,[46] 5-chloroindole **41d** was converted to the 5-morpholino derivative **44**.

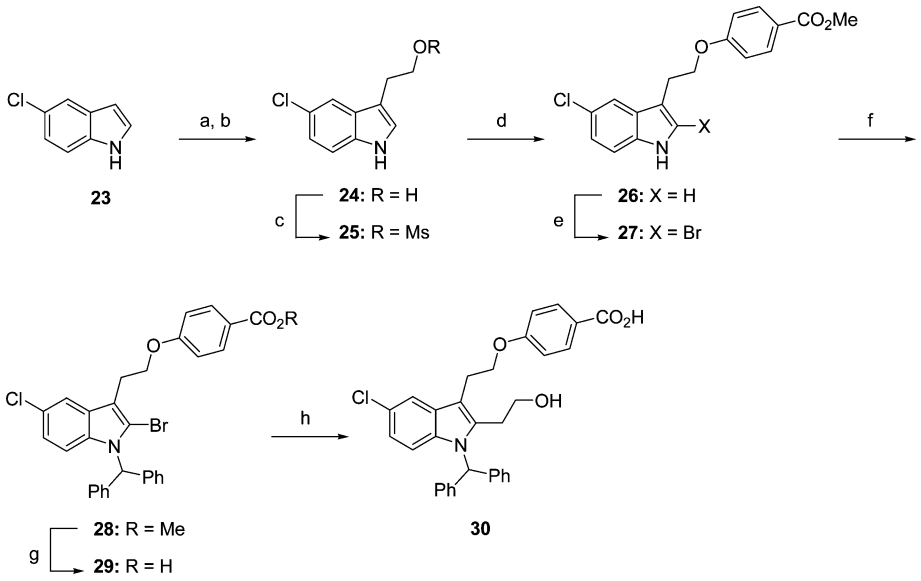
The preparation of reverse sulfonamide **50** is depicted in Scheme 5. Aldehyde **12b** was homologated in a two-step sequence. Borohydride reduction of the resulting aldehyde **46** and subsequent bromination produced bromide **48**. Displacement of the bromine with Na_2SO_3 afforded the sodium sulfonate. The sulfonyl chloride was then prepared and coupled without purification with benzyl amine. Finally, ester hydrolysis yielded sulfonamide **50**.

Scheme 6 shows the preparation of derivatives with a three-carbon linker at C2. Wittig olefination of aldehyde **12b**, followed by allyl deprotection and hydrogenation, afforded carboxylic acid **52**. Reduction to the alcohol and bromination resulted in bromide **55**, which was converted to sulfonamide **57** by reaction with α-toluenesulfonamide and subsequent ester hydrolysis. Bromide **55** was reacted with benzyl mercaptan, and the resulting thioether was oxidized with MCPBA. Ester hydrolysis afforded sulfone **59**.

Functionalization of the C3 benzoic acid (Scheme 7) yielded compounds **60** and **61**. Primary amide **60** was formed by treating carboxylic acid **41d** with CDI and NH_4OH. Reduction of acid **41d** to alcohol **61** was carried out by conversion to the acid fluoride and $NaBH_4$ reduction.[47]

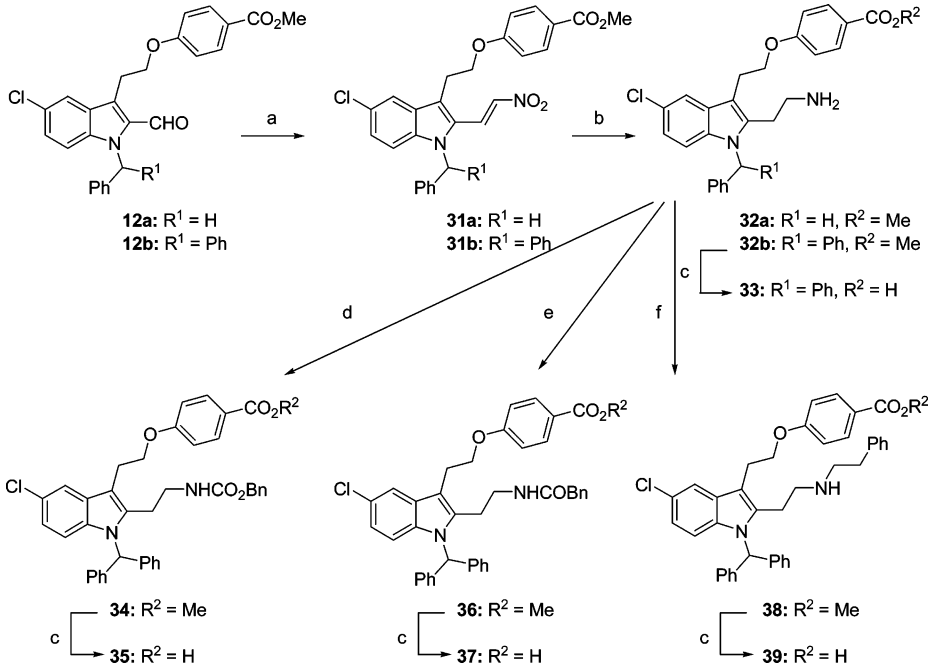
Scheme 8 depicts the synthesis of *m*- and *o*-carboxylates **75a** and **75b**. Iodoaniline **62** was N-alkylated then subjected to Sonogashira coupling and cyclization[48] to form indole **65**. The alcohol was then masked as a silyl ether. Acylation at C3 and reduction of the resulting ketoester intermediate using excess

Scheme 2[a]



[a] Reagents: (a) $(COCl)_2$, Et_2O, then MeOH, Et_3N; (b) $LiAlH_4$, THF; (c) MsCl, Et_3N, CH_2Cl_2; (d) methyl 4-hydroxybenzoate, NaH, DMF; (e) NBS, CCl_4; (f) NaH, Ph_2CHBr, DMF; (g) 1 N NaOH, THF, MeOH; (h) NaH, *t*-BuLi, ethylene oxide, THF.

Scheme 3[a]



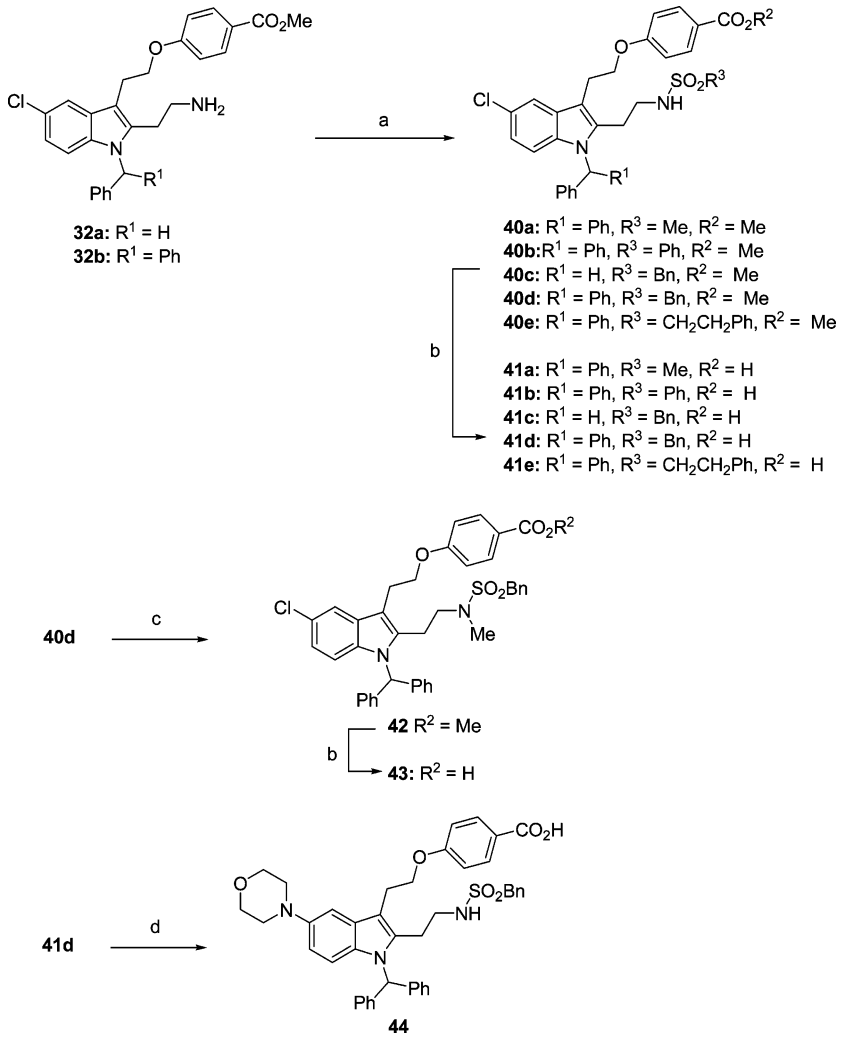
[a] Reagents: (a) NH_4OAc, $MeNO_2$; (b) Zn(Hg), concd HCl, THF; (c) 1 N NaOH, MeOH, THF; (d) BnOCOCl, Et_3N, CH_2Cl_2; (e) BnCOCl, sat. $NaHCO_3$, CH_2Cl_2; (f) $PhCH_2CHO$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$.

BH_3•Me_2S afforded alcohol **67**, which underwent Mitsunobu reaction with the two hydroxybenzoate isomers **68a** and **68b**. For each benzoate Mitsunobu product, the silyl ether was converted in a four-step sequence via the azide to the amines **73a** and **73b**. Sulfonylation and ester hydrolysis of amines **73a** and **73b** afforded meta- and ortho-substituted benzoic acids **75a** and **75b**, respectively.

The syntheses of the 5-nitroindoles **92** and **93** are shown in Scheme 9. 4-Nitroaniline (**79**) was iodinated and then N-alkylated with benzhydryl bromide to afford aniline **81**, which was reacted with alkyne **78** to afford an inseparable mixture of two indole regioisomers **82** and **83** (ca. 1:1.5 ratio).[48] The mixture of alcohols was mesylated and converted to the azides **86** and **87**. Following reduction, amines **88** and **89** were separated by flash chromatography and identified by NMR analysis. Each isomer was then converted separately to the corresponding sulfonamide. Ester hydrolysis afforded the carboxylic acids **92** and **93**.

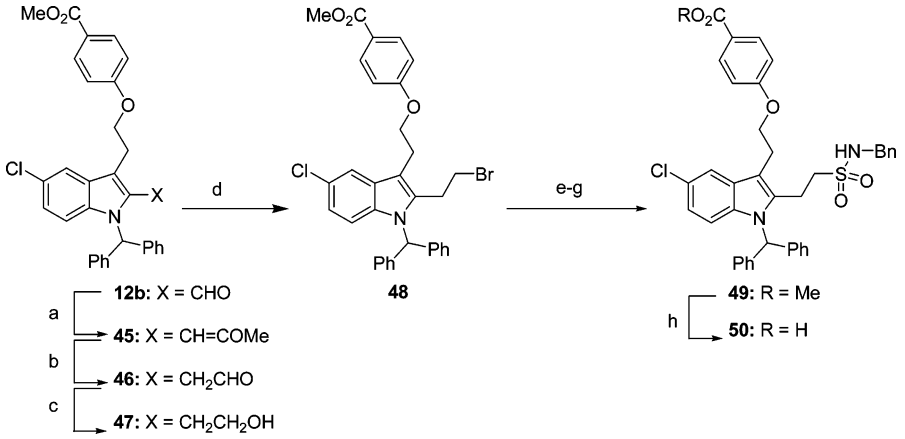
6-Chloroindole derivative **105** was synthesized according to Scheme 10. Treatment of 4-chloro-2-nitrotoluene (**96**) with diethyl oxalate and cyclization in the presence of iron yielded indole **97** in a modified Reissert indole synthesis.[49] The ester was reduced with $LiAlH_4$ and oxidized with MnO_2 to afford aldehyde **99**. N-Alkylation with benzhydryl bromide afforded aldehyde **100**, which then underwent Henry reaction, $LiAlH_4$ reduction to the amine, and sulfonylation to afford intermediate

Scheme 4[a]



[a] Reagents: (a) R^3SO_2Cl, sat. $NaHCO_3$ or DIEA, CH_2Cl_2; (b) 1 N NaOH, MeOH, THF; (c) Ag_2O, MeI (d) morpholine, $Pd_2(dba)_3$, NaO*t*-Bu, bis(*t*-Bu)biphenyl, toluene.

Scheme 5[a]

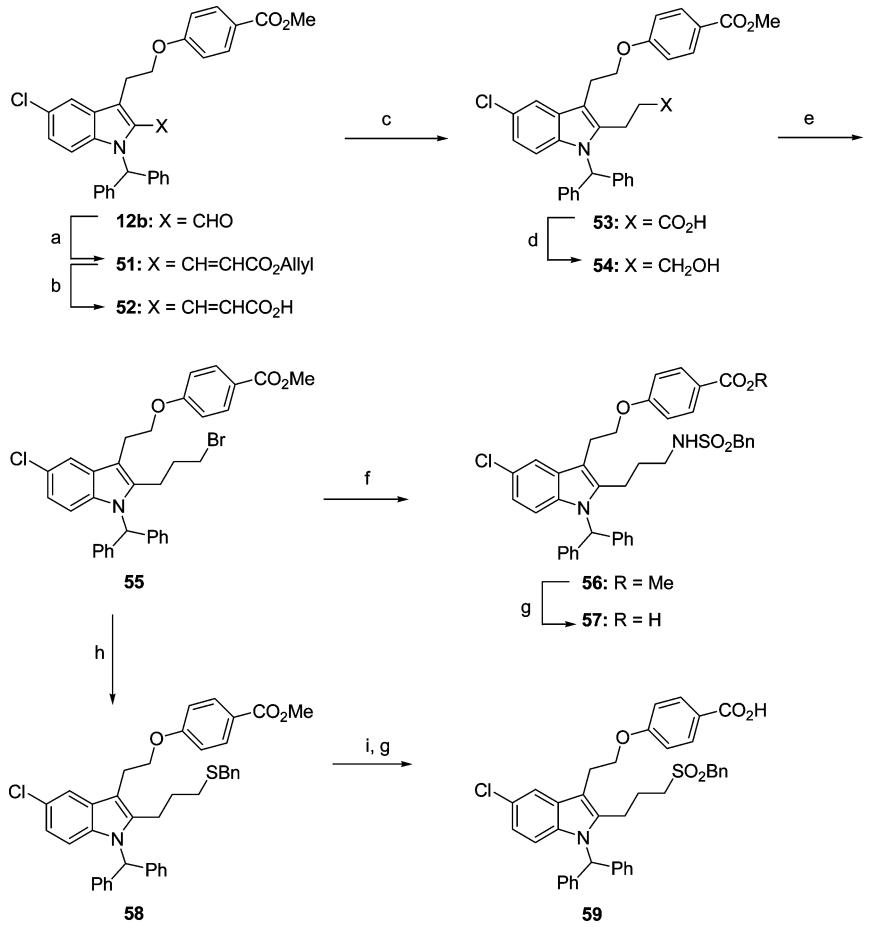


[a] Reagents: (a) $Ph_3P{=}CHOMe$, THF; (b) NaI, TMSCl, MeCN; (c) $NaBH_4$, THF−MeOH; (d) CBr_4, DPPP, CH_2Cl_2; (e) Na_2SO_3, H_2O−dioxane; (f) $SOCl_2$, DMF, CH_2Cl_2; (g) $BnNH_2$, sat. $NaHCO_3$, CH_2Cl_2; (h) 1 N NaOH, THF, MeOH.

103. The benzoate moiety was introduced by reductive alkylation[42,43] with methyl 4-(2,2-diethoxyethoxy)benzoate (**94**).[50] Ester hydrolysis afforded indole **105**.

N-Isopropyl and substituted benzyl indole derivatives were prepared using the reaction sequence in Scheme 11. 4-Chloro-2-iodoaniline (**106**) underwent reductive amination[51] with acetone to afford **107a**. Alkylation of **106** with 3,4-dichlorobenzyl bromide afforded **107b**. These iodides were each coupled with 3-butyn-1-ol and cyclized to the indoles **109a** and **109b** respectively; silyl ether formation then afforded **110a** and **110b**. Following C3 reductive alkylation[42,43] with methyl 4-(2-oxoethoxy)benzoate (**95**), the indole derivatives were converted to

Scheme 6[a]



[a] Reagents: (a) $Ph_3P{=}CHCO_2Allyl$, THF; (b) $Pd(PPh_3)_4$, morpholine, THF; (c) H_2, 5% Pt/C, MeOH; (d) $(COCl)_2$, CH_2Cl_2; then $Zn(BH_4)_2$, TMEDA, THF; (e) PS−PPh_3, CBr_4, CH_2Cl_2; (f) NaH, $PhCH_2SO_2NH_2$, DMF; (g) 1 N NaOH, MeOH, THF; (h) NaH, $PhCH_2SH$, DMF; (i) MCPBA, CH_2Cl_2.

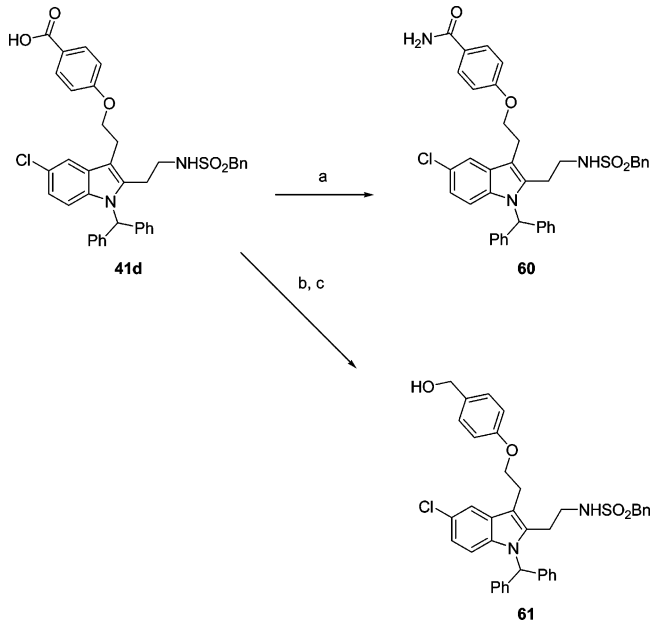
the C2 amines in a three-step sequence. Sulfonylation and ester hydrolysis afforded indoles **117a** and **117b**.

Results and Discussion

In our initial efforts to increase the potency of our indole cPLA$_2\alpha$ inhibitors, derivatives with a one- or two-carbon linker at C2 were examined (Table 1). Compared to the C2 methyl derivative **7**, some improvement in potency was observed in the one carbon alcohol **14** in the RWB assay, but the two-carbon alcohol **30** gave no improvement. Among the two-carbon amine derivatives studied, the sulfonamides (e.g., **41a**, **41b**, **41d**, **41e**) offered improved potency compared to compound **7**. Phenylmethane sulfonamide **41d**, a potent inhibitor of cPLA$_2\alpha$ in both the GLU micelle and RWB assays, represented an important advancement in this area.

Further exploration of the SAR of the benzyl sulfonamide is revealed in Table 2. Sulfonamide **22b** illustrates the importance of a two-atom linker between the indole core and sulfonamide: shifting the sulfonamide functionality one atom closer to the indole while keeping the overall linker length to the benzyl substituent the same (compound **22b** vs compound **41d**) resulted in a 20-fold loss of potency in the RWB assay. Compound **57**, with a three-carbon linker to the sulfonamide, showed only a 2-fold loss in the same assay. The large loss of potency observed upon N-methylation of the sulfonamide (compound **43**), reversal of the sulfonamide (compound **50**), and replacement of the sulfonamide with the analogous sulfone (compound **59**) or amine (compound **39**) illustrates the significance of the sulfonamide functionality for inhibition of cPLA$_2\alpha$.

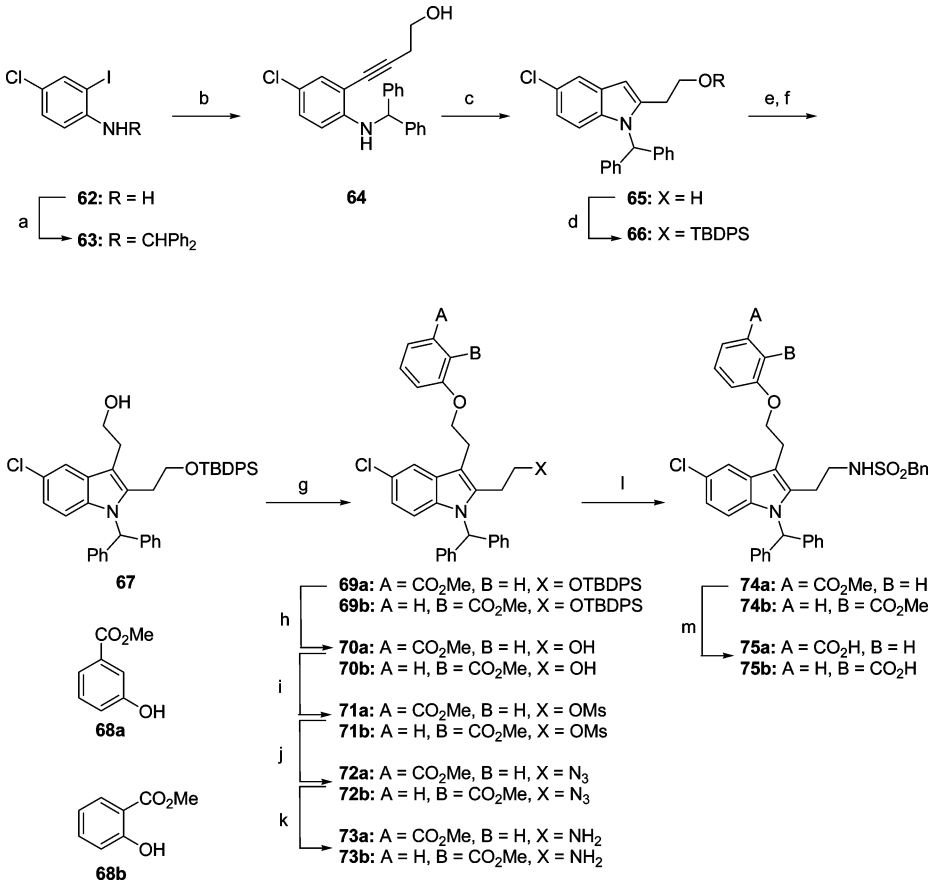
Scheme 7[a]



[a] Reagents: (a) CDI, NH_4OH, THF; (b) cyanuric fluoride, PYR, CH_2Cl_2; (c) $NaBH_4$, MeOH.

The sulfonamide was then held constant while other portions of the inhibitor were systematically varied. As shown in Table 3, neither an amide (compound **60**) nor an alcohol (compound **61**) were tolerated as replacements for the benzoic acid.

Scheme 8[a]



[a] Reagents: (a) Ph_2CHBr, DIEA, TBAI, DMF; (b) 3-butyn-1-ol, $PdCl_2(PPh_3)_2$, CuI, Et_3N; (c) CuI, DMF; (d) TBDPSCl, Imid, CH_2Cl_2; (e) $(COCl)_2$, CH_2Cl_2, MeOH, Et_3N; (f) $BH_3{\cdot}Me_2S$, THF; (g) **68a** or **68b**, DIAD, PPh_3, THF; (h) TBAF, THF; (i) MsCl, Et_3N, CH_2Cl_2; (j) NaN_3, DMF; (k) H_2, Pd/C, MeOH; (l) $BnSO_2Cl$, sat. $NaHCO_3$, CH_2Cl_2; (m) 1 N NaOH, THF, MeOH.

Compounds **75a** and **75b** illustrate the strong preference for a *p*-carboxylic acid over ortho and meta analogues.

The effect of changing the indole C5 and C6 substituents is shown in Table 4. The 6-chloro- and 5-nitro-substituted analogues (compounds **105** and **92**, respectively) were equipotent or nearly equipotent to the 5-chloro lead **41d**, while the 5-morpholino derivative **44** showed a modest loss in activity. Thus a fairly dramatic change in steric bulk results in a relatively small change in potency. In compound **93**, the C2 and C3 substituents are reversed compared to compound **92**, resulting in a dramatic decrease in potency. This analogue demonstrates that not only is each part of the pharmacophore essential, but also that the relative position of each of these pharmacophores is required for activity.

The benzhydryl group has a number of potential liabilities: it contributes to the high molecular weight and lipophilicity of these analogues and may be a site for oxidative metabolism. Table 5 reveals that replacement of the benzhydryl substituent with benzyl (compound **41c**) has a deleterious effect on the potency, and that further substitution of the *N*-benzyl substituent to partially restore the lipophilicity (compound **117b**) results in a further loss of potency. The isopropyl group (compound **117a**) was also not tolerated.

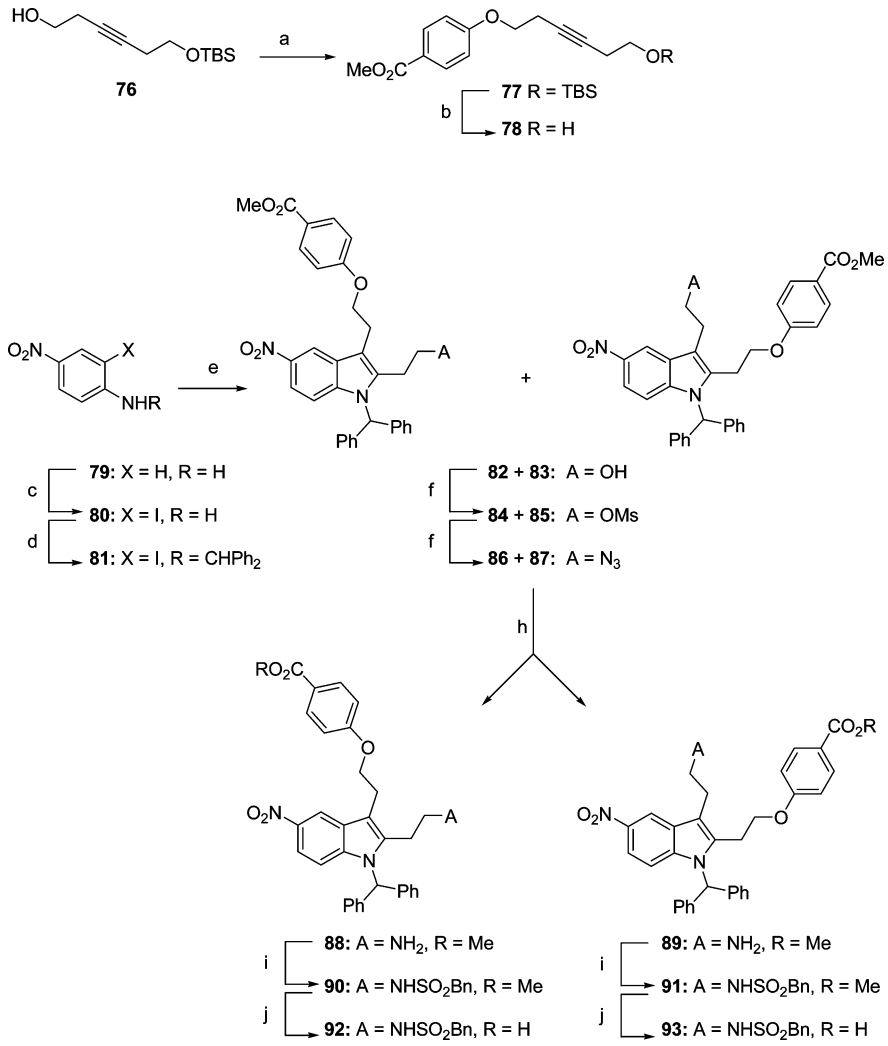
To summarize the SAR of our indole inhibitors of $cPLA_2\alpha$, we have defined a three-part pharmacophore, in which the *N*-benzhydryl group, C2 extended sulfonamide, and C3 benzoic acid moiety all are required for potent $cPLA_2\alpha$ inhibition as determined by the GLU micelle assay (an isolated enzyme assay using purified human $cPLA_2\alpha$) and a whole blood assay in which pooled rat blood is stimulated with calcium ionophore. Sulfonamide **41d** is one of the more potent compounds in the two primary assays.

Pharmacokinetics. We then examined the pharmacokinetics of compound **41d** in rats at 2 mg/kg iv and observed a high plasma clearance of 69 mL/min/kg. This clearance is similar to that of compound **8** (44 mL/min/kg), a lead compound with 15-fold less potency in the RWB assay. The oral bioavailability of compound **41d** when dosed at 5 mg/kg is 12%.

In an effort to make analogues with reduced clearance, substitution on the sulfonamide moiety was explored and compounds **118**−**123** were prepared using the same route used for the preparation of compound **41d**. As shown in Table 6, addition of chlorine substituents to various positions of the phenylmethane moiety led to analogues in which potency was maintained in both the GLU micelle and rat whole blood assays. Three of these analogues (**121**, **122**, and **123**) displayed significantly reduced iv clearance in rat versus the unsubstituted compound (**41d**). Oral bioavailability was determined for the three analogues, and based on data obtained with an oral dose of 5 mg/kg in a standard MC/Tween formulation, compound **123** offered significantly higher oral bioavailability (29%) than **121**(1.5%) and **122** (3%). Because of its potency and superior oral exposure, compound **123** was selected for further study.

However, the oral bioavailability of **123** decreased by approximately 4-fold to 8% when dosed at 20 mg/kg in MC/Tween formulation. A similar decrease in bioavailability with increasing oral dose was observed with compound **41d**. Clearly, a scalable formulation was required for the evaluation of the

Scheme 9[a]



[a] Reagents: (a) methyl 4-hydroxybenzoate, DEAD, Ph_3P; (b) TBAF; (c) ICl, concd HCl (d) Ph_2CHBr, DIEA; (e) **78**, LiCl, KOAc, $Pd(OAc)_2$; (f) MsCl, Et_3N; (g) NaN_3, DMSO; (h) Ph_3P, H_2O; (i) $BnSO_2Cl$, sat. $NaHCO_3$, CH_2Cl_2; (j) 1N NaOH, THF, MeOH.

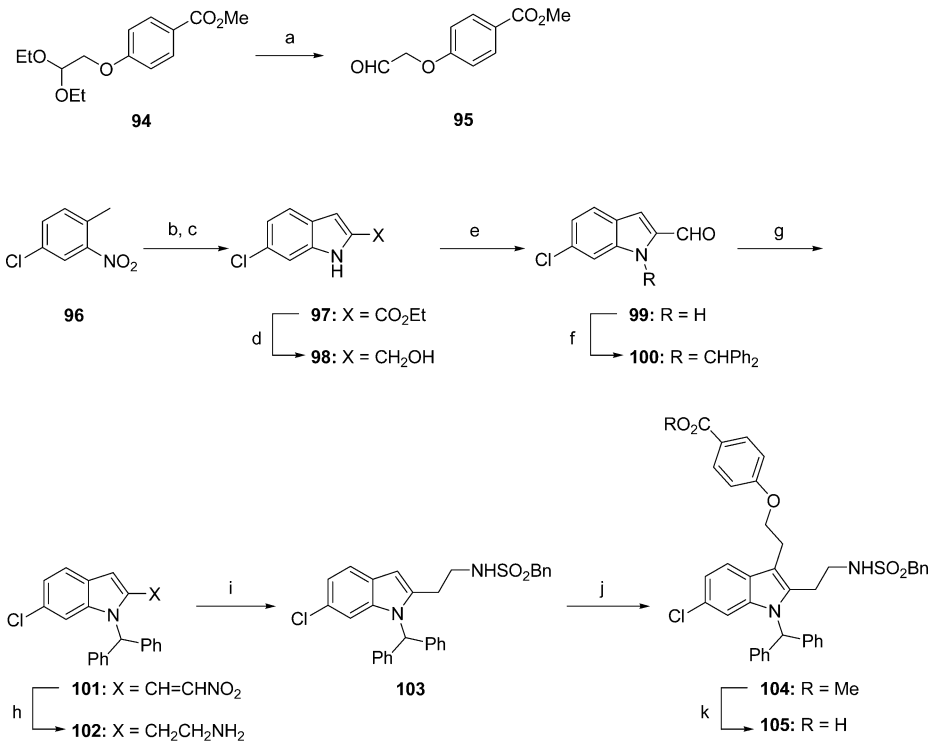
oral efficacy of lead compound **123** in animal models. Several formulations were examined for **123**, and a lipid-based formulation composed of 55.5% Phosal 53 medium chain triglyceride (MCT), 5.6% Tween 80, 16.7% Labrasol, and 22.2% propylene carbonate offered consistent oral exposures when compound **123** was dissolved at 37.5 mg compound per mL vehicle, diluted with water where necessary and dosed at 4 mL/kg to give doses ranging from 5 to 150 mg/kg (Table 6).

Compound **123** was analyzed in secondary assays to determine additional information related to its binding to cPLA$_2\alpha$, its selectivity for cPLA$_2\alpha$, and its inhibitory effect on downstream inflammatory mediators in a human whole blood assay.

Isothermal Calorimetry Data. Since cPLA$_2\alpha$ acts at the membrane interface, it is theoretically possible that compound **123** is disrupting the membrane interface. However, this is highly unlikely since there are >7000 molecules of detergent or lipid (Triton X-100 and DTPC) for every molecule of **123** at the IC_{50} in the GLU micelle assay. Nevertheless, the affinity and stoichiometry of compound **123** for human cPLA$_2\alpha$ were determined using isothermal calorimetry at 30 °C using buffer conditions similar to that of the GLU micelle assay. An exothermic reaction was observed. The binding isotherm displayed a good fit ($CHI^2 = 12011.4$) with a single site model ($N = 0.9988$), indicating that one molecule of compound **123** binds to one molecule of cPLA$_2\alpha$. The K_d was 139 nM, in agreement with that IC_{50} seen in the GLU micelle assay (150 nM). Furthermore, no binding of compound **123** was observed when the active site of cPLA$_2\alpha$ was covalently modified by methyl arachindonyl fluorophosphonate (MAFP) prior to the titration experiment. Thus compound **123** inhibits cPLA$_2\alpha$ through direct binding at or near the active site.

Selectivity Assays. To further examine the selectivity of compound **123**, its inhibition of PLA_2 isoforms was determined using PAPC (1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphocholine) liposomes to assess activity against the β and γ isoforms which are ~35% identical in the catalytic domain, and PAPE (1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphoethanolamine) liposome assays to monitor inhibition of type II secreted PLA_2 (sPLA$_2$). Compound **123** inhibited cPLA$_2\alpha$ in the PAPC liposome assay at 80% at a concentration of 37 nM. In contrast, compound **123** displayed no inhibition of cPLA$_2\beta$ or cPLA$_2\gamma$ at 1 μM in the PAPC assay. Compound **123** inhibited cPLA$_2\alpha$ in the PAPE liposome assay at 73% at a concentration of 37 nM, while it inhibited sPLA$_2$ at 16% @ 1 μM. Additional isoforms of cPLA$_2$ that are most closely related to cPLA$_2\beta$ have been identified in the last year.[52] We expect that the lack of activity seen against cPLA$_2\beta$, which is the most closely conserved, will also be observed for the new isoforms.

Scheme 10[a]



[a] Reagents: (a) TFA, H_2O, CH_2Cl_2; (b) EtOK, EtOH, EtO_2CCO_2Et, Et_2O; (c) Fe, AcOH, EtOH; (d) $LiAlH_4$, THF; (e) MnO_2, THF; (f) NaH, Ph_2CHBr, TBAI, DMF; (g) NH_4OAc, $MeNO_2$; (h) LAH, THF; (i) $BnSO_2Cl$, sat. $NaHCO_3$, CH_2Cl_2; (j) acetal **94**, Et_3SiH, TFA, CH_2Cl_2; (k) 1 N NaOH, THF, MeOH.

MC-9 Assay Data. The MC-9 assay is a murine mast cell that can be activated via cross-linking of the IgE receptor with a defined antigen to initiate degranulation and production of both prostaglandins and leukotrienes. The cell line is also useful because exogenous arachidonic acid can be added to initiate production of prostaglandin synthesis, thus bypassing cPLA$_2\alpha$. In this cell assay, a cPLA$_2\alpha$ inhibitor should block both prostaglandin and leukotriene production upon IgE stimulation but be inactive when exogenous arachidonic acid is added. Compound **123** inhibited the production of prostaglandins ($PGF_2\alpha$) and leukotrienes (LTB_4 and $LTC_4/D_4/E_4$) with comparable IC_{50}s of 20−30 nM. In contrast, when cPLA$_2\alpha$ inhibition was bypassed by the addition of exogenous arachidonic acid, the inhibition of $PGF_2\alpha$ was less than 50% at 1 μM, which indicates that compound **123** is indeed inhibiting cPLA$_2\alpha$ to give balanced inhibition of both prostaglandins and leukotrienes and not a downstream target such as COX. Consistent with the MC-9 data, compound **123** was inactive against COX-1 and COX-2 at 20 μM, which is nearly 100 times the IC_{50} in the MC-9 cells.

Human Whole Blood Data. Stimulation of human whole blood with calcium ionophore, A23187, results in the production of leukotrienes and multiple COX-1 derived prostaglandins. In this assay we routinely monitor by ELISA the products of the COX-1/thromboxane synthase pathway with TXB_2, the COX-1/PGE_2 synthase pathway with PGE_2, the COX-1 products with $PGF_2\alpha$, and the 5-LO/FLAP/LTA_4 hydrolase pathway with LTB_4. We have also determined the inhibition of PAF synthesis, which is generated from the lyso-phosphatidylcholine generated by cPLA$_2\alpha$. A cPLA$_2\alpha$ inhibitor should block the production of all pathways. Compound **123** was tested in a human whole blood assay using blood from 15 different donors. At 0.3 μM, **123** blocked the production of TXB_2, PGE_2, $PGF_2\alpha$, and LTB_4, as indicated in Table 7. Using similar methods, it was determined that the IC_{50} of compound **123** for PAF based on four experiments with two donors was 0.3 μM. Compound **123** was also tested for its ability to inhibit 12- and 15-HETE, which are derived from arachidonic acid via the 12- and 15-lipoxygenase pathways and the IC_{50}s were ~0.3 μM. The activity of **123** in these assays is consistent with its behavior as a cPLA$_2\alpha$ inhibitor in the GLU micelle and RWB assays and demonstrates that **123** effectively inhibited the production of PAF and all the arachidonate metabolites tested.

Compound **123** was then evaluated in two animal models of inflammation.

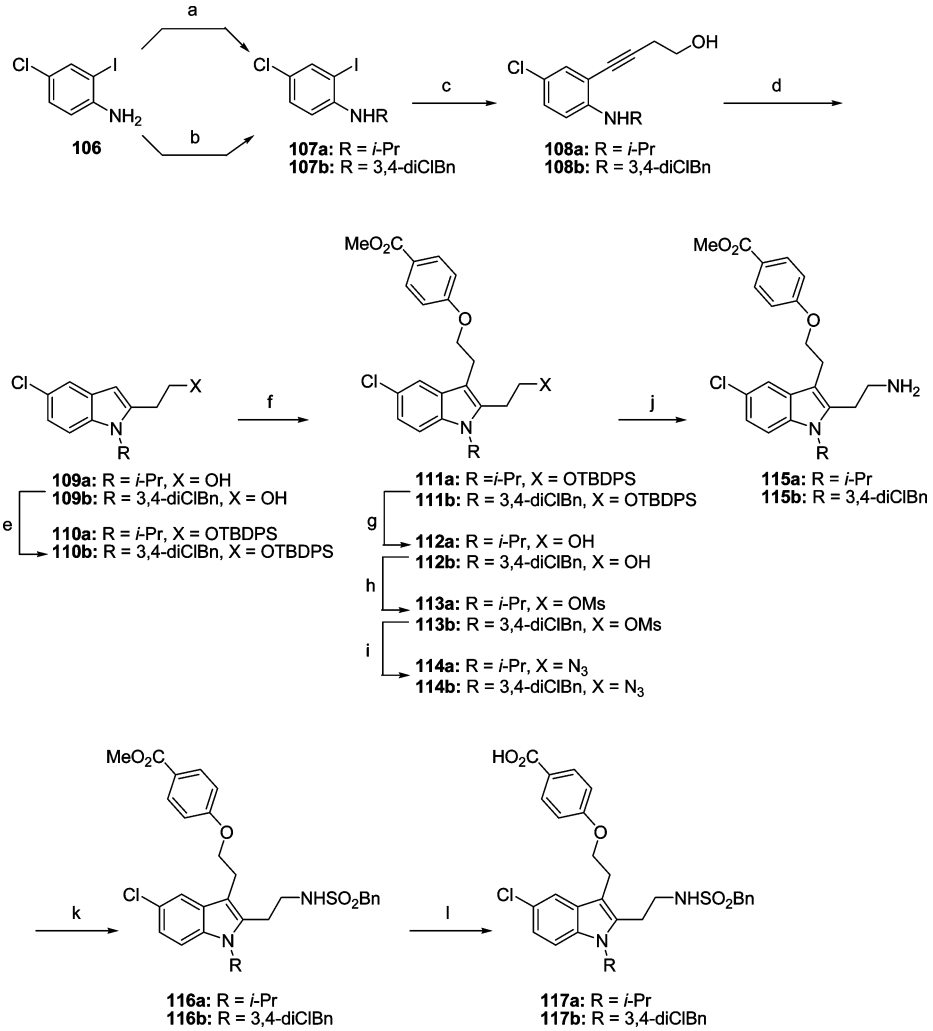
Rat Carrageenan Air Pouch Model. This acute model of inflammation is primarily driven by COX-2 and has been used previously to characterize COX-2 selective inhibitors.[53,54] In the rat carrageenan air pouch model, carrageenan is injected into a subcutaneous air pouch on rats and the amount of PGE_2 present in the air pouch exudate is measured *ex vivo*. Compound **123** was orally efficacious in this model and displayed an ED_{50} of 8 mg/kg, demonstrating that it can inhibit COX-2 derived PGE_2 formation *in vivo*.

Rat Carrageenan Paw Edema (CPE) Model. The CPE model is an acute inflammation model that is primarily driven by prostaglandins.[55,56] It has been highly predictive of NSAID and COX-2 utility. Inhibitor **123** was orally efficacious at reducing carrageenan-induced paw swelling: from dose−response studies, it has been determined that the ED_{50} of **123** is 40 mg/kg.

Conclusion

Starting from 2-methyl indole **7**, the introduction of sulfonamides on extended linkers at C2 resulted in inhibitors of cPLA$_2\alpha$ with substantial improvements as measured by the GLU micelle and rat whole blood (RWB) assays. One of the more potent compounds was **41d**, which displayed an IC_{50} of 0.11 μM in the GLU micelle assay and an IC_{50} of 0.12 μM in the RWB

Scheme 11[a]



[a] Reagents: (a) Acetone, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (b) NaH, 3,4-dichlorobenzyl bromide, DMF; (c) 3-butyn-1-ol, $PdCl_2(PPh_3)_2$, CuI, Et_3N; (d) CuI, DMF; (e) TBDPSCl, Imid, DMF; (f) aldehyde **95**, Et_3SiH, TFA, CH_2Cl_2; (g) TBAF, THF; (h) MsCl, Et_3N, THF; (i) NaN_3, DMSO; (j) PPh_3, H_2O, THF; (k) $BnSO_2Cl$, sat. $NaHCO_3$, CH_2Cl_2; (l) 1 N NaOH, THF, MeOH.

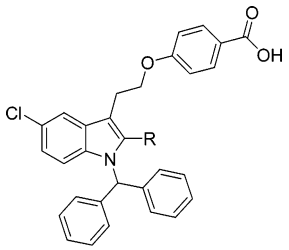
assay. Because **41d** showed high clearance (69 mL/min/kg) in rat, chlorine substituents were added to the phenylmethane moiety, and potency was maintained. Analysis of the pharmacokinetics of these analogues led to the discovery of Ecopladib (compound **123)**, a compound with equivalent potency to **41d** and significantly reduced clearance (14 mL/min/kg). Compound **123** binds directly to cPLA$_2\alpha$ as measured by isothermal calorimetry and is selective without activity toward the closely related β and γ isoforms, and the unrelated type II sPLA$_2$. Compound **123** is active in cells and maintains potency in a human whole blood assay. In the latter, compound **123** inhibited PAF production and both prostaglandin and leukotriene pathways in a balanced manner indicative of cPLA$_2\alpha$ inhibition. Compound **123** was orally efficacious in the rat carrageenan air pouch (ED_{50} 8 mg/kg) and rat carrageenan paw edema (ED_{50} 40 mg/kg) models, which are both indicative of inhibition of COX-2 mediated prostaglandin production. On the basis of these and other data, compound **123** has advanced to Phase I clinical trials; the results of these studies will be reported in due course.

Experimental Section

General Procedures. All solvents and reagents were used as obtained. All reaction mixtures were stirred using a magnetic stir bar and reactions were conducted at room temperature unless otherwise noted. Solutions were dried with $MgSO_4$ unless otherwise noted. Proton NMR spectra were recorded at 300 MHz on a Varian Gemini 2000 or on a 400 MHz Bruker AV-400 spectrometer using TMS (δ 0.0) as a reference. Combustion analyses were obtained using a Perkin-Elmer Series II 2400 CHNS/O analyzer. CHN analyses were carried out by Robertson-Microlit. Low-resolution mass spectra were obtained using a Micromass Platform Electrospray Ionization Quadrapole mass spectrometer. High-resolution mass spectra were obtained using a Bruker (Billerica, MA) APEXIII Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an actively shielded 7 T superconducting magnet (Magnex Scientific Ltd., UK) and an external Bruker APOLLO electrospray ionization (ESI) source. Flash chromatography was performed using EM Science 230−400 mesh silica gel or Biotage flash columns packed with KP-SIL 60 Angstrom silica gel. Thin-layer chromatography (TLC) was performed using EMD 250 μm prescored silica gel 60 F_{254} plates. Preparative HPLC was run using a Waters Prep 4000 LC system or a Waters 2525 Binary Gradient system. Purity in two solvent systems (H_2O-CH_3CN and H_2O-MeOH) was determined using an Agilent 1100 HPLC instrument, and all final compounds were >95% pure (see Supporting Information for details).

General Procedure for Ester Hydrolysis. To a solution of the ester (1.0 mmol) in inhibitor free THF (20 mL) was added 1 N aq NaOH (3.0 mL, 3.0 mmol) and MeOH (10 mL). The mixture was heated at 50 °C until the ester starting material was consumed (TLC analysis in 50% EtOAc−hexanes). The reaction mixture was concentrated, and the residue was diluted with H_2O (10 mL) and

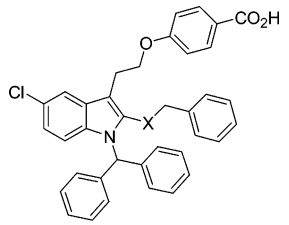
Table 1. Initial Exploration of C2 SAR



compd	R	GLU IC_{50}[a] (μM)	RWB IC_{50}[b] (μM)
7	CH_3	2.7	7.0
14	CH_2OH	2.3	2.2
18	CH_2NH_2	7.0	31% @ 10 μM
20	CH_2NHCO_2Bn	1.2	0.27[c]
22a	CH_2NHSO_2Bn	4.2	6.4
30	CH_2CH_2OH	5.5	8.0
33	$CH_2CH_2NH_2$	31% @ 20 μM	28% @ 10 μM
35	$CH_2CH_2NHCO_2Bn$	1.6	1.1
37	$CH_2CH_2NHCOBn$	5.9	1.8
41a	$CH_2CH_2NHSO_2Me$	0.65	0.9
41b	$CH_2CH_2NHSO_2Ph$	3.0	1.0
41d	$CH_2CH_2NHSO_2Bn$	0.11	0.12
41e	$CH_2CH_2NHSO_2CH_2CH_2Ph$	0.52	0.63

[a] See Experimental Section for the GLU micelle assay protocol. [b] See Experimental Section for the rat whole blood (RWB) assay protocol. [c] Note that compound **20** is more active in RWB than expected from the GLU IC_{50}, but the IC_{50} in a human whole blood assay was 1.7 μM.

Table 2. Linker Exploration at C2



compd	X	GLU IC_{50} (μM)	RWB IC_{50} (μM)
41d	$CH_2CH_2NHSO_2$	0.11	0.12
22b	$CH_2NHSO_2CH_2$	5.0	2.2
57	$CH_2CH_2CH_2NHSO_2$	0.26	0.26
43	$CH_2CH_2NMeSO_2$	2.5	4.0
50	$CH_2CH_2SO_2NH$	11	12% @ 1.25 μM[a]
59	$CH_2CH_2CH_2SO_2$	3.0	2.5
39	$CH_2CH_2NHCH_2$	4.0	2.5

[a] The highest concentration tested was 1.25 μM.

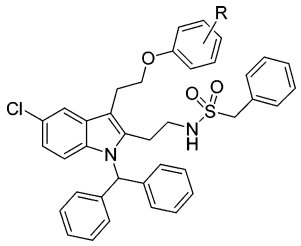
acidified to pH 1 using 1 N HCl. The resulting mixture was extracted with EtOAc (2 × 20 mL). The organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried, and concentrated. The residue was lyophilized to afford the carboxylic acid.

General Procedure for Sulfonylation of Amines via Schotten−Baumann Reaction. To a solution of the amine (1.0 mmol) in CH_2Cl_2 (10 mL) were added sulfonyl chloride (1.2 mmol) and sat. $NaHCO_3$ (10 mL). The resulting suspension was stirred until the amine was consumed (TLC analysis in 10% MeOH−CH_2Cl_2). The mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (20 mL) and brine, dried, and concentrated. Purification of the crude product by flash chromatography (EtOAc−hexanes) afforded the sulfonamide.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-formyl-1*H*-indol-3-yl]ethoxy}benzoate (12b). To a solution of methyl indole **11**[42] (0.923 g, 1.8 mmol) in CCl_4 (50 mL) were added NBS (0.710 g, 4.0 mmol) and benzoyl peroxide (0.010 g). The resulting mixture was heated to reflux for 2.5 h. The mixture was cooled to room temperature, and the solvent was evaporated. To a solution of the crude dibromide in acetone (180 mL) were added Ag_2CO_3 (0.551 g, 2.0 mmol) and H_2O (18 mL), and the mixture was stirred overnight. The reaction mixture was diluted with H_2O (80 mL) and extracted with EtOAc (350 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography afforded formyl indole **12b** (0.750 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 4.19−4.48 (m, 2 H), 6.67 (d, J = 9.1 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.96−7.49 (m, 10 H), 7.74 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H), 8.22 (s, 1 H), 10.21 (s, 1 H).

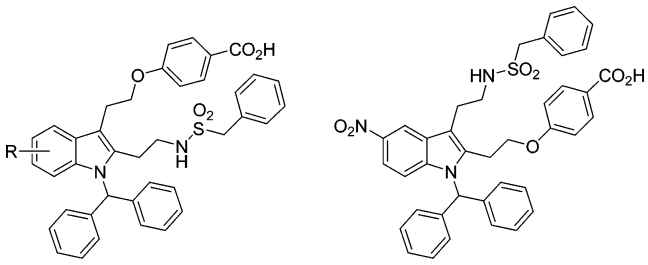
Methyl 4-{2-[1-Benzhydryl-5-chloro-2-(hydroxymethyl)-1*H*-indol-3-yl]ethoxy}benzoate (13). To a solution of aldehyde **12b** (6.09 g, 12 mmol) in THF (100 mL) and MeOH (100 mL) at 0 °C

Table 3. SAR of C3 Benzoic Acid



compd	R	GLU IC_{50} (μM)	RWB IC_{50} (μM)
41d	*p*-CO_2H	0.11	0.12
60	*p*-$CONH_2$	6.7	5.0
61	*p*-CH_2OH	30	38% @ 2.5 μM
75a	*m*-CO_2H	16.5	10
75b	*o*-CO_2H	35% @ 200 μM	NA @ 10 μM

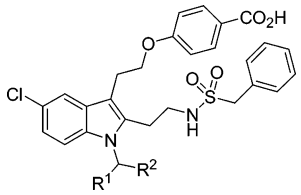
Table 4. Exploration of Indole Substitution



93

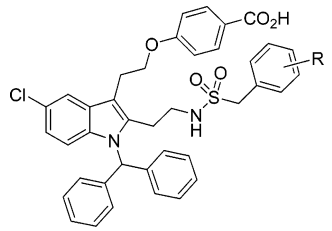
compd	R	GLU IC_{50} (μM)	RWB IC_{50} (μM)
41d	5-Cl	0.11	0.12
105	6-Cl	0.16	0.16
44	5-morpholino	0.60	0.24
92	5-NO_2	0.12	0.09
93	--	28	13% @ 10 μM

Table 5. Benzhydryl Replacements



compd	R^1	R^2	GLU IC_{50} (μM)	RWB IC_{50} (μM)
41d	Ph	Ph	0.11	0.12
41c	Ph	H	5.0	10
117a	Me	Me	90	25% @ 10 μM
117b	3,4-dichloro-Ph	H	18	34% @ 10 μM

Table 6. Substitution of Phenylmethane Moiety



compd	R	GLU IC_{50} (μM)	RWB IC_{50} (μM)	rat IV Cl 2 mg/kg (mL/min/kg)	rat %F MC/Tween formulation	rat %F Phosal formulation
41d	H	0.11	0.12	69	12 (5 mg/kg) 3.9 (20 mg/kg)	-
118	2-Cl	0.052	0.053	>200	-	-
119	4-Cl	0.12	0.16	31	-	-
120	2,3-Cl	0.11	0.13	121	-	-
121	2,4-Cl	0.10	0.10	6.4	1.5 (5 mg/kg)	-
122	3,5-Cl	0.19	0.13	8.3	3.0 (5 mg/kg) 1.8 (20 mg/kg)	-
123	3,4-Cl	0.15	0.11	14	29 (5 mg/kg) 8 (20 mg/kg)	6.3 (5 mg/kg) 12 (25 mg/kg) 16 (100 mg/kg) 19 (150 mg/kg)

Table 7. Inhibition of Inflammatory Mediators in Human Whole Blood by **123** at 0.3 μM[a]

product	% inhib	std dev
TXB_2	53	16
PGE_2	72	13
$PGF_2\alpha$	60	15
LTB_4	60	23

[a] Compound **123** was tested using blood from 15 different donors.

was slowly added $NaBH_4$ (0.530 g, 14 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. The mixture was concentrated partially, diluted with H_2O (400 mL), and extracted with EtOAc (3 × 200 mL). The organic phase was washed with H_2O and brine and dried (Na_2SO_4) to afford 6.1 g (~100%) of crude alcohol **13**, a pale yellow foam. Flash chromatography of 0.200 g of the crude product (20 → 50% EtOAc−hexanes) afforded **13** (0.145 g, 73%), a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (t, J = 6.2 Hz, 1 H), 3.28 (t, J = 6.1 Hz, 2 H), 3.88 (s, 3 H), 4.24 (t, J = 6.1 Hz, 2 H), 4.76 (d, J = 6.1 Hz, 2 H), 6.58 (d, J = 8.6 Hz, 1 H), 6.82−6.93 (m, 3 H), 7.10−7.16 (m, 5 H), 7.19 (s, 1 H), 7.28−7.35 (m, 5 H), 7.56 (d, J = 2.0 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 2 H).

4-{2-[1-Benzhydryl-5-chloro-2-(hydroxymethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (14). Crude methyl ester **13** (0.14 g, 0.28 mmol) was hydrolyzed according to the general procedure for ester hydrolysis. Preparative reverse phase HPLC purification and lyophilization afforded **14** (0.070 g, 50%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.23 (t, J = 6.9 Hz, 2 H), 4.22 (t, J = 7.1 Hz, 2 H), 4.63 (s, 2 H), 5.45 (s, 1 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.84 (dd, J = 8.8, 2.3 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.05−7.17 (m, 4 H), 7.26−7.46 (m, 7 H), 7.69 (d, J = 2.0 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{31}H_{26}ClNO_4$ + Na] 534.1442 found 534.1432.

Methyl 4-{2-[2-(Azidomethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (16). To a solution of crude alcohol **13** (5.0 g, 9.5 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (1.7 mL, 12 mmol) and MsCl (0.81 mL, 10 mmol). After 1.5 h, additional MsCl (0.20 mL, 2.5 mmol) was added. After 2 h, the mixture was evaporated. The crude mesylate **15** was dissolved in DMF (350 mL) and treated with NaN_3 (6.2 g, 95 mmol). The mixture was stirred overnight at 80 °C. It was then cooled to room temperature and poured into a mixture of sat. NH_4Cl (250 mL) and H_2O (250 mL). The mixture was extracted with EtOAc (1 L). The organic phase was washed with H_2O and brine, dried, and concentrated. Flash chromatography (10% EtOAc−hexanes) afforded azide **16** (3.95 g, 75%) as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (t, J = 6.7 Hz, 2 H), 3.88 (s, 3 H), 4.22 (t, J = 6.8 Hz, 2 H), 4.50 (s, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.82−6.94 (m, 3 H), 7.01 (s, 1 H), 7.07−7.15 (m, 4 H), 7.28−7.37 (m, 6 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H).

Methyl 4-{2-[2-(Aminomethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate (17). Azide **16** (0.600 g, 1.1 mmol) and Ph_3P (0.570 g, 2.2 mmol) were stirred in THF (50 mL) for 5 h. H_2O (6 mL) was added, and the mixture was stirred at 60 °C overnight. The mixture was concentrated, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (150 mL). The organic phase was washed with H_2O and brine, dried, and concentrated. Flash chromatography (1 → 5% MeOH−CH_2Cl_2) afforded **17** (0.50 g, 87%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (t, J = 6.4 Hz, 2 H), 3.88 (s, 3 H), 3.98 (s, 2 H), 4.22 (t, J = 6.4 Hz, 2 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.79−6.91 (m, 3 H), 7.13 (dd, J = 6.7, 2.4 Hz, 4 H), 7.27−7.38 (m, 6 H), 7.54 (d, J = 2.0 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

4-{2-[2-(Aminomethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]-ethoxy}benzoic Acid (18). Methyl ester **17** (0.060 g, 0.11 mmol) was hydrolyzed according to the general procedure to afford 0.058 g (100%) of carboxylic acid **18**, a beige solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.33 (t, J = 5.9 Hz, 2 H), 2.01 (s, 2 H), 2.32 (t, J = 5.9 Hz, 2 H), 4.67 (d, J = 8.8 Hz, 1 H), 4.81−4.95 (m, 3 H), 5.13−5.25 (m, 4 H), 5.38 (t, J = 6.2 Hz, 7 H), 5.70 (s, 1 H), 5.96 (d, J = 7.7 Hz, 2 H).

Methyl 4-{2-[1-Benzhydryl-2-({[(benzyloxy)carbonyl]amino}-methyl)-5-chloro-1*H*-indo l-3-yl]ethoxy}benzoate (19). Amine **17** (0.15 g, 0.28 mmol) was stirred with benzyl chloroformate (0.041 mL, 0.28 mmol) and Et_3N (0.10 mL, 0.71 mmol) in CH_2Cl_2 (5 mL) at 0 °C for 3 h. The mixture was washed with H_2O (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10 → 20% EtOAc−hexanes) afforded carbamate **19** (0.097 g, 52%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 2 H), 3.88 (s, 3 H), 4.23 (t, J = 5.8 Hz, 2 H), 4.62 (s, 2 H), 5.02−5.05 (m, 3 H), 6.53 (d, J = 9.1 Hz, 1 H), 6.78−6.95 (m, 3 H), 7.08 (s, 4 H), 7.19−7.35 (m, 11 H), 7.37 (d, J = 4.5 Hz, 1 H), 7.53 (d, J = 1.8 Hz, 1 H), 7.86 (d, J = 8.8 Hz, 2 H).

4-{2-[1-Benzhydryl-2-({[(benzyloxy)carbonyl]amino}methyl)-5-chloro-1*H*-i ndol-3-yl]ethoxy}benzoic Acid (20). Methyl ester **19** (0.097 g, 0.15 mmol) was hydrolyzed according to the general procedure. Flash chromatography (20 → 50% EtOAc−hexanes) of the crude product and lyophilization afforded carboxylic acid **20** (0.021 g, 22%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.28 (t, J = 7.1 Hz, 2 H), 4.24 (t, J = 6.8 Hz, 2 H), 4.47 (d, J = 5.3 Hz, 2 H), 4.98 (s, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.84 (dd, J = 9.0, 2.1 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 7.1 Hz, 4 H), 7.16 (s, 1 H), 7.21−7.30 (m, 5 H), 7.30−7.44 (m, 6 H), 7.69 (d, J = 2.3 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 7.89−8.03 (m, 1 H); HRMS: calcd for [$C_{39}H_{33}ClN_2O_5$ + H] 645.2151 found 645.2143; Anal. $C_{39}H_{33}ClN_2O_5$: C, H, N.

Methyl 4-[2-(1-Benzhydryl-2-{[(benzylsulfonyl)amino]methyl}-5-chloro-1*H*-indol-3-yl)ethoxy]benzoate (21a). Amine **17** (0.19 g, 0.36 mmol) underwent sulfonylation using the general Schotten−Baumann procedure with α-toluenesulfonyl chloride (0.082 g, 0.43 mmol) for 1.5 h. Flash chromatography (20 → 40% EtOAc−hexanes) of the product afforded **21a** (0.15 g, 61%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (t, J = 5.9 Hz, 2 H), 3.88 (s, 3 H), 4.13−4.19 (m, 2 H), 4.24 (s, 2 H), 4.29 (d, J = 6.1 Hz, 2 H), 4.54 (t, J = 5.1 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 2 H), 6.86 (dd, J = 9.0, 2.1 Hz, 1 H), 7.04−7.11 (m, 4 H), 7.22−7.39 (m, 12 H), 7.51 (d, J = 1.8 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{38}H_{32}ClN_2O_5S$ + H] 665.2092 found 665.1865.

Methyl 4-{2-[1-Benzhydryl-5-chloro-2-({[(2-phenylethyl)-sulfonyl]amino}methyl)-1*H*-in dol-3-yl]ethoxy}benzoate (21b). Amine **17** (0.22 g, 0.40 mmol) underwent sulfonylation using the general Schotten−Baumann procedure with 2-phenylethanesulfonyl chloride[57,58] (0.14 g, 0.68 mmol) for 1 h. Flash chromatography (20 → 30% EtOAc−hexanes) of the crude sulfonamide afforded **21b** (0.152 g, 52%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92−3.09 (m, 2 H), 3.13−3.28 (m, 4 H), 3.84−3.92 (m, 3 H), 4.23 (t, J = 5.9 Hz, 2 H), 4.30−4.41 (m, 3 H), 6.55 (d, J = 8.6 Hz, 1 H), 6.84−6.96 (m, 3 H), 7.04−7.11 (m, 5 H), 7.13 (s, 1 H), 7.21−7.34 (m, 10 H), 7.54 (d, J = 1.8 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 2 H).

4-[2-(1-Benzhydryl-2-{[(benzylsulfonyl)amino]methyl}-5-chloro-1*H*-indol-3 -yl)ethoxy]benzoic Acid (22a). Methyl ester **21a** (0.15 g, 0.22 mmol) was hydrolyzed according to the general procedure. The crude carboxylic acid was purified by preparative reverse-phase HPLC and lyophilized to afford **22a** (0.049 g, 39%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.23 (t, J = 7.2 Hz, 2 H), 4.20 (t, J = 7.3 Hz, 2 H), 4.28 (d, J = 5.6 Hz, 2 H), 4.44 (s, 2 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.86 (dd, J = 9.0, 2.1 Hz, 1 H), 6.97 (d, J = 9.1 Hz, 2 H), 7.04−7.16 (m, 4 H), 7.23 (s, 1 H), 7.25−7.50 (m, 11 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.87 (d, J = 9.1 Hz, 2 H), 7.91 (t, J = 5.6 Hz, 1 H); HRMS: calcd for [$C_{38}H_{33}ClN_2O_5S$ + H] 665.18715 found 665.18648.

4-{2-[1-Benzhydryl-5-chloro-2-({[(2-phenylethyl)sulfonyl]-amino}methyl)-1 *H*-indol-3-yl]ethoxy}benzoic Acid (22b). Methyl ester **21b** (0.13 g, 0.14 mmol) was hydrolyzed according to the general procedure to afford **22b** (0.11 g, 89%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.88−3.05 (m, 2 H), 3.20−3.45 (m, 4 H), 4.23 (t, J = 7.2 Hz, 2 H), 4.38 (d, J = 5.6 Hz, 2 H), 6.50 (d, J = 9.1 Hz, 1 H), 6.87 (dd, J = 9.0, 2.1 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.11 (dd, J = 7.6, 1.8 Hz, 4 H), 7.15−7.47 (m, 12 H), 7.73 (d, J = 2.0 Hz, 1 H), 7.84 (d, J = 9.1 Hz, 2 H), 7.89 (t, J = 6.2 Hz, 1 H); HRMS: calcd for [$C_{40}H_{37}ClN_2O_5S$ + H] 679.2028 found 679.2028.

2-(5-Chloro-1*H*-indol-3-yl)ethanol (24). To a solution of 5-chloroindole (**23**) (30 g, 199 mmol) in Et_2O (600 mL) at 0 °C was added $(COCl)_2$ (19 mL, 219 mmol). The resulting yellow slurry was stirred at 0 °C for 1.5 h and at room temperature for 1.5 h. The reaction was cooled to 0 °C, and MeOH (75 mL, 1.9 mol) and Et_3N (150 mL, 1.1 mol) were added. The mixture was stirred at 0 °C for 1 h and then warmed to room temperature over 4 h. The reaction mixture was cooled to 0 °C, and the precipitate was filtered and washed with H_2O, followed by cold Et_2O−EtOAc (2:1), and dried to afford the oxalic ester, a white solid (44.2 g, 94%). To a solution of the ester in THF (1 L) at 0 °C was added $LiAlH_4$ (1.0 L of a 1 M soln in Et_2O, 1.0 mol) via cannula. The reaction mixture was allowed to warm to room temperature over 2 h and then heated to 70 °C for 3 h. The mixture was cooled to 0 °C and quenched by the successive addition of H_2O (38 mL), 15% aq NaOH (38 mL) and H_2O (110 mL) to form a precipitate which was filtered through Celite. The filtrate was concentrated, extracted with EtOAc, washed with brine, dried, filtered, and concentrated to afford the pure alcohol **24** (31.3 g, 86%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76 − 2.86 (m, 2 H), 3.59 − 3.68 (m, 2 H), 4.60 − 4.67 (m, 1 H), 7.04 (d, J = 2.0 Hz, 1 H), 7.22 (s, 1 H), 7.35 (d, J = 2.0 Hz, 1 H), 7.78 (s, 1 H), 11.02 (s, 1 H).

Methyl 4-[2-(5-Chloro-1*H*-indol-3-yl)ethoxy]benzoate (26). To a solution of alcohol **24** (1.0 g, 5.1 mmol) in CH_2Cl_2 at 0 °C were added Et_3N (0.86 mL, 6.1 mmol) and MsCl (0.42 mL, 5.4 mmol). After 20 min, the mixture was diluted with EtOAc, washed with brine, dried, filtered, and concentrated. The residue was azeotroped twice with benzene to afford the mesylate **25**, which was used in the next step without further purification. To a solution of methyl 4-hydroxybenzoate (1.0 g, 6.5 mmol) in DMF (20 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.25 g, 6.5 mmol). The mixture was warmed to room temperature over 20 min, and then a solution of mesylate **25** (∼5.1 mmol) was added in DMF (5 mL). The reaction mixture was stirred at 40 °C overnight, diluted with EtOAc, washed with brine, dried, filtered, and concentrated. Flash chromatograghy (20% EtOAc−hexanes) afforded methyl benzoate **26** (0.62 g, 37%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.15 (t, J = 6.9 Hz, 2 H), 3.8 (s, 3 H), 4.27 (t, J = 6.9 Hz, 2 H), 7.00 − 7.10 (m, 3 H), 7.20 − 7.36 (m, 2 H), 7.65 (s, 1 H), 7.91 (d, J = 7.5 Hz, 2 H,), 11.15 (s, 1 H).

Methyl 4-{2-[2-Bromo-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (28). To a solution of indole **26** (0.60 g, 1.8 mmol) in CCl_4 (10 mL) was added NBS (0.34 g, 1.9 mmol). The solution was heated at 77 °C for 2.5 h, cooled to room temperature, diluted with EtOAc, and washed with sat. $NaHCO_3$ and brine. The organic layer was dried, filtered, and concentrated to afford bromide **27**, which was carried onto the next step directly. To a solution of bromide **27** in DMF (8 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.073 g, 1.8 mmol). The mixture was allowed to warm to room temperature over 15 min, and benzyhydryl bromide was added (0.54 g, 2.16 mmol). After 2 h, EtOAc was added, and the mixture was washed with brine, dried, filtered, and purified by flash chromatography (50% EtOAc−hexanes) to afford the title compound **28** (0.70 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.24 (t, J = 6.7 Hz, 2 H), 3.81 (s, 3 H), 4.27 (t, J = 6.7 Hz, 2 H,), 6.65 (d, J = 8.9 Hz, 1 H), 6.95 (dd, J = 8.9, 1 H), 7.01 (d, J = 8.9 Hz, 2 H), 7.05 −7.15 (m, 3 H), 7.29 (s, 1 H), 7.1 − 7.41 (m, 7 H), 7.79 (d, J = 2.1 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethox y}benzoic Acid (30). To a solution of the ester **28** (0.40 g, 7.0 mmol) in THF (10 mL) was added NaOH (5 M, 7.0 mL, 35 mmol) followed by MeOH (∼7 mL) to afford a homogeneous solution. The mixture was stirred overnight, neutralized with NaH_2PO_3 pH 3 buffer, extracted with EtOAc, washed with brine, dried, filtered, and concentrated to afford carboxylic acid **29** as an off-white solid (0.38 g, 95%). This material was used without further purification. To a solution of acid **29** (0.20 g, 0.36 mmol) in THF (2 mL) was added NaH (60% dispersion in mineral oil, 0.040 g, 1.0 mmol). The mixture was stirred 15 min, cooled to −95 °C, and *tert*-BuLi (0.87 mL, 0.84 M in pentane, 0.74 mmol) was added dropwise. After 5 min, ethylene oxide was bubbled through the reaction mixture. The reaction mixture was allowed to warm to room temperature, quenched with NaH_2PO_3 pH 3 buffer, extracted with EtOAc, washed with brine, dried, and concentrated. Flash chromatography afforded the title compound **30** (0.06 g, 32%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.86 − 2.98 (m, 2 H), 3.01 − 3.11 (m, 2 H), 4.31 (t, J = 6.2 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2 H), 4.52 − 4.61 (m, 1 H), 6.89 (dd, J = 1.5 Hz, 1H,), 6.47 (d, J = 8.9 Hz, 1 H), 7.00 (d, J = 8.9 Hz, 2 H), 7.23 (s, 1 H),

7.26 − 7.42 (m, 10 H), 7.75 (d, J = 1.6 Hz, H), 7.90 (d, J = 8.5 Hz, 2 H); HRMS: calcd for [$C_{32}H_{28}ClNO_4$ +H] 526.1780 found 526.1772.

Methyl 4-(2-{5-Chloro-1-(diphenylmethyl)-2-[(*E*)-2-nitrovinyl]-1*H*-indol-3-yl}ethoxy)benzoate (31b). Aldehyde **12b** (15 g, 28.6 mmol), NH_4OAc (8.8 g, 114 mmol), and $MeNO_2$ (150 mL) were heated to reflux for 4 h. The mixture was cooled to room temperature and partitioned between brine (500 mL) and EtOAc (400 mL). The aqueous phase was separated and extracted with EtOAc (400 mL). The organic extracts were washed with brine, dried, and concentrated until the product began to crystallize. Cooling and filtration yielded vinyl nitro compound **31b** (12.4 g, 76%). Concentration of the mother liquors and flash column chromatography of the residue (eluting with 1% EtOAc−toluene) afforded additional **31b** (3.7 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, J = 6.0 Hz, 2 H), 3.88 (s, 3 H), 4.33 (t, J = 5.9 Hz, 2 H), 6.82 (t, J = 9.3 Hz, 3 H), 6.99−7.06 (m, 2 H), 7.06−7.18 (m, 4 H), 7.29−7.40 (m, 6 H), 7.58 (d, J = 13.5 Hz, 1 H), 7.66 (d, J = 1.6 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H), 8.02 (d, J = 13.7 Hz, 1 H).

Methyl 4-{2-[2-(2-Aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate (32b). To a solution of vinyl nitro derivative **31b** (12.4 g, 22 mmol) in THF (400 mL) was added concd HCl (53 mL, 1.8 mmol) and Zn(Hg) amalgam[45] freshly prepared from Zn dust (29 g, 440 mmol) and $HgCl_2$ (2.9 g, 6 mmol) in 5% aq HCl. Additional THF (100 mL) was used to rinse the sides of the reaction flask. The reaction was exothermic. After 1 h the solution phase became almost colorless. The reaction mixture was filtered through Celite, washing with THF (100 mL). The organic phase was treated with concd NH_4OH (50 mL) and partially concentrated on the rotary evaporator. The resulting mixture was diluted with concd NH_4OH (50 mL) and extracted with CH_2Cl_2 (500 mL). The organic extracts were washed with brine, dried, and concentrated. Flash chromatography (1 → 10% MeOH−CH_2Cl_2) afforded **32b** (7.65 g, 65%) as a pale yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (t, J = 7.3 Hz, 2 H,) 2.98 (t, J = 7.4 Hz, 2 H), 3.25 (t, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 4.22 (t, J = 7.0 Hz, 2 H), 6.51 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.88 (d, J = 9.1 Hz, 2 H), 6.94 (s, 1 H), 7.03−7.18 (m, 4 H), 7.28−7.38 (m, 6 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H).

4-{2-[2-(2-Aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]-ethoxy}benzoic Acid (33). Methyl ester **32b** (0.13 g, 0.24 mmol) was hydrolyzed according to the general procedure to afford carboxylic acid **33** (0.082 g, 61%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 − 2.87 (m, 2 H), 3.18 − 3.27 (m, 2 H), 4.24 (t, J = 6.5 Hz, 2 H), 6.56 (d, J = 9.0 Hz, 1 H), 6.85 (dd, J = 9.0, 2.0 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.10−7.13 (m, 4 H), 7.18 (s, 1 H), 7.35−7.38 (m, 7 H), 7.74 (d, J = 2.0 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H); HRMS: calcd for[$C_{32}H_{29}ClN_2O_3$ + H] 525.1945 found, 525.1933.

Methyl 4-{2-[2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-chloro-1-(diphenylmethyl)-1 *H*-indol-3-yl]ethoxy}benzoate (34). Amine **32b** (0.10 g, 0.19 mmol) was stirred with benzyl chloroformate (0.026 mL, 0.19 mmol) and Et_3N (0.065 mL, 0.46 mmol) in CH_2Cl_2 (4 mL) at 0 °C for 1 h and at room temperature for 1 h. The mixture was washed with H_2O (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10 → 20% EtOAc−hexanes) afforded carbamate **34** (0.092 g, 74%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, J = 7.1 Hz, 2H), 3.18−3.27 (m, 4H), 3.90 (s, 3H), 4.20 (t, J = 6.9 Hz, 2H), 4.82 (t, J = 5.8 Hz, 1H), 5.04 (s, 2H), 6.49 (d, J = 9.0 Hz, 1H), 6.79−6.86 (m, 3H), 7.01 (s, 1H), 7.10−7.12 (m, 4H), 7.27−7.31 (m, 11H), 7.54 (d, J = 1.6 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H).

4-{2-[2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-chloro-1-(diphenylmethyl) -1*H*-indol-3-yl]ethoxy}benzoic Acid (35). Methyl ester **34** (0.092 g, 0.14 mmol) was hydrolyzed according to the general procedure and concentrated to afford carboxylic acid **35** (0.080 g, 89%), a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98 (t, J = 6.9 Hz, 2 H), 3.07−3.29 (m, 4 H), 4.20 (t, J = 6.5 Hz, 2 H), 4.99 (s, 2 H), 6.44 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.0 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.07−7.14 (m, 5 H), 7.19 (s, 1 H), 7.25−7.43 (m, 10 H), 7.58 (t, J = 5.6 Hz, 1 H), 7.65 (d, J = 2.0 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{40}H_{34}ClN_2O_5$ +H] 659.2307 found 659.2303.

Methyl 4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)(methyl)-amino]ethyl}-5-chloro-1*H*-in dol-3-yl)ethoxy]benzoate (36). To a CH_2Cl_2 (4 mL) solution of amine **32b** (0.100 g, 0.19 mmol) were added sat. $NaHCO_3$ (2 mL) and phenylacetyl chloride (0.025 mL, 0.19 mmol). The resulting biphasic mixture was stirred at room temperature for 1 h, diluted with sat. $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (20 mL). The organic phase was washed with H_2O and brine, dried, and concentrated. Flash chromatography (20 → 40% EtOAc−hexanes) afforded amide **36** (0.099 g, 96%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87−3.30 (m, 6 H), 3.48 (s, 2 H), 3.88 (s, 3 H), 4.16 (t, J = 6.7 Hz, 2 H), 5.43 (t, J = 5.8 Hz, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.71−6.91 (m, 3 H), 6.93−7.18 (m, 7 H), 7.26 (dd, J = 4.4, 1.9 Hz, 9 H), 7.52 (d, J = 1.9 Hz, 1 H), 7.94 (d, J = 9.1 Hz, 2 H).

4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)(methyl)amino]ethyl}-5-chloro-1 *H*-indol-3-yl)ethoxy]benzoic Acid (37). Methyl ester **36** (0.099 g, 0.15 mmol) was hydrolyzed according to the general procedure and concentrated to afford carboxylic acid **37** (0.083 g, 86%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.86−3.05 (m, 2 H) 3.07−3.32 (m, 4 H) 3.40 (s, 2 H) 4.21 (t, J = 6.6 Hz, 2 H) 6.47 (d, J = 8.8 Hz, 1 H) 6.80 (dd, J = 8.7, 1.8 Hz, 1 H) 6.98 (d, J = 8.8 Hz, 2 H) 7.03−7.15 (m, 4 H) 7.16−7.47 (m, 12 H) 7.65 (d, J = 2.2 Hz, 1 H) 7.85 (d, J = 8.8 Hz, 2 H) 8.31 (t, J = 5.6 Hz, 1 H); HRMS: calcd for [$C_{40}H_{35}ClN_2O_4$ + H] 643.2358 found 643.2347.

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[(2-phenylethyl)-amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (38). A solution of amine **32b** (0.150 g, 0.28 mmol) in 1,2-dichloroethane (2 mL) was stirred with phenylacetaldehyde (0.052 mL, 0.36 mmol) for 30 min. $NaBH(OAc)_3$ (0.095 g, 0.45 mmol) was added in one portion, and the mixture was stirred for 1 h, poured into sat. $NaHCO_3$ (20 mL), and extracted with EtOAc (45 mL). The organic extracts were washed with H_2O and brine, dried, and concentrated. Flash chromatography (1 → 5% MeOH−CH_2Cl_2) afforded amine **38** (0.049 g, 27%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57−2.79 (m, 6 H), 2.99 (t, J = 7.4 Hz, 2 H), 3.22 (t, J = 7.0 Hz, 2 H), 3.88 (s, 3 H), 4.13−4.25 (m, J = 7.0, 7.0 Hz, 2 H), 6.50 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 6.87 (d, J = 9.1 Hz, 2 H), 6.93 (s, 1 H), 7.01−7.13 (m, 6 H), 7.15−7.36 (m, 9 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H).

4-[2-(1-Benzhydryl-5-chloro-2-{2-[(2-phenylethyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (39). Methyl ester **38** (0.049 g, 0.076 mmol) was hydrolyzed according to the general procedure to afford the amine hydrochloride **39** (0.051 g, 100%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.81−2.91 (m, 2 H) 2.96 (s, 2 H) 3.12 (s, 2 H) 3.17−3.30 (m, 4 H) 4.25 (t, J = 7.0 Hz, 2 H) 6.55 (d, J = 9.1 Hz, 1 H) 6.85 (dd, J = 8.9, 2.1 Hz, 1 H) 6.98 (d, J = 8.8 Hz, 2 H) 7.04−7.17 (m, 4 H) 7.17−7.30 (m, 4 H) 7.30−7.45 (m, 8 H) 7.71 (d, J = 1.9 Hz, 1 H) 7.86 (d, J = 8.8 Hz, 2 H) 8.86 (s, 1 H); HRMS: calcd for [$C_{40}H_{37}ClN_2O_3$ + H] 629.2566 found 629.2561.

Methyl 4-[2-[5-Chloro-1-(diphenylmethyl)-2-{2-[(methylsulfonyl)amino]ethyl}-1*H*-indo l-3-yl)ethoxy]benzoate (40a). To a solution of amine **32b** (0.30 g, 0.56 mmol) in CH_2Cl_2 (8 mL) were added Et_3N (0.19 mL, 1.4 mmol) and MsCl (0.043 mL, 0.56 mmol). The mixture was stirred for 10 min, diluted with sat. $NaHCO_3$ (40 mL), and extracted with CH_2Cl_2 (2 × 40 mL). The organic phase was washed with brine (40 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20 → 50% EtOAc−hexanes) afforded methyl sulfonamide **40a** (0.32 g, 92%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3 H), 3.04 (t, J = 6.7 Hz, 2 H), 3.12−3.37 (m, 4 H), 3.88 (s, 3 H), 4.17−4.35 (m, 3 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.76−6.91 (m, 3 H), 6.95 (s, 1 H), 7.09 (dd, J = 5.9, 3.2 Hz, 4 H), 7.28−7.39 (m, 6 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[(phenylsulfonyl)-amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (40b). To a solution of amine **32b** (0.10 g, 0.19 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (0.065 mL, 0.46 mmol) and benzenesulfonyl chloride (0.024 mL, 0.19 mmol). The mixture was stirred for 10 min, diluted with sat. $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10 → 20% EtOAc−hexanes) afforded phenyl sulfonamide **40b** (0.11 g, 90%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92−2.95 (m, 2 H), 3.08−3.19 (m, 4 H), 3.88 (s, 3 H), 4.18 (t, J = 6.7 Hz, 2 H), 4.68 (t, J = 6.0 Hz), 6.53 (d, J = 9.0 Hz, 1 H), 6.78−6.84 (m, 3 H), 6.91 (s, 1 H), 7.03−6.06 (m, 4 H), 7.26−7.29 (m, 5 H), 7.34−7.40 (m, 2 H), 7.47−7.53 (m, 2 H), 7.64 (dd, J = 8.3, 1.2 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)amino]-ethyl}-5-chloro-1*H*-indol-3-yl)ethoxy]benzoate (40d). Amine **32b** (2.0 g, 3.7 mmol) underwent sulfonylation using the general Schotten−Baumann procedure with α-toluenesulfonyl chloride (0.71 g, 3.7 mmol) for 1 h. Flash chromatography (0 → 1% MeOH−CH_2Cl_2) of the crude sulfonamide afforded **40d** (2.2 g, 86%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78−2.92 (m, 2 H), 2.99−3.11 (m, 2 H), 3.18 (t, J = 6.3 Hz, 2 H), 3.88 (s, 3 H), 4.05 (s, 2 H), 4.11 (t, J = 6.0 Hz, 1 H), 4.20 (t, J = 6.5 Hz, 2 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.78−6.93 (m, 4 H), 7.01−7.13 (m, 5 H), 7.13−7.22 (m, 3 H), 7.21−7.38 (m, 7 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(2-phenylethyl)-sulfonyl]amino}ethyl)-1*H*-in dol-3-yl]ethoxy}benzoate (40e). Amine **32b** (0.200 g, 0.37 mmol) underwent Schotten−Baumann sulfonylation with 2-phenylethanesulfonyl chloride[57] (0.140 g, 0.68 mmol) according to the general procedure for 1 h. Flash chromatography (25% EtOAc−hexanes) of the crude product afforded **40e** (0.210 g, 81%) as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89−2.99 (m, 4 H), 2.99−3.08 (m, 2 H), 3.12 (t, J = 7.6 Hz, 2 H), 3.22 (t, J = 6.7 Hz, 2 H), 3.88 (s, 3 H), 4.00 (t, J = 6.3 Hz, 1 H), 4.23 (t, J = 6.6 Hz, 2 H), 6.53 (d, J = 9.3 Hz, 1 H), 6.78−6.89 (m, 3 H), 6.91 (s, 1 H), 7.03−7.10 (m, 6 H), 7.16−7.35 (m, 9 H), 7.54 (d, J = 1.8 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H).

4-[2-[5-Chloro-1-(diphenylmethyl)-2-{2-[(methylsulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (41a). Methyl ester **40a** (0.32 g, 0.51 mmol) was hydrolyzed according to the general procedure to afford carboxylic acid **41a** (0.29 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.81 (s, 3 H), 3.08 (br s, 4 H), 3.20 (t, J = 6.5 Hz, 2 H), 4.24 (t, J = 6.7 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.9, 2.1 Hz, 1 H), 6.99 (d, J = 9.1 Hz, 2 H), 7.11 (dd, J = 7.3, 4.8 Hz, 5 H), 7.26 (br s, 1 H), 7.31−7.46 (m, 6 H), 7.67 (d, J = 2.2 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{33}H_{31}ClN_2O_5S$ + H] 603.1715 found 603.1701.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[(phenylsulfonyl)amino]ethyl}-1*H*-indol-3 -yl)ethoxy]benzoic Acid (41b). Methyl ester **40b** (0.114 g, 0.17 mmol) was hydrolyzed according to the general procedure to afford **41b** (0.101 g, 90%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.77−2.90 (m, 2 H), 2.94−3.06 (m, 2 H), 3.13 (t, J = 6.3 Hz, 2 H), 4.19 (t, J = 6.3 Hz, 2 H), 6.50 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.93 (d, J = 8.8 Hz, 2 H), 7.00−7.10 (m, 5 H), 7.28−7.39 (m, 6 H), 7.49 (appar t, J = 7.4 Hz, 2 H), 7.53−7.59 (m, J = 7.4 Hz, 1 H), 7.63−7.70 (m, 3 H), 7.84 (d, J = 8.8 Hz, 2 H), 7.90 (t, J = 5.8 Hz, 1 H); HRMS: calcd for [$C_{38}H_{33}ClN_2O_5S$ + H] 665.1872 found 665.1864.

4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)amino]ethyl}-5-chloro-1*H*-indol-3 -yl)ethoxy]benzoic Acid (41d). Methyl ester **40d** (2.2 g, 3.2 mmol) was hydrolyzed according to the general procedure to afford **41d** (2.1 g, 95%), a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (s, 4 H), 3.09−3.25 (m, 2 H), 4.16−4.33 (m, 4 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.90−7.17 (m, 8 H), 7.18−7.48 (m, 12 H), 7.66 (d, J = 1.9 Hz, 1 H), 7.86 (d, J = 8.8 Hz, 2 H); MS (ESI) m/z 677.51 ((M − H)$^-$); Anal. calcd for $C_{39}H_{35}ClN_2O_5S$: C, H, N.

4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(2-phenylethyl)sulfonyl]-amino}ethyl)-1 *H*-indol-3-yl]ethoxy}benzoic Acid (41e). Methyl ester **40e** (0.18 g, 0.25 mmol) was hydrolyzed according to the general procedure to afford **41e** (0.15 g, 85%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81−2.92 (m, 2 H), 3.05−3.18 (m, 6 H), 3.21 (t, J = 6.8 Hz, 2 H), 4.25 (t, J = 6.7 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.0 Hz, 1 H), 6.98 (d, J = 9.1 Hz, 2 H), 7.03−7.17 (m, 7 H), 7.15−7.38 (m, 9 H), 7.40 (s, 1 H), 7.67 (d, J = 2.0 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{40}H_{37}ClN_2O_5S$ + H] 693.2190 found 693.2185.

Methyl 4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)(methyl)-amino]ethyl}-5-chloro-1*H*-in dol-3-yl)ethoxy]benzoate (42). A suspension of **40d** (0.100 g, 0.14 mmol) and Ag_2O (0.033 g, 0.14 mmol) in MeI (2 mL) was stirred overnight. The mixture was concentrated and filtered through Celite, washing with CH_2Cl_2. Concentration of the organic phase and flash chromatography (0 → 1% MeOH−CH_2Cl_2) afforded **42** (0.096 g, 94%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3 H), 2.78−2.94 (m, 2 H), 2.96−3.09 (m, 2 H), 3.16 (t, J = 6.6 Hz, 2 H), 3.89 (s, 3 H), 4.09 (s, 2 H), 4.18 (t, J = 6.7 Hz, 2 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 6.82−6.93 (m, 3 H), 7.00−7.11 (m, 4 H), 7.16−7.40 (m, 11 H), 7.52 (d, J = 1.9 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 2 H).

4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)(methyl)amino]ethyl}-5-chloro-1*H*-indol-3-yl)ethoxy]benzoic Acid (43). Methyl ester **42** (0.096 g, 0.13 mmol) was hydrolyzed according to the general procedure to afford **43** (0.088 g, 94%) as a pale yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 3 H), 2.80−2.96 (m, 2 H), 2.95−3.12 (m, 2 H), 3.15 (t, J = 6.3 Hz, 2 H), 4.20 (t, J = 6.3 Hz, 2 H), 4.37 (s, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.2 Hz, 1 H), 6.90−7.14 (m, 6 H), 7.17−7.47 (m, 12 H), 7.65 (d, J = 1.2 Hz, 1 H), 7.87 (d, J = 8.8 Hz, 2 H); HRMS: calcd for [$C_{40}H_{37}ClN_2O_5S$ + H] 693.2185 found 693.2199.

Methyl 4-(2-{5-Chloro-1-(diphenylmethyl)-2-[(*E*)-2-methoxyvinyl]-1*H*-indol-3-yl}ethox y)benzoate (45). KHMDS (3.2 g, 16 mmol) was added to a mixture of (methoxymethyl)triphenylphosphonium chloride (5.5 g, 16 mmol) in THF (80 mL) at −78 °C. The mixture was then stirred at 0 °C for 10 min. To the dark red suspension was added a 0 °C solution of aldehyde **12b** (2.8 g, 5.3 mmol) in THF (40 mL) via cannula. The mixture was stirred for 1 h at 0 °C and 2 h at room temperature and then poured into sat. NH_4Cl (200 mL). The mixture was extracted with Et_2O (2 × 80 mL). The organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (5 → 20% EtOAc−hexanes) afforded vinyl ether **45** (1.2 g, 40%), a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 − 3.27 (m, 2 H), 3.61 (s, 3 H), 3.88 (s, 3 H), 4.23 (t, J = 7.0 Hz, 2 H), 5.44 (d, J = 12.9 Hz, 1 H), 6.59 (d, J = 8.8 Hz, 1 H), 6.74−6.98 (m, 4 H), 7.05−7.17 (m, 4 H), 7.19−7.44 (m, 8 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-oxoethyl)-1*H*-indol-3-yl]ethoxy}benzoate (46). To a solution of vinyl ether **45** (0.50 g, 0.91 mmol) in MeCN (25 mL) were added NaI (0.16 g, 1.1 mmol) and TMSCl (0.14 mL, 1.1 mmol).[59] The orange suspension was stirred for 20 min, and 0.5 M aq $Na_2S_2O_3$ (100 mL) was then added. The mixture was extracted with EtOAc (3 × 50 mL). The organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10 → 20% EtOAc−hexanes) afforded aldehyde **46** (0.22 g, 44%), an off-white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (t, J = 6.3 Hz, 2 H), 3.87 (s, 5 H), 4.19 (t, J = 6.3 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 1 H), 6.72−6.95 (m, 4 H), 7.07 (d, J = 3.8 Hz, 4 H), 7.31 (m, 6 H), 7.57 (t, J = 1.9 Hz, 1 H), 7.79−8.13 (m, 2 H), 9.37 (d, J = 1.4 Hz, 1 H).

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethoxy}benzoate (47). To a solution of aldehyde **46** (0.22 g, 0.40 mmol) in THF (10 mL) and MeOH (10 mL) at 0 °C was added $NaBH_4$ (0.018 g, 0.48 mmol). After 40 min, the mixture was concentrated. H_2O (30 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated to

afford alcohol **47** (0.19 g, 87%), a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J = 5.8 Hz, 1 H), 3.12 (t, J = 6.5 Hz, 2 H), 3.26 (t, J = 6.7 Hz, 2 H), 3.62−3.84 (m, 2 H), 3.88 (s, 3 H), 4.27 (t, J = 6.6 Hz, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.7, 2.1 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.99 (s, 1 H), 7.10 (dd, J = 5.5, 3.3 Hz, 4 H), 7.28−7.44 (m, 6 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[2-(2-Bromoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (48). To a solution of alcohol **47** (0.19 g, 0.35 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added CBr_4 (0.42 g, 0.42 mmol) and bis(diphenylphosphino)propane (0.14 g, 0.35 mmol). After 1 h the ice bath was removed and the reaction mixture warmed to room temperature overnight. The reaction mixture was concentrated partially, and Et_2O (40 mL) was added. The precipitate was filtered, and the organic phase was concentrated. Flash chromatography (5 → 20% EtOAc−hexanes) afforded bromide **48** (0.15 g, 69%), a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10−3.30 (m, 4 H), 3.30−3.44 (m, 2 H), 3.88 (s, 3 H), 4.24 (t, J = 6.5 Hz, 2 H), 6.56 (d, J = 8.8 Hz, 1 H), 6.80−6.94 (m, 4 H), 7.10 (dd, J = 6.0, 2.7 Hz, 4 H), 7.29−7.38 (m, 3 H), 7.38−7.53 (m, 2 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.70 (dd, J = 10.7, 7.4 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-2-{2-[(benzylamino)sulfonyl]ethyl}-5-chloro-1*H*-indol-3-yl) ethoxy]benzoate (49). A mixture of bromide **48** (0.17 g) and Na_2SO_3 (0.042 g, 0.33 mmol) was heated to reflux in H_2O (20 mL) and dioxane (20 mL) for 5 d. The mixture was concentrated and lyophilized. To a suspension of the crude sodium sulfonate in CH_2Cl_2 (20 mL) were added DMF (0.022 mL, 0.28 mmol) and $SOCl_2$ (0.082 mL, 1.1 mmol). After 1 h the mixture was concentrated and azeotroped with toluene. The residue was suspended in CH_2Cl_2 (10 mL), and benzylamine (0.057 mL, 1.1 mmol) and sat. $NaHCO_3$ (5 mL) were added. The mixture was stirred overnight, and then the organic phase was separated and washed with H_2O and brine, dried, and concentrated. Flash chromatography (10 → 50% EtOAc−hexanes) afforded slightly impure product, which was further purified by preparative TLC (35% EtOAc−hexanes) to afford 0.0094 g (4% from alcohol **47**) of the methyl ester **48**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, J = 10.9, 5.1 Hz, 2 H), 3.15 (t, J = 6.3 Hz, 2 H), 3.27−3.40 (m, 2 H), 3.87 (s, 3 H), 4.11 (d, J = 6.0 Hz, 2 H), 4.14−4.27 (m, 2 H), 4.41 (t, J = 5.9 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.78−6.92 (m, 4 H), 7.07 (d, J = 3.6 Hz, 4 H), 7.14−7.40 (m, 11 H), 7.53 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

4-[2-(1-Benzhydryl-2-{2-[(benzylamino)sulfonyl]ethyl}-5-chloro-1*H*-indol-3 -yl)ethoxy]benzoic Acid (50). Methyl ester **49** (0.0094 g, 0.014 mmol) was hydrolyzed according to the general procedure to afford 0.009 g (98%) of the title acid, a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, J = 11.3, 5.2 Hz, 2 H), 3.16 (t, J = 6.2 Hz, 2 H), 3.28−3.43 (m, 2 H), 4.12 (d, J = 6.3 Hz, 2 H), 4.15−4.31 (m, 2 H), 4.57 (t, J = 5.9 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.78−6.91 (m, 4 H), 7.06 (dd, J = 6.0, 2.7 Hz, 4 H), 7.17−7.40 (m, 11 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.99 (d, J = 8.5 Hz, 2 H).

Methyl 4-{2-[2-[(1*E*)-3-(Allyloxy)-3-oxoprop-1-en-1-yl]-5-chloro-1-(diphenylmethyl)-1 *H*-indol-3-yl]ethoxy}benzoate (51). A solution of aldehyde **12b** (5.0 g, 9.2 mmol) and allyl (triphenylphosphoranylidene)acetate (5.0 g, 13.9 mmol) in THF (250 mL) was stirred for 1 h. The reaction mixture was diluted with EtOAc (500 mL) and washed with H_2O (2 × 125 mL) and brine (2 × 125 mL). The organic layer was dried and concentrated to afford a yellow oil which was dissolved in 50 mL 50% EtOAc−hexanes and filtered through a plug of SiO_2. Concentration afforded olefin **51** (5.23 g, 91% yield), a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (t, J = 6.6 Hz, 2 H), 3.71 (s, 3 H), 4.09 (t, J = 6.7 Hz, 2 H), 4.49 (d, J = 5.8 Hz, 2 H), 5.02−5.25 (m, 2 H), 5.66−5.91 (m, 1 H), 6.11 (d, J = 15.9 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.70 (d, J = 9.1 Hz, 2 H), 6.77 (dd, J = 8.9, 2.1 Hz, 1 H), 6.85 (s, 1 H), 6.89−7.00 (m, 4 H), 7.10−7.21 (m, 6 H), 7.47 (d, J = 1.9 Hz, 1 H), 7.56 (d, J = 16.2 Hz, 1 H), 7.79 (d, J = 8.8 Hz, 2 H).

(2*E*)-3-(5-Chloro-1-(diphenylmethyl)-3-{2-[4-(methoxycarbonyl)phenoxy]ethyl}-1*H*-indol-2-yl)acrylic Acid (52). To a mixture of indole **51** (6.12 g, 9.8 mmol) and $Pd(PPh_3)_4$ (1.12 g, 1.0 mmol) in THF (75 mL) was added morpholine (8.60 mL, 9.8 mmol) dropwise over 20 min, and the resulting mixture was stirred for 4 h. The reaction mixture was poured into EtOAc (250 mL) and extracted with 1 N NaOH (2 × 75 mL). The combined aqueous extracts were acidified with 1 N HCl and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine (50 mL), dried, and concentrated to afford carboxylic acid **52** (5.40 g, 97%), a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (t, J = 6.5 Hz, 2 H), 3.70 (s, 3 H), 4.10 (t, J = 6.6 Hz, 2 H), 6.08 (d, J = 15.9 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.69 (d, J = 9.1 Hz, 2 H), 6.78 (dd, J = 8.9, 2.1 Hz, 1 H), 6.86 (s, 1 H), 6.89−6.98 (m, 4 H), 7.11−7.19 (m, 6 H), 7.48 (d, J = 1.6 Hz, 1 H), 7.63 (d, J = 15.9 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 2 H)

3-(5-Chloro-1-(diphenylmethyl)-3-{2-[4-(methoxycarbonyl)-phenoxy]ethyl}-1*H*-indol-2-yl)propanoic Acid (53). To a solution of carboxylic acid **52** (0.400 g, 0.70 mmol) in MeOH (15 mL) was added 5% Pt/C (80 mg) as a slurry MeOH (5 mL). The suspension was stirred under H_2 atmosphere (1 atm) for 24 h. The H_2 was then evacuated, and additional 5% Pt/C (80 mg) in MeOH (5 mL) was added. The suspension was stirred under H_2 atmosphere (1 atm) for an additional 24 h. ^{1}H NMR of an aliquot of the reaction mixture indicated that the reaction was complete. The mixture was filtered through Celite and the filtrate evaporated to afford carboxylic acid **53** (0.320 g, 79%), a yellow-green solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (t, J = 6.7 Hz, 2 H), 3.69 (s, 3 H), 4.08 (t, J = 6.7 Hz, 2 H), 4.34 (d, J = 5.8 Hz, 2 H), 5.54 (t, J = 5.5 Hz, 2 H), 6.49 (d, J = 9.1 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 2 H), 6.74 (dd, J = 8.9, 2.1 Hz, 1 H), 6.85 (s, 1 H), 6.88−6.98 (m, 4 H), 7.08−7.22 (m, 6 H), 7.44 (d, J = 1.9 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(3-hydroxypropyl)-1*H*-indol-3-yl]ethoxy} benzoate (54). To a solution of carboxylic acid **53** (0.10 g, 0.20 mmol) in CH_2Cl_2 (1 mL) was added $(COCl)_2$ (0.034 g, 0.30 mmol), and the mixture was stirred for 1 h. The mixture was then evaporated to dryness, and the residue was dissolved in a mixture of Et_2O (1 mL) and TMEDA (0.027 mL). To this solution was added $Zn(BH_4)_2$[60] (0.35 mL of a soln in Et_2O), and the mixture was stirred for 15 min and then quenched by the addition of H_2O (1 mL). The mixture was diluted with Et_2O (10 mL), and the organic layer was dried and concentrated. Flash chromatography (10% EtOAc−hexanes) afforded alcohol **54** (0.081 g, 83%), a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.68 (m, 2 H), 2.67−2.86 (m, 2 H), 3.07 (t, J = 7.0 Hz, 2 H), 3.46 (t, J = 5.9 Hz, 2 H), 3.70 (s, 3 H), 4.04 (t, J = 7.0 Hz, 2 H), 6.32 (d, J = 8.8 Hz, 1 H), 6.61 (dd, J = 8.9, 2.1 Hz, 1 H), 6.71 (d, J = 9.1 Hz, 2 H), 6.75 (s, 1 H), 6.88−6.99 (m, 4 H), 7.10−7.19 (m, 6 H), 7.36 (d, J = 1.6 Hz, 1 H), 7.69−7.85 (m, 2 H).

Methyl 4-{2-[2-(3-Bromopropyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (55). To a solution of alcohol **54** (0.104 g, 0.20 mmol) in CH_2Cl_2 (2 mL) was added PS−PPh_3 (0.116 g, 1.61 mmol/g, 0.20 mmol) followed by CBr_4 (0.125 g, 0.40 mmol). The suspension was stirred for 2 h, filtered, and concentrated. The resulting orange oil was purified via column chromatography with 2% EtOAc−hexanes to give bromide **55** (0.100 g, 86%), a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.93 (m, 2 H), 2.74−2.90 (m, 2 H), 3.06 (t, J = 6.9 Hz, 2 H), 3.20 (t, J = 6.0 Hz, 2 H), 3.71 (s, 3 H), 4.04 (t, J = 7.0 Hz, 2 H), 6.33 (d, J = 8.8 Hz, 1 H), 6.63 (dd, J = 8.8, 2.2 Hz, 1 H), 6.67−6.75 (m, 3 H), 6.92 (dd, J = 5.9, 3.7 Hz, 4 H), 7.11−7.18 (m, 6 H), 7.36 (d, J = 2.2 Hz, 1 H), 7.79 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[2-{3-[(Benzylsulfonyl)amino]propyl}-5-chloro-1-(diphenylmethyl)-1*H*-in dol-3-yl]ethoxy}benzoate (56). A solution of α-toluenesulfonamide (0.033 g, 0.20 mmol) in DMF (0.5 mL) was added to a suspension of NaH (0.008 g, 60% dispersion in mineral oil, 0.20 mmol) in DMF (0.5 mL). After 30 min, a solution of bromide **55** (0.100 g, 0.20 mmol) in DMF (0.5 mL) was added. After 1 h, the mixture was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic layer was

washed with water (2 × 5 mL) and brine (2 × 5 mL), dried, and evaporated to afford a yellow oil which was purified via column chromatography (5% EtOAc−hexanes) to afford sulfonamide **56** (0.020 g, 17% yield), a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.33 (m, 2 H), 2.37−2.61 (m, 4 H), 2.87 (t, J = 6.9 Hz, 2 H), 3.70 (s, 3 H), 3.77 (s, 2 H), 3.94 (t, J = 7.1 Hz, 2 H), 6.31 (d, J = 8.8 Hz, 1 H), 6.52 (s, 1 H), 6.57−6.71 (m, 3 H), 6.77−6.89 (m, 4 H), 6.94−7.00 (m, 1 H), 7.01−7.14 (m, 10 H), 7.31 (d, J = 1.9 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 2 H).

4-{2-[2-{3-[(Benzylsulfonyl)amino]propyl}-5-chloro-1-(diphenylmethyl)-1*H* -indol-3-yl]ethoxy}benzoic Acid (57). Hydrolysis of methyl ester **56** (0.020 g, 0.02 mmol) using the general procedure afforded carboxylic acid **57** (0.013 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27−1.48 (m, 2 H), 2.58−2.80 (m, 4 H), 3.00 (t, J = 6.7 Hz, 2 H), 3.98−4.14 (m, 5 H), 6.35 (d, J = 8.8 Hz, 1 H), 6.56−6.74 (m, 4 H), 6.83−6.96 (m, 4 H), 7.05−7.20 (m, 11 H), 7.35 (d, J = 1.9 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 2 H).

Methyl 4-{2-[2-[3-(Benzylthio)propyl]-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]etho xy}benzoate (58). A solution of benzyl mercaptan (0.211 g, 1.7 mmol) in DMF (1 mL) was added to a suspension of NaH (0.074 g, 60% in mineral oil, 1.9 mmol) in DMF (1 mL). After 30 min a solution of bromide **55** (0.260 g, 0.40 mmol) in DMF (0.5 mL) was added. After 1 h the mixture was quenched with H_2O and extracted with EtOAc (10 mL). The organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL), dried, and concentrated. Column chromatography (5% EtOAc−hexanes) afforded thioether **58** (0.160 g, 57%), a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49−1.66 (m, 2 H), 2.23 (t, J = 6.9 Hz, 2 H), 2.69 (dd, J = 9.2, 6.7 Hz, 2 H), 3.02 (t, J = 7.1 Hz, 2 H), 3.40 (s, 2 H), 3.71 (s, 3 H), 4.00 (t, J = 7.1 Hz, 2 H), 6.30 (d, J = 8.8 Hz, 1 H), 6.61 (dd, J = 8.9, 2.1 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 3 H), 6.91 (dd, J = 5.6, 3.7 Hz, 4 H), 6.96−7.07 (m, 5 H), 7.10−7.18 (m, 6 H), 7.34 (d, J = 2.2 Hz, 1 H), 7.74−7.84 (m, 2 H).

4-{2-[2-[3-(Benzylsulfonyl)propyl]-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (59). To a solution of thioether **58** (0.075 g, 0.10 mmol) in CH_2Cl_2 (1 mL) was added 55% MCPBA (0.075 g, 0.20 mmol). After 2 h the reaction mixture was diluted with EtOAc (25 mL) and washed with sat. $NaHCO_3$ and brine, dried, and evaporated. Flash chromatography (15% EtOAc−hexanes) afforded the sulfone (0.052 g, 66%), a yellow oil. Hydrolysis of the sulfone methyl ester (0.060 g, 0.10 mmol) using the general procedure afforded the carboxylic acid **59** (0.049 g, 85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.58−1.78 (m, 2 H), 2.81 (dd, J = 8.9, 6.5 Hz, 2 H), 2.88−3.05 (m, 4 H), 4.03 (t, J = 6.5 Hz, 2 H), 4.15 (s, 2 H), 6.35−6.41 (m, 1 H), 6.63 (dd, J = 6.7, 2.1 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 6.89 (d, J = 6.0 Hz, 4 H), 7.00 (d, J = 6.6 Hz, 4 H), 7.09−7.29 (m, 9 H), 7.47 (d, J = 1.9 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (118). To the methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate amine **32b** (215 mg, 0.4 mmol) was added (2-chlorophenyl)methanesulfonyl chloride (0.45 g, 2.0 mmol) using the Schotten−Baumann general procedure to generate the sulfonamide methyl ester (250 mg, 86% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88−2.97 (m, 2 H), 3.01−3.11 (m, 2 H), 3.18 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 4.19 (t, J = 6.5 Hz, 1 H), 4.26 (t, J = 6.0 Hz, 1 H), 4.34 (s, 2 H), 6.50 (t, J = 8.8 Hz, 1 H), 6.78−6.93 (m, 4 H), 7.02−7.12 (m, 4 H), 7.14−7.28 (m, 2 H,) 7.28−7.36 (m, 7 H), 7.41 (d, J = 7.1 Hz, 1 H), 7.53 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 2 H).

The ester from above (250 mg, 0.3 mmol) was hydrolyzed according to the general procedure to afford **118** (237 mg, 90% yield) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (d, J = 14.0 Hz, 2 H), 3.02−3.13 (m, 2 H), 3.19 (t, J = 6.5 Hz, 2 H), 4.21 (t, J = 6.5 Hz, 2 H), 4.34 (s, 2 H), 4.48 (t, J = 5.9 Hz, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.78−6.94 (m, 4 H), 7.03−7.12 (m, 4 H), 7.14−7.25 (m, 2 H), 7.28−7.35 (m, 7 H), 7.41 (dd, J = 7.4, 1.9 Hz, 1 H), 7.53 (d, J = 2.2 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 2 H); HRMS calcd for [$C_{39}H_{34}Cl_2N_2O_5S$ + H] 713.1638 found 713.1644.

4-{2-[5-Chloro-2-(2-{[(4-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (119). The sulfonamide ester was prepared from methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}-benzoate amine **32b** (100 mg, 0.19 mmol) and [(4-chloromethyl)-phenyl]methanesulfonyl chloride (52 mg, 0.23 mmol) according to the Schotten−Baumann general procedure and purified using flash chromatography (20 → 40% EtOAc-hexanes) to afford the sulfonamide methyl ester (98 mg, 73% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (q, J = 6.9 Hz, 2 H), 3.07 (t, J = 7.4 Hz, 2 H), 3.18 (t, J = 6.5 Hz, 2 H), 3.87 (s, 3 H), 3.98 (s, 2 H), 4.17−4.36 (m, 3 H), 6.52 (d, J = 8.8 Hz, 2 H), 6.83 (appar d, J = 8.5 Hz, 3 H), 6.89 (s, 1 H), 7.00−7.13 (m, 6 H), 7.17−7.25 (m, 2 H), 7.28−7.39 (m, 5 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

The ester from above (98 mg, 0.13 mmol) was hydrolyzed according to the general procedure to afford the title acid (95 mg, 99% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.02 (br s, 4 H), 3.12−3.25 (m, 2 H), 4.22 (t, J = 7.1 Hz, 2 H), 4.28 (s, 2 H), 6.46 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.03−7.15 (m, 5 H), 7.17−7.50 (m, 11 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.86 (d, J = 8.5 Hz, 2 H). HRMS calcd for [$C_{39}H_{34}Cl_2N_2O_5S$ + H] 713.1638 found 713.1643.

4-{2-[5-Chloro-2-(2-{[(2,3-dichlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (120). To the methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate amine **32b** (215 mg, 0.4 mmol) was added (2,3-dichlorophenyl)methanesulfonyl chloride (0.51 g, 2.0 mmol) according to the Schotten−Baumann procedure to generate the sulfonamide methyl ester (154 mg, 50% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (d, J = 8.0 Hz, 2 H), 3.03−3.13 (m, 2 H), 3.18 (t, J = 6.6 Hz, 2 H), 3.86 (s, 3 H), 4.20 (t, J = 6.6 Hz, 2 H), 4.33 (s, 2 H), 4.39 (s, 1 H), 6.52 (d, J = 9.1 Hz, 1 H), 6.77−6.86 (m, 3 H), 6.91 (s, 1 H), 7.03−7.11 (m, 4 H), 7.27−7.35 (m, 8 H), 7.40 (dd, J = 8.0, 1.4 Hz, 1 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H).

The ester from above (154 mg, 0.2 mmol) was hydrolyzed by stirring with KOH (67 mg, 1.0 mmol) in THF (5 mL), MeOH (5 mL), and H_2O (2 mL). The reaction mixture was monitored by TLC (10% MeOH−CH_2Cl_2) for the disappearance of starting material. The mixture was stirred overnight at room temperature and then concentrated, diluted with H_2O, and acidified to pH 2−4 using 1 M HCl. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated to afford the desired product **120** (134 mg, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88−3.00 (m, 2 H,) 3.04−3.15 (m, 2 H), 3.19 (t, J = 6.3 Hz, 2 H), 4.22 (t, J = 6.6 Hz, 2 H), 4.34 (s, 2 H), 4.52 (t, J = 6.2 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.78−6.94 (m, 4 H), 7.03−7.21 (m, 5 H), 7.31 (d, 7 H), 7.39 (dd, J = 8.1, 1.5 Hz, 1 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S$ + H] 747.1249 found 747.1254.

4-{2-[5-Chloro-2-(2-{[(2,4-dichlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (121). To methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate amine **32b** (215 mg, 0.4 mmol) was added (2,4-dichlorophenyl)methanesulfonyl chloride (0.51 g, 2.0 mmol) according to the general Schotten−Baumann procedure to generate sulfonamide methyl ester (323 mg, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (d, J = 7.7 Hz, 2 H), 3.04−3.14 (m, 2 H), 3.19 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 4.21 (t, J = 6.5 Hz, 3 H), 4.27 (s, 2 H), 6.79−6.88 (m, 3 H), 6.91 (s, 1 H), 7.03−7.11 (m, 4 H), 7.17 (dd, J = 8.2, 2.2 Hz, 1 H), 7.28−7.38 (m, 8 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

The ester from above (323 mg, 0.42 mmol) was hydrolyzed according to the general procedure to afford **121** (302 mg, 90% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88−3.01 (m, 2 H), 3.05−3.16 (m, 2 H), 3.20 (t, J = 6.6 Hz, 2 H), 4.23 (t, J = 6.5 Hz, 3 H), 4.27 (s, 2 H), 4.54 (s, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.78−6.94 (m, 4 H), 7.02−7.11 (m, 4 H), 7.16 (dd, J = 8.4, 2.1 Hz, 1 H), 7.28−7.37 (m, 8 H), 7.53 (d, J = 2.2 Hz, 1 H), 7.99

(d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S$ + H] 747.1249 found 747.1255.

4-{2-[5-Chloro-2-(2-{[(3,5-dichlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (122). The sulfonamide was prepared from methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}-benzoate amine **32b** (100 mg, 0.19 mmol) and (3,5-dichlorophenyl)-methanesulfonyl chloride (60 mg, 0.23 mmol) according to the Schotten−Baumann procedure and purified using flash chromatography (20 → 40% EtOAc-hexanes) to afford the sulfonamide methyl ester (142 mg, 100% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70−2.98 (m, 2 H), 3.04−3.16 (m, 2 H), 3.20 (t, J = 6.5 Hz, 2 H), 3.86 (s, 3 H), 3.90 (s, 2 H), 4.23 (t, J = 6.3 Hz, 2 H), 4.42 (t, J = 6.2 Hz, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.75−6.88 (m, 3 H), 6.92 (s, 1 H), 7.02−7.15 (m, 6 H), 7.22−7.39 (m, 7 H), 7.55 (d, J = 2.2 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H).

The ester intermediate (142 mg, 0.19 mmol) was hydrolyzed according to the general procedure to afford **122** (136 mg, 98% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.92−3.24 (m, 6 H), 4.23 (t, J = 6.7 Hz, 2 H), 4.38 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.05−7.26 (m, 5 H), 7.36 (d, J = 5.2 Hz, 8 H), 7.55 (t, J = 5.8 Hz, 1 H), 7.59 (d, J = 3.6 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.86 (d, J = 8.8 Hz, 2 H); HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S$ + H] 747.1249 found 747.1249.

4-{2-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (Ecopladib, 123). The sulfonamide was prepared from methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}-benzoate amine **32b** (1.9 g, 3.50 mmol) and (3,4-dichlorophenyl)-methanesulfonyl chloride (0.93 g, 3.60 mmol) according to the Schotten−Baumann procedure and purified using flash chromatography (20 → 50% EtOAc-hexanes) to afford the sulfonamide methyl ester (2.33 g, 87% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (q, J = 6.8 Hz, 2 H), 3.10 (t, J = 7.6 Hz, 2 H), 3.20 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 3.93 (s, 2 H), 4.19−4.37 (m, 3 H), 6.55 (d, J = 9.1 Hz, 1 H), 6.77−6.87 (m, 3 H), 6.91 (s, 1 H), 6.99 (dd, J = 8.2, 1.9 Hz, 1 H), 7.07 (dd, J = 6.5, 2.9 Hz, 4 H), 7.27−7.40 (m, 8 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H).

The ester (2.33 g, 3.1 mmol) was hydrolyzed according to the general procedure to afford **123** (2.29 g, ∼100% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.88−3.25 (m, 6 H), 4.23 (t, J = 6.7 Hz, 2 H), 4.35 (s, 2 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.2 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.05−7.15 (m, 5 H), 7.26 (dd, J = 8.2, 1.9 Hz, 1 H), 7.31−7.41 (m, 6 H), 7.46 (t, J = 5.9 Hz, 1 H), 7.53 (d, J = 8.2 Hz, 1 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.86 (d, J = 8.8 Hz, 2 H); HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S$ + H] 747.1249 found 747.1249; Anal. Calcd for ($C_{39}H_{33}Cl_3N_2O_5S$): C, H, N.

GLU Micelle Assay. The assay was carried in a 96-well format using a fluorescent plate reader with a 355 nm excitation filter and a 460 nm emission filter (Lab Systems Fluoroscan II, Helsinki, Finland). The assay buffer contained 940 μM Triton X-100, 50 mM HEPES pH 7.4, 0.3 mM EDTA, 1 mM $CaCl_2$ and 300 mM KCl. DTPC (1, 2-*O*-tetradecyl-*sn*-glycero-3-phosphocholine, Avanti) at a final concentration of 120 μM was added the day of the experiment and GLU (7-hydroxycoumarinyl-γ-linolenate, Biomol Research Lab, Inc.) at a final concentration of 90 μM was added immediately prior to each assay.

Compounds (10 μL) dissolved in DMSO were placed in duplicate wells of a black 96-well plate. Wells corresponding to the positive and negative controls contained DMSO without inhibitors. Just prior to the experiment, 200 μL assay buffer containing 90 μM GLU and 120 μM DTPC was added to all wells in the assay plate. Assay buffer (50 μL) was added to the negative, and 50 μL of cPLA$_2\alpha$ solution (5 mg/mL in assay buffer) was added to all other wells to initiate the reaction. The final concentration of enzyme was 1 μg/mL. The content of each well was mixed gently during the addition of the enzyme, and the plate was rapidly transferred to the fluorescent plate reader. The increase in fluorescence was read every 4 min for 84 min. The slope of the resulting line was determined and the inhibition was calculated.

Rat Whole Blood Assay. Fresh blood was collected in heparinized tubes by cardiac puncture of male Sprague−Dawley rats. Aliquots of blood (0.6 mL) were incubated with 6 μL of vehicle (DMSO) containing various concentrations of the test compounds. After 15 min preincubation at 37 °C, blood was stimulated with 6 μL of calcium ionophore A23187 (Sigma C-7522) in DMSO for 10 min at 37 °C. The final concentration of A23187 was 5 μM. DMSO (6 μL) was added in the unstimulated controls. The reactions were stopped by mixing 60 μL of cold EDTA to give a final concentration of 20 mM. The blood was centrifuged at 6500 rpm for 10 min on a microcentrifuge to obtain plasma. A 70 μL aliquot of plasma was mixed with 400 μL of cold methanol for protein precipitation. After incubation at −80 °C for 30 min, the supernatant was obtained by centrifuging at 6500 rpm for 10 min and was assayed for TXB_2 according to the manufacturer's procedure (Assay Designs, Inc.).

Human Whole Blood Assay. Fresh blood was collected in heparinized tubes by venipuncture of healthy male volunteers. Aliquots of blood (0.9 mL) were incubated with 9 μL of DMSO vehicle containing various concentrations of test compound. After 15 min preincubation at 37 °C, the blood was stimulated with 9 μL of calcium ionophore A23187 (Sigma C-7522) in DMSO for 15 min at 37 °C. The final concentration of A23187 was 30 μM. The unstimulated controls received 9 μL of DMSO. The reactions were stopped by mixing 100 μL of cold EDTA and processed as described for the rat whole blood assay. Supernatant was assayed for TXB_2, LTB_4, PGE_2, and $PGF_2\alpha$ according to the manufacturer's procedures (Assay Designs, Inc.).

The PAF assay was performed in an identical manner to the above procedure, except the reactions were stopped by adding cold MeOH (2 mL) spiked with D4-PAF (25 ng/mL) which served as an internal standard.

The products were extracted with $CHCl_3$ (4 mL), and the samples in the $CHCl_3$ layer were applied to a silica column (Varian, Walnut Creek, CA, cat. # 12113036) which had been preconditioned with $CHCl_3$ (5 mL). The column was washed with EtOH (5 mL), and then the PAF was eluted with MeOH−H_2O (4 mL, 3:1, v/v). The eluate was dried under vacuum.

In order to cleave the phosphocholine from the PAF, the dried product was suspended in PBS (300 μL), and 5 units of phospholipase C (Sigma, St. Louis, MO, P9439) and Et_2O (1 mL) were added. The sample was rotated for 2 h, and the Et_2O layer containing the 1-*O*-hexadecyl-2-acetyl-glycerol was transferred to a new tube and dried under vacuum. The 1-*O*-hexadecyl-2-acetyl-glycerol was dissolved in CH_2Cl_2 (200 μL), and 2,3,4,5,6-pentafluorobenzoyl chloride (50 μL/mL) and DMAP (50 μL/mL) were added. The resulting mixture was incubated at room temperature for 30 min. The samples were dried, resuspended in decane (50 μL), and transferred to GC vials.

The samples were analyzed by GC-MS (HP6890 series GC with an NP5973 Mass Selective Detector, Hewlett-Packard (Agilent), Palo Alto, CA) using a HP-5MS column (cat. # 19091S-433). Samples (2 μL) were injected in splitless mode at an injector temperature of 280 °C and helium gas (15 psi) as carrier. The injector was purged at 1.5 min. The column temperature was held at 180 °C for 1 min and then increased to 250 °C at 20 °C/min and held at 250 °C for 25 min. The transfer line to the mass detector was maintained at 280 °C. The mass detector was operated in the negative chemical ionization mode with methane as the reagent gas. The detection parameters were optimized using the autotune program provided with the instrument. The molecular ions of the pentafluorobenzoyl derivatives of 1-*O*-hexadecyl-2-acetylglycerol and 1-*O*-7,7,8,8-d_4-hexadecyl-2-acetyl-*sn*-glycerol were monitored at *m*/*z* of 552 and 556, respectively. The ratio of signal intensity at *m*/*z* 552 to 556 multiplied by the amount of D4-PAF internal standard added to the sample gave the amount of PAF generated in the A23187-stimulated blood.

Isothermal Calorimetry. Purified human cPLA$_2\alpha$ was dialyzed in 50 mM HEPES pH 7.4, 0.3 mM EDTA, 1 mM $CaCl_2$, and 300

mM KCl. DMSO and Trixon-X-100 were added to make a 2 mL protein solution consisting of 2.5 μM cPLA$_2\alpha$, 1% DMSO, and 940 μM Trixon-X-100. A stock solution of compound (7.85 mM in 100% DMSO) was diluted with the dialysis buffer in which cPLA$_2\alpha$ was dialyzed previously to make 2 mL working solution that contained 78.5 μM compound **123**, 940 μM Triton-X-100, and 1% DMSO. A control solution containing the dialysis buffer, 940 μM Triton-X-100 and 1% DMSO was made, and both solutions were degassed. The cPLA$_2\alpha$ protein solution was loaded carefully into the sample cell of the calorimeter (VP-Isothermal Titration Calorimeter, Microcal Inc., Northampton, MA), while the syringe was filled with compound **123** working solution (250 μL). The titration was carried out at 30 °C. A total of 20 injections (10 μL each) of the compound were made, and settings were as recommend by Microcal. A separate control experiment was done in which compound **123** was titrated against the buffer solution without any protein to determine the background. The data were analyzed using the Origin software supplied with the VP-Isothermal Titration Calorimeter, and the binding parameters were determined.

MC-9 Assay. MC-9 cells were grown in suspension with 10 units/mL murine IL-3 and 10% heat-inactivated fetal bovine serum in RPMI media supplemented with 2 mM L-glutamine, 100 units/mL penicillin, and 100 μg/mL streptomycin. The day before the assay, cells were seeded at 4×10^5 cells/mL in the same media and aforementioned additives. Murine IgE specific for Anti-DNP (5 μL of a 27.5 ng/mL stock added per 200 mL of media) was added to prime the IgE receptor, and the cells were grown overnight.

On the day of the assay, the cells were pelleted and washed in serum-free RPMI that does not contain phenol red. The cells were then resuspended in 10 mL of the same serum-free media at 4×10^6 cells/mL. IL-3 (24 Units/mL) was added, and the cells were transferred to the 37 °C room where the assay was conducted.

Duplicate 96-well polypropylene plates containing inhibitors in 2 μL in DMSO were prewarmed to 37 °C, and 200 μL of cells was added to columns on the plate in 20-s intervals. Following 15 min of preincubation, the cells were stimulated by adding DNP-BSA to one plate and arachidonic acid to the duplicate plate. Stimulation and all other manipulations were done one column at a time in 20-s intervals. After an additional 4 min, 180 μL of the cell suspension was transferred to a plate on ice containing 20 μL of 20 mM EDTA per well to quench the reaction. The plate was then centrifuged at 1500 rpm for 10 min to pellet the cells, 150 μL of supernatant was transferred to fresh plates, and the production of prostaglandins and leukotrienes was determined according to the manufacturer's procedures (Assay Designs, Inc.).

Cyclooxygenase Assay. A colorimetric COX assay (Cayman, cat. # 760111) was used to measure inhibition of both COX-1 and COX-2. SC-560-7 (Cayman, cat. # 70340) was used as the reference compound for selective COX-1 inhibition and Celecoxib was used as the reference for COX-2 inhibition. The assay was performed according to the manufacturer's directions.

Pharmacokinetics in Rats. Male Sprague−Dawley rats (200−300 g, Taconic, Germantown, NY) were used for PK assessment. For iv administration, animals ($n = 3$) received a single bolus dose of 2 mg/kg in vehicle (50% PEG-400, 50% DSMO) via tail vein injection. For oral administration, rats ($n = 3$) were dosed via gavage at 5 mg/kg in MC/Tween vehicle (0.5% methylcellulose and 2% Tween 80) or Phosal vehicle (55.5% Phosal 53 MCT, 5.6% Tween 80, 16.7% Labrasol, and 22.2% propylene carbonate) with test compound dissolved at 37.5 mg/mL vehicle, diluted with water, and dosed at 4 mL/kg. Blood samples were collected over a period of 24 h via jugular cannulae. Plasma concentrations of cPLA$_2\alpha$ inhibitors were determined by LC/MS/MS. The pharmacokinetic parameters (AUC and clearance) were calculated with noncompartment method (WinNonlin, version 4.0, Pharsight Corp., Mountain View, CA).

Rat Carrageenan Air Pouch Model. Male Sprague−Dawley rats were anesthetized, and 10−20 mL of filtered air was injected subcutaneously under the dorsal skin to form a pouch. Three and six days later, the pouches were reinflated with 10−15 mL of sterile air. On the seventh day, the test compound was dissolved in vehicle (55.5% Phosal 53 MCT, 5.6% Tween 80, 16.7% Labrasol, and 22.2% propylene carbonate) to give 37.5 mg of test compound per mL of vehicle. This test compound in vehicle was diluted with water to the appropriate concentration and dosed at 4 mL/kg. Vehicle treated animals received the same amount of vehicle as the animals treated with the highest dose of compound. Two hours later, 2 mL of a 1% solution of carrageenan (Viscarin carrageenan type GP-209NF from FMC Corporation, Philadelphia, PA) in saline was injected into the pouch. Six hours after the carrageenan injection, the rats were individually sacrificed and the contents of the pouch were harvested. The amount of fluid recovered was measured. An aliquot of the exudate was centrifuged at 6500 rpm for 10 min, and 300 μL of each supernatant was precipitated with MeOH (800 μL) precooled to 0 °C. The samples were well vortexed and were kept at −80 °C overnight. The samples were centrifuged again and assayed for PGE_2 (Assay Design Inc., Ann Arbor, MI) to locate the PGE_2 production within the linear range of the PGE_2 standard curve. To minimize the difference in binding environments for the standards and samples, the standard curve was generated in a 1% solution of carrageenan that was mixed with assay buffer to the same dilution as the samples. The approximate ED_{50} value was extrapolated from the dose−response curve.

Rat Carrageenan Paw Edema (CPE) Model. Male Sprague−Dawley rats weighing 190−250 g from Taconic Farms were housed for 1 week prior to experimentation and fed food and water *ad libitum*. The protocol for the CPE model was adapted from procedures previously described.[55,61] The volume of the left hind footpad of the rat was measured using an Ugo Basile plethysmometer prior to dosing. The animal was then dosed orally with the test compound in Phosal vehicle (55.5% Phosal 53 MCT, 5.6% Tween 80, 16.7% Labrasol, and 22.2% propylene carbonate), orally with 10 mg/kg of Naproxen in phosal vehicle, or with vehicle alone as described above. Two hours after dosing, 60 μL of 1% carrageenan in sterile H_2O was injected subplantar into the left hind footpad. The paw volume measurement was repeated 3 h after the carrageenan injection. Inhibition was calculated using the following formula: percent inhibition = {1− [(3 h paw volume − 0 h paw volume (test group)]/[3 h paw volume − 0 h paw volume (vehicle group)]} × 100. There were 10 rats in each test group and the data represented is from four separate experiments.

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Note Added after ASAP Publication. This manuscript was released ASAP on February 17, 2007 with an error in the caption of Scheme 8. The correct version was posted on February 19, 2007.

Supporting Information Available: Purity of final compounds as determined by HPLC in two solvent systems; details of CHN data for compounds **21**, **43d**, **123**; experimental procedures for the preparation of compounds **10, 12a, 31a, 32a, 40c, 41c, 44, 60, 61, 63-67, 69-75, 77, 78, 80-95, 97-105,** and **107-117**. This material is available free of charge via the Internet at http://pubs.acs.org.

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